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EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

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- Encourage and support research into the effective treatment of opiate addiction and facilitate the communication of research results particularly through its journal- Heroin Addiction and Related Clinical Problems, the EUROPAD web site and the associations conference programme.
- Develop a European network to facilitate communication and co-operation among individuals and organisations working in addiction treatment services throughout Europe.
- Build an International network of "partner" societies and organisation to enable Europe to play its part in the continuing development of opiate addiction treatment. Build an International network of "partner" societies and organisation to enable Europe to play its part in the continuing development of opiate addiction treatment.

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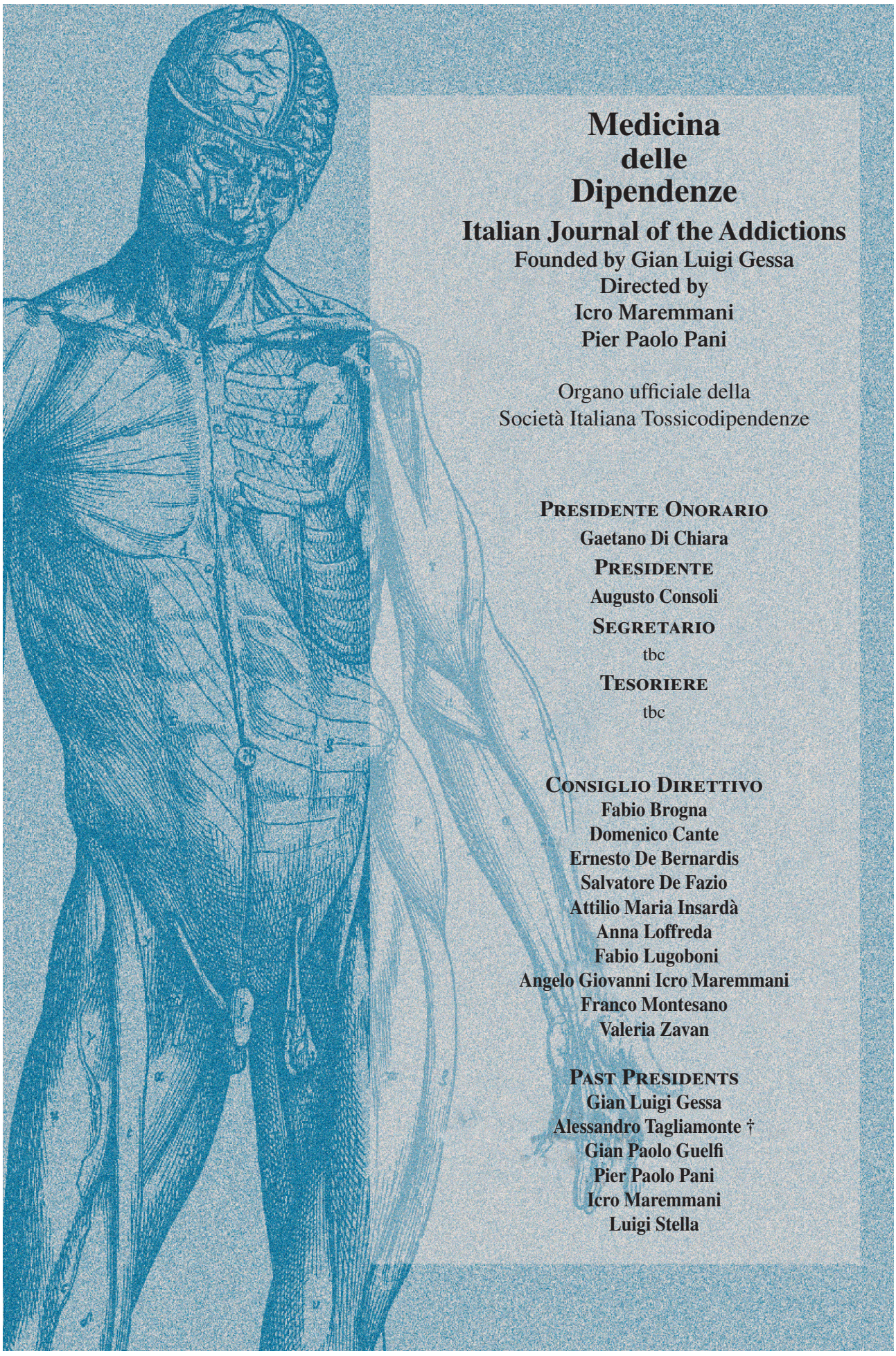

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Impact of opium tincture and exercise in the management of opioid withdrawal: Assessing behavioural and neuroendocrine changes in Opioid Use Disorder patients

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Summary

Background: In this study, we investigated whether the exercise would reduce the severity of dependence, stress, anxiety, depression, craving and serum levels of cortisol, and increase anandamide (AEA) and brain-derived neurotrophic factor (BDNF) in opioid use disorder patients receiving the opium tincture (OT). This study was a pretest-posttest quasi- experimental design. **Methods**: Two groups of opioid-dependent patients (32 out of 47 men) were treated with OT and/or OT/exercise for 11 months. Both groups completed the questionnaires of Leeds Dependence, Depression Anxiety Stress Scales, Desire for Drug Questionnaire before and after treatment. Also, venous blood was taken after 8 hours fasting before and after treatment to measure serum levels of cortisol, AEA, and BDNF. **Results**: We found no significant difference in the pretest–posttest difference scores of the severity of dependence, depression, stress, anxiety, craving, and levels of biomarkers in both groups and between two groups of patients receiving OT and OT/exercise. However, a comparison of pretest and posttest of two groups showed that maintenance treatment with OT significantly decreased the severity of dependence, depression, anxiety, stress and craving for opioid and increased serum level of BDNF in both groups of patients receiving OT and OT/exercise. **Conclusions**: We conclude that maintenance treatment with OT may be beneficial in the management of opioid withdrawal, but not exercise.

Key Words: Opiate use disorder, Opium tincture, Psychological dependence, Craving and Neuroendocrine

1. Introduction

Chronic exposure to opioids hijacks the brain's reward system that leads to the craving and motivational drive to drug-seeking behaviour **[18, 38, 40, 42, 54]**. Opiates addiction is associated with neuropsychological impairments during drug use and abstinence, including cognitive, decision making and inhibitory control deficits **[6]**, anxiety **[31, 37, 46]**, major depression, and bipolar disorder **[5, 11, 16, 39, 41]**. These negative emotional conditions and stress are potent stimulator of the craving and relapse following abstinence **[33, 51, 57, 60, 62]**. Animal and human studies have been shown that the hypothalamus-pituitary-adrenal (HPA) activation **[49]** and increased cortisol levels **[13, 35, 64, 65]**, following opioid abstinence induced-stress may contribute to the vulnerability for relapse **[9, 21]**. However, other studies have been shown that opioid addiction decreased cortisol levels **[19, 61]**. Neuro-hormonal mechanisms may be underlying reward and opioid-related behaviours including the negative emotional aspects caused

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by abstinence. In this regard, the endocannabinoid system appears to play a major role in brain reward processes [58]. The endocannabinoid system exhibits antidepressant effects partly through brain-derived neurotrophic factor (BDNF) [27]. It has been shown that a deficient endocannabinoid system is associated with anxiety and depression which in turn lead to relapse [50, 56], a possible increase in cortisol levels [29] and a decrease in BDNF levels [14] after substance abstinence. However, there are conflicting reports that serum BDNF levels increased [67], and/or decreased [66] after heroin abstinence. On the other hand, serum levels of cortisol, BDNF and the endocannabinoid anandamide (AEA) still require further investigations in opioid use disorder patients following abstinence. Thus, reversing these drug-induced behavioural and neuro-hormonal changes may prove useful in the treatment of relapse.

In recent years, maintenance therapy with opium tincture (OT) has been widely used as a new strategy for the treatment of drug dependence, detoxification and withdrawal symptoms in various parts of the world such as France, Germany, Thailand and Iran [15, 30, 48, 59]. The maintenance therapy with OT is the second most common medication after methadone maintenance treatment (MMT), as a national drug abuse treatment that has gained growing popularity in Iran [48]. The effects of OT on the negative emotional states and relapse have not yet been reported. Thus, the positive therapeutic aspects of OT still need further study. Given the high risk of relapse in opioid use disorder patients [8], these patients need complementary therapeutic methods in order to provide a comprehensive treatment. Recent studies have shown that exercise is associated with a reduction of anxiety in humans [28] and rodents [23, 26, 44], a reduction in voluntary morphine consumption [26], and an increase in BDNF levels [44] in rodents. Previous studies have suggested that the increment in circulating AEA during exercise, by increasing BDNF levels, provides a mechanism for the neuroplastic and antidepressant effects of exercise [27]. Also, exercise by increasing cortisol plays an important role in adaptation and mitigation of stress at different levels [17]. Thus, an important question is whether voluntary exercise could blunt the deleterious effects of opioid during abstinence in opioid use disorder patients receiving maintenance treatment using OT. The aim of the present study was to investigate current hypotheses that the voluntary exercise could reduce the severity of dependence, stress, anxiety, depression, craving and serum levels of cortisol, and increase serum levels of AEA and BDNF in opioid use disorder patients receiving maintenance treatment with OT.

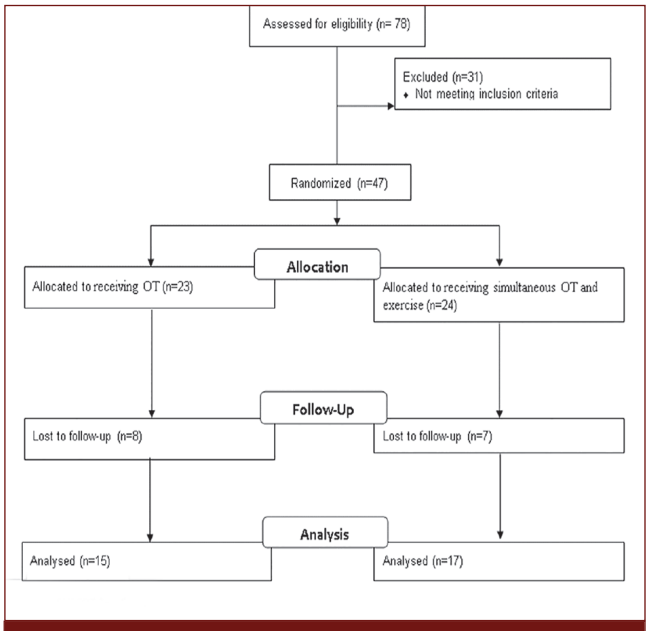

Figure 1. CONSORT flow diagram

2. Methods

2.1. Study design

At first, 78 volunteers were interviewed to assess their eligibility; out of 47 persons who entered the pretest, 15 withdrew from the study and 32 remained and completed the treatment course. OT (Temad, Iran) contains 1% anhydrous morphine. The flow diagram displays the progress of all participants through the trial (**Figure 1**). Both groups of patients in the present study received maintenance treatment with OT using the DST method of Congress 60, which involves 14 stages of decreasing dosage of opium tincture with an average treatment duration of approximately 11 months. The DST method is a formula by which the dose of OT was tapered every 21 days, which means maintaining the daily dosage for 21 days. The initial dose of OT was administered based on previous daily opioid use in each patient. This protocol was accompanied by self-help programmes including peer counseling and recreational activities in the presence of companions (family, friends, peers) within Congress 60 [63]. The exercise group voluntarily performed their aerobic exercises such as football, volleyball, running, and tug-of-war, 3 times a week for approximately 120 min, under the supervision of a physical education teacher. In each session warm-up exercises, including stretching, jogging, and cycling by 60-70 % Vo2max (maximum oxygen uptake) were performed. At the end of each time trial, subjects sat down to recover. The height and body mass index (BMI) of each patient were measured to estimate of the Vo2max by a previously developed regression equation [47]. Both groups, after providing demographic data, completed the questionnaires of Leeds Dependence (LDQ), the

Depression Anxiety Stress Scales (DASS), and the Desire for Drug Questionnaire (DDQ) before and after treatment. Venous blood samples were taken after 8 hours fasting before and after treatment to measure serum levels of cortisol, AEA, and BDNF. The screening urine test was done before and after treatment. According to the Congress 60 protocol, physical exercise is not mandatory during maintenance therapy with OT.

2.2. Sample

In this randomized controlled trial, patients with opioid dependence were men, aged 30-48 years, who were recruited from Congress 60 (as a voluntary non-governmental organization (NGO) of Addiction Recovery Community, Tehran, Iran) and completed the study. The inclusion/exclusion patient selection criteria prior to treatment were based on DSM-IV-TR criteria. Patients were literate and signed written informed consent in advance and were then tested following ethics committee guidelines and regulations. The present study was approved by the Ethics Committee of Semnan University of Medical Sciences (IR.SEMUMS.REC.1397.010) and received the Iranian Registry of Clinical Trials (IRCT20200502047268N2). Opiate was the only drug used by the patients for 12-18 years before the study. In the present study, patients were not allowed to be currently undertaking MMT and/or any other treatment during abstinence. Patients had no history of professional athlete and use psychiatric drugs. They had no cognitive impairment, head trauma, stroke, seizures, HIV infection, cardiovascular and psychiatric disorders. The treatment groups were matched with respect to age, education level, and marital status. The patients were then randomized into the two groups using a pre-test and post-test design: Receiving OT, receiving simultaneous OT and exercise (OT/EX). The positive and negative urine test results for opioids were required before and after treatment, respectively, which was according to the Congress 60 routine protocol.

2.3. Assessment

2.3.1. Addiction Severity Index (ASI)

History of opioid use was assessed using the Addiction Severity Index (ASI). The Leeds Dependence Questionnaire (LDQ) is a 10-item questionnaire based on a four-point Likert scale. The LDQ was designed to measure dependence upon a variety of substances and the degree of dependency from mild to severe. Cronbach's alpha coefficient and test-retest reliability were 0.94 and 0.95, respectively **[52]**.

2.3.2. The Depression Anxiety Stress Scales (DASS) questionnaire

The DASS is a 42-item self-reported test for measuring depression, anxiety and stress, as defined by Lovibond and Lovibond. Scores for the depression, anxiety and stress scales are determined by summing the scores for the relevant 14 items. Cronbach's alpha coefficient was 0.966 for total score, 0.947 for the depression scale, 0.897 for the anxiety scale and 0.933 for the stress scale, indicated acceptable fit **[12, 36]**.

2.3.3. Desire for Drug Questionnaire (DDQ)

The DDQ is a questionnaire which was developed by Franken et al. **[24]** to assess drug craving. The DDQ includes 14 questions for three main craving components, desire and intention to drug use, negative reinforcement for drug use, and drug abuse control. This questionnaire is based on a seven-step Likert-scale score. Cronbach's alpha was reported to be 0.89 and 0.85 for general credit questionnaire **[24, 25]**.

2.3.4. Serum levels of cortisol, AEA and BDNF

Venous blood samples were taken after 8 hours fasting and then centrifuged at 2500 rpm, at 15°C. Serum was separated and kept frozen (-80ºC) pending analysis. Serum levels of cortisol (ELISA kit, Monobind Inc, USA), AEA (Human Anandamide (AEA), Eliza Kit, E3875Hu, China) and Human BDNF (Eliza Kits, E1302HU, China) were measured by enzyme-linked immunosorbent assay kits according to the manufacturer's instructions.

2.4. Statistical analysis

The quantitative data was shown as Mean ±Standard deviation (SD); and frequency and percentage of descriptive analysis were displayed. The normality of quantitative variables was done by Shapiro-Wilk test. Comparison between the two groups performed by Chi-square, Fisher's exact test, Mann-Whitney test and T-test, as required. Paired t test and Wilcoxon test were used to determine the differences between the pretest and posttest results, as required (see tables). We used the Pearson correlation test to examine the association between the pretest-posttest difference scores of the instant craving and depression, anxiety and stress. The level of statistical significance was set at $P<0.05$.

3. Results

3.1. Demographic variables

Patients in the two groups did not differ on any of the demographic variables examined ($p>0.05$, **Table 1**), except for the mean value of Vo2max, which

Table 1. Demographic details for opioid use disorder patients receiving OT and OT/EX

	Groups		
	Opium Tincture (n = 15)	Opium Tincture and Exercise (n = 17)	
Age (years) (Mean ± SD)	37.1 ± 4.6	39.6 ± 5.6	0.18[a]
Educational status N (%)			0.350[b]
Primary school	1 (6.7)	1 (5.9)	
Guidance school	7 (46.7)	4 (23.5)	
Diploma	4 (26.7)	8 (47.1)	
Higher education	3 (20.0)	4 (23.5)	
Marital status, N (%)			0.589[c]
Married	13 (86.7)	16 (94.1)	
Single	2 (13.3)	1 (5.9)	
Duration of opium addiction (years) (Mean ± SD)	15.46 ± 2.3	14/70 ± 2.4	0.390[b]
Family History of drug abuse N (%)	7 (46.7)	7 (41.2)	0.755[d]
Addiction treatment history N (%)	7 (46.7)	3 (17.6)	0.077[f]
Physical illness history N (%)	2 (13.3)	1 (5.9)	0.589[c]
Daily doses of opium (g) (Mean ± SD)	4.3 ± 4.54	2.55 ± 1.48	0.313[b]
Body Mass Index (kg/m) (Mean ± SD)	26.5 ± 4.7	25.04 ± 3.8	0.333[a]
Maximom dose of OT (ml) (Mean ± SD)	13.93 ± 3.7	11.2 ± 4.44	0.082[b]
Treatment Duration (months) (Mean ± SD)	10.6 ± 1.05	10.41 ± 0.5	0.882[b]
Vo2 max (Mean ± SD)	35.6 ± 2.9	46.8 ± 3.8	0.001[a]

[a]T-teset [b]Mann-Whitney [c]Chi-Square [d]Fisher's exact test

were 35.6 and 46.8 ml/kg/min in groups receiving OT and OT/EX, respectively, with a statistically significant difference (p=0.001). On average, patients reported opioid use for around 15.08 years.

3.2. The Addiction Severity Index (ASI)

The ASI data is shown in **Table 2**. The Student's t test revealed a significant decrease in the score of the ASI after treatment. This finding indicates that the score of the ASI was lower in both groups of patients receiving OT and OT/EX after treatment during the post-test (both, p=0.001). No changes were instead observed for the intensity of opioid dependency before treatment during the pre-test (p>0.05). Also, no significant differences between the two groups were found in the ASI score before and after treatment and also between the pretest-posttest difference score. Yet, analyzing the LDQ items (**Table 3**), the OT group shows higher subscores in items 3 (p= 0.04) and 7 (p= 0.021), indicating that there is a compulsion to start and continue to take drugs before treatment.

3.3. The Depression Anxiety Stress Scale (DASS)

Table 2 shows the mean score of depression, anxiety and stress before and after the experimental session in each study group. There were no significant changes in the scores of depression, anxiety and stress before treatment in both groups of patients receiving OT and OT/EX (p>0.05). A comparison of pretest and posttest scores showed significant differences in depression (p=0.002 and p=0.001), anxiety (p=0.004 and p=0.001) and stress (both, p=0.001) scores before and after treatment in both groups of patients receiving OT and OT/EX, respectively. But, there were no significant differences in the pretest–posttest difference scores of depression, anxiety and stress in both groups of patients receiving OT and OT/EX (p>0.05). Also, no significant differences between the two groups were found in each of the scores of depression, anxiety and stress before and after treatment. This finding indicates that the scores of depression, anxiety and stress were lower in both groups of patients receiving OT and OT/EX after treatment during the post-test.

3.4. Data related to Desire for Drug Questionnaire (DDQ)

Data of the desire for drug questionnaire (DDQ) are shown in **Table 2**. There was no significant change in the total score of the DDQ to assess instant craving for opioid before treatment in both groups of patients receiving OT and OT/EX (p>0.05). Also, there was no significant difference in the pretest–posttest difference score of the instant craving for opioid in both groups of patients receiving OT and OT/EX (p>0.05). A comparison between pretest and posttest total score of the instant craving for opioid showed conversely a

Table 2. Mean±Standard Deviation (SD) of the Desire for Drug Questionnaire (DDQ) and Depression Anxiety Stress Scale (DASS-42) before and after exercise in two groups

	Groups		
	Opium Tincture (n = 15)	Opium Tincture and Exercise (n = 17)	P-Value
Addiction Severity Index (ASI)			
Pretest	23.27 ± 4.7	19.4 ± 6.4	0.066[c]
Posttest	1.73 ± 3.6	0.82 ± 2	0.749[a]
P-value	0.001[d]	0.001[d]	-
Difference (Pretest-Posttest)	21.5 ± 5.1	18.5 ± 7.07	0.19[c]
DDQ			
Pretest	60.46 ± 18.87	51.52 ± 25.8	0.478[a]
Posttest	19.46 ± 7.6	14.82 ± 1.84	0.132[a]
P-value	0.001[b]	0.001[b]	-
Difference (Pretest-Posttest)	41 ± 17.05	36.7 ± 25.4	0.58[c]
Depression Anxiety Stress Scale (DASS-42)			
Depression			
Pretest	17.87 ± 10.93	19 ± 11	0.774[a]
Posttest	10.7 ± 8.06	6.29 ± 6.23	0.089[b]
P-value	0.002[c]	0.001[c]	_
Difference (Pretest-Posttest)	7.1 ± 7.5	12.7 ± 11.09	0.11[b]
Anxiety			
Pretest	15.1 ± 9.2	15.8 ± 9.1	0.833[a]
Posttest	9.13 ± 7.82	5.53 ± 3.26	0.261[b]
P-value	0.004[d]	0.001[c]	_
Difference (Pretest-Posttest)	6 ± 6.6	10.3 ± 9.1	0.143[a]
Stress			
Pretest	22.53 ± 9.6	25.76 ± 9.5	0.349[a]
Posttest	12.6 ± 8.3	10.65 ± 7.08	0.479[a]
P-value	0.001[c]	0.001[c]	_
Difference (Pretest-Posttest)	9.93 ± 6.95	15.11 ± 11.03	0.128[a]

[a] Mann-Whitney [b] Wilcoxon [c] T-test [d]Paired T-Test

Table 3. Mean± Standard Deviation (SD) of the Leeds Dependence Questionnaire (LDQ) score

	Pre-Test			Post-Test		
	OT (n = 15)	OT/EX (n = 17)	P-value	OT (n = 15)	OT/EX (n = 17)	P-value
1. Mind conflict	2.2± 1.01	1.88± 1.05	0.76	0.13± 0.35	0	0.12
2. Clear consumption	2.6± 0.73	2± 1.11	0.35	0.06± 0.25	0	0.27
3. Compulsion to take opium	2.53± 0.83	1.88± 0.85	0.04[a]		0	0.12
4. Planning consumption	2.46± 0.91	2.29± 0.84	0.12	0.06± 0.25	0	0.27
5. High effect	2.6± 0.73	2.17± 0.8	0.17	0.26± 0.79	0.11± 0.48	0.36
6. Number of assumptions	3.4± 4.9	4.17± 6.68	0.52	0.06± 0.25	0	0.27
7. Compulsion to continue using opium	2.53± 0.83	1.29± 1.31	0.021a	0.6± 1.24	0.17± 0.52	0.15
8. Primary importance of the effect	1.86± 1.35	2.11± 1.05	0.33	0.33± 0.89	0.35± 0.44	0.5
9. Concern about the need to maintain the effect	1.66± 1.17	1.82± 1.07	0.31	0.53±1.12	0.05± 0.24	0.21
10. Cognitive set	2.26± 1.16	1.41± 1.32	0.31	0.13± 0.35	0	0.12

Table 4. Mean±Standard Deviation (SD) of serum levels of cortisol, BDNF and anandamide (AEA) before and after exercise in the two groups

	Groups		
	Opium Tincture (n = 15)	Opium Tincture and Exercise (n = 17)	P-Value
Cortisol (µg/dl)			
Pretest	16.41 ± 7.48	16.46 ± 6.35	0.823[a]
Posttest	14.43 ± 5.99	15.47 ± 7.03	0.657[c]
P-value	0.650[b]	0.653[b]	_
Difference (Pretest-Posttest)	1.98 ± 10.32	0.99 ± 10.01	0.786[c]
BDNF (ng/ml)			
Pretest	2.33 ± 0.27	2.29 ± 0.51	0.261[a]
Posttest	2.66 ± 0.74	2.89 ± 0.9	0.455[a]
P-value	0.017[b]	0.001[b]	_
Difference (Pretest-Posttest)	- 0.328 ± 0.62	- 0.599 ± 0.71	0.246[a]
AEA (ng/ml)			
Pretest	7.5 ± 2.4	7.7 ± 3.5	0.628[a]
Posttest	9.27 ± 4.6	11.93 ± 11.6	0.602[a]
P-value	0.088[b]	0.407[b]	_
Difference (Pretest-Posttest)	- 1.76 ± 3.84	- 4.22 ± 10.18	0.882[a]

[a] Mann-Whitney [b] Wilcoxon [c] T-test [d]Paired T-Test

significant difference in both groups of patients receiving OT and OT/EX (both, p=0.001) before and after treatment, respectively. Also, no significant differences between the two groups were found in the total score of the instant craving for opioid before and after treatment. This finding indicates that patients who received OT or OT/EX obviously experienced less craving in the post-treatment period than before treatment.

3.5. Serum levels of cortisol, BDNF and AEA

Results of serum levels of cortisol, BDNF and AEA are shown in **Table 4** before and after exercise in each group. There were no significant changes in the serum levels of cortisol, BDNF and AEA before treatment in both groups of patients receiving OT and OT/EX (p>0.05). Also, there were no significant differences in the pretest–posttest difference serum levels of cortisol, BDNF and AEA in both groups of patients receiving OT and OT/EX (p>0.05). A comparison of pretest and posttest serum level of BDNF showed conversely significant differences in both groups of patients receiving OT (p=0.017) and OT/EX (p=0.001) before and after treatment, respectively. Also, no significant differences between the two groups were found in each of the serum levels of cortisol, BDNF and AEA before and after treatment. This finding indicates that the serum level of BDNF was higher in both groups of patients receiving OT and OT/EX after treatment during the post-test.

3.6. Correlations between the pretest-posttest difference scores of the instant craving and depression, anxiety and stress

We found a significant correlation in the total of patients receiving OT or OT/EX, between the pretest-posttest difference scores of the instant craving and depression (r=0.46, p=0.008), anxiety (r=0.37, p=0.039) and stress (r=0.39, p=0.029) (**Figure 2**).

4. Discussion

We found no significant difference in the pretest–posttest difference scores of the severity of dependence, depression, stress, anxiety, craving, and levels of cortisol, BDNF and AEA in both groups of patients receiving OT and OT/EX. Also, we found no significant differences between the two groups for all above-mentioned cases before and also after treatment. However, a comparison of pretest and posttest of the two groups showed that maintenance treatment with OT using the DST method for 11 months can attenuate the severity of opioid dependence, depression, anxiety, stress and score of the craving for opioid in both groups of patients receiving OT and OT/EX. Thus, the observed effects could not be due to exercise. It has been found that endogenous protective factors (including the neurotransmitters and hormone levels) are in many ways affected by addiction **[63]**. Our findings suggest that OT alone can provoke and restore endogenous protective factors that are probably common components of exercise, which in turn could improve addiction-relevant behaviours.

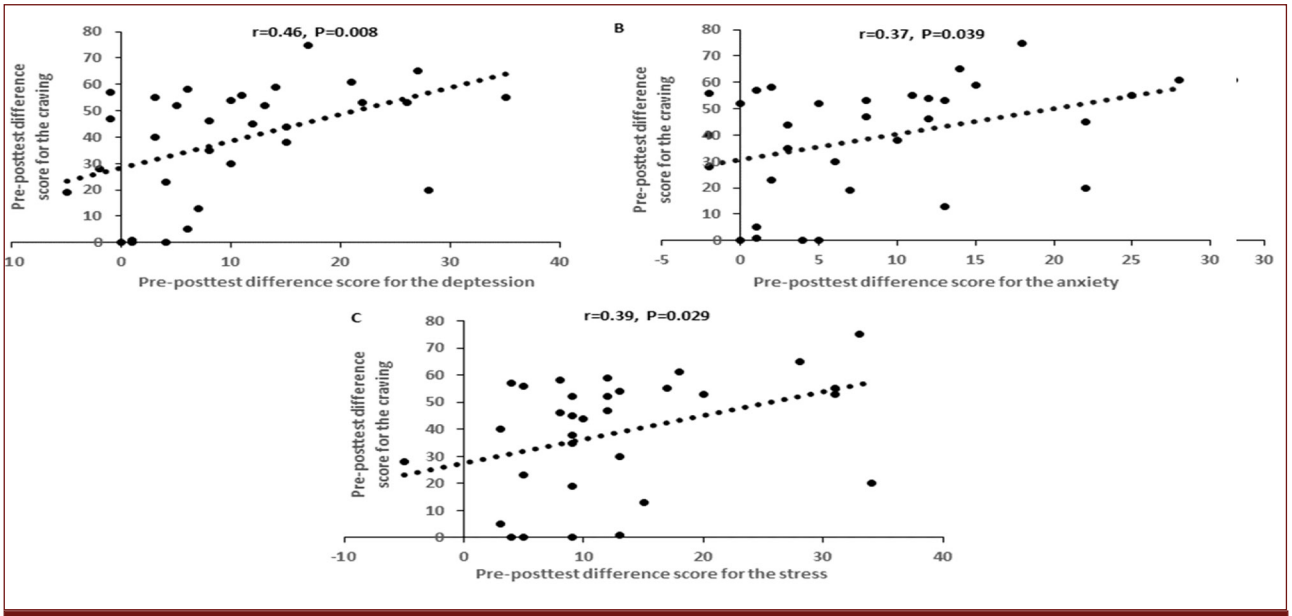

Figure 2. Correlations in the total of patients receiving OT or OT/EX, between the pretest-posttest difference scores

The possibility that the two effects of OT and exercise are independent cannot be ignored. In fact, our previous findings have been shown that exercise (voluntary, treadmill, and swimming) decreased the severity of physical and psychological dependence and craving in animal models of addiction **[1, 20, 26, 44]**. A number of possible reasons for the lack of exercise-induced effects in this study have been proposed including; the amount of exercise, the physical ability and fitness according to age and job of the volunteers in our study. It seems that the amount of exercise is an important stimulus, which can increase the serum concentration of AEA and BDNF, which in turn influences the neuroplastic, reward and antidepressant effects of exercise **[27]**. Given the above-mentioned reasons, this amount of exercise probably was unable to generate significant and considerable effects. Therefore, maintenance treatment with OT could reduce opioid induced-addictive behaviours. These results are consistent with previous studies showing that maintenance treatment with OT can lead to a state of sedation **[59]**, reduce craving, withdrawal symptoms, and create a strong motivation **[15]**, also improving physical and psychological health, and socioeconomic status **[4]**. Creating a strong motivation in opioid addicts may be due to reduced physical dependence, including pain and diarrhea **[48]** following receiving OT.

Another interesting finding was that maintenance treatment with OT could increase the BDNF protein levels in serum of opioid addicts, but it had no effect on serum concentration of cortisol and AEA. There are conflicting reports that serum BDNF levels increased **[66]** and decreased **[2]** one month after heroin abstinence. In this regard, our previous animal studies showed that the development of dependence on morphine enhanced levels of BDNF in the ventral tegmental area (VTA) **[32]**, hippocampal **[45]** and serum **[53]** of the morphine-dependent rats. Conversely, spontaneous morphine withdrawal decreased BDNF in the VTA, nucleus accumbens (NAc) **[32]** and serum **[53]** of morphine withdrawn rats. Also, our previous study also showed that the injection of BDNF receptor antagonist (ANA-12) during the development of dependence on morphine exacerbated the severity of physical morphine dependence **[53]**. It seems that the enhanced levels of BDNF during the induction and expression of morphine dependence might be expected as a result of compensatory mechanism in order to reduce dependence. However, the underlying mechanism of the elevated BDNF levels following receiving OT in the current study is not known. A possible explanation could be that the low levels of morphine in the OT by enhancing BDNF levels may have reduced the scores of depression, anxiety and stress in patients receiving OT. This finding is consistent with the previous studies, suggesting that BDNF may be a mechanism to promote neuroplasticity in the face of a stressor **[34]**, and to produce anti-anxiety and depressive like effects **[7, 22, 43]** of OT. Another possible explanation could be that the low levels of morphine in the OT regulated the release of endogenous opioids which in turn help to restore the release of dopamine and also BDNF. These factors may play a crucial role in motivational control **[10]** of goal-directed behaviour to reduce craving. We found that OT or exercise did not influence the levels of cortisol and AEA in both groups of patients receiving OT and OT/EX, which may be due to the small number of samples in our study. We also found that the higher scores of

depression, anxiety and stress in the patients receiving OT were significantly associated with the higher score of craving. This finding suggested that negative emotional states including stress, anxiety and depression might be responsible for drug craving and drug-seeking behaviour in opioid use disorder patients, which is in line with previous studies **[3, 55, 62]**. Thus, reversing or preventing the psychological dependence due to opioid addiction might be useful in the treatment of relapse after periods of abstinence. It seems that the decreased scores of depression, anxiety and stress following maintenance treatment with OT reduced the score of craving in opioid use disorder patients. We cannot rule out a possible beneficial effect of exercise in the present study. Future studies should require follow-up, multiple clinical involvement, the most suitable type and intensity of exercise (voluntary, treadmill and swimming) to obtain optimal benefits in opioid use disorder patients receiving OT. Also, in order to examine the effectiveness of exercise as an addiction management treatment option, physical exercise could be done 6 months after opioid withdrawal.

Limitations: In this study, 15 patients were excluded from the study and did not complete the study, which resulted in a small number of samples. That, in turn, could lead to a lack of the effectiveness of exercise in this study.

5. Conclusion

Our results demonstrate that maintenance treatment with OT may attenuate the severity of opioid dependence, depression, anxiety, stress and craving, and increased serum BDNF levels in opioid use disorder patients, but have no significant effects on serum levels of cortisol and AEA. Also, voluntary exercise was not effective in the management of opioid withdrawal. Thus, the maintenance treatment with OT may be beneficial for treating opioid addiction. Our results could suggest the application of exercise along with maintenance treatment with OT as a useful therapeutic strategy for the management of opioid withdrawal in opioid use disorder patients with follow-up studies that utilize a larger number of samples and appropriate intensity of exercise.

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Contributors

All authors were responsible for the study design. M.B, R.T, S.S, M.H. and H.M.G. performed the experiments. H.MG and R.T supervised the project. R. G and H.M.G analysed the data. All authors reviewed and then approved the definitive version of the manuscript and and provided feedback on the final manuscript.

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Conflict of interest

All authors have no conflict of interest.

Ethics

Authors confirm that the study submitted was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The study has received IRB review/approval. The present study was approved by the Ethics Committee of Semnan University of Medical Sciences (IR.SEMUMS.REC.1397.010) and received the Iranian Registry of Clinical Trials (IRCT20200502047268N2).

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HEROIN ADDICTION & RELATED CLINICAL PROBLEMS

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Reasons behind use of heroin and stimulants: a functional perspective

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Summary

Background: This research describes the different reasons or functions (motives) behind drugs and examines the associated factors. **Methods**: The study sample consisted of 761 synthetic stimulant users, 50 heroin users, and 85 drug users who used both stimulants and heroin. **Results**: Multiple linear regression analysis indicated that heroin users mainly used drugs to change their mood, while stimulant users used drugs for sexual effects, socialization and increasing self-confidence. The frequency of drug use for sexual effects and socialization was higher among male users. In comparison, the frequency of drug use to reduce weight and kill time was higher among female users. Young users reported that they used drugs mainly to reduce weight. Those who initiated drug use at an early age reported using drugs for socialization, changing their mood, and killing time. The participants who used drugs more frequently got high scores on all the dimensions about motives behind the use of drugs except the dimension 'reducing weight'. **Conclusions**: Prevention and intervention efforts need to be tailored accordingly to address the needs of different groups based on their specific motives behind the use of drugs because the treatments which help in the reduction of weight or in coping with depression are likely to be different.

Key Words: Reasons; drug use; function; China

1. Introduction

According to the guidelines from the United Nations Office on Drugs and Crime **[44]**, synthetic stimulants include amphetamine-type stimulants (ATS) such as amphetamine, methamphetamine (MA), "ecstasy" (i.e., 3-, 4-methylenedioxymethamphetamine (MDMA) and its analogues), and new psychoactive substances (NPS) (e.g., cocaine) **[14, 25, 30]**. Opiates are a subset of opioids comprising various products derived from the opium poppy. Common opiates include opium, morphine and heroin. The UNODC **[44]** indicated that, by the end of 2018, an estimated total of 30.4 million people, all over the world, had used opiates, and 27.2 million had used amphetamines (amphetamine, MA and pharmaceutical stimulants). China is one of the countries battling with the stimulant and opiate epidemic. Earlier, heroin was the only opiate drug being used in China. By the end of 2018, there were about 2,148,000 drug users in China, including 1,186,000 MA (55.2 %) and 807,000 (37.5 %) heroin users **[42]**.

For better prevention and control of the use of illegal substances, it is vital to improve our understanding of the motives behind substance use **[6]**. There are numerous motives for illicit drug use, which vary from broad general statements (e.g., 'to get "high"') to specific purposes taking into account the specific 'functions' of the drug (e.g. 'to reduce weight' or to 'enhance sex drive'). The term 'function' is intended to characterize the primary or multiple reasons (motives) behind using a particular substance in terms of the actual consequences that the users expect **[5, 6]**. The function has been viewed as a useful means of understanding how dispositional and environmental variables impact the use of drugs **[38]**.

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Stimulants and opiates can elicit different functions. For example, stimulants (such as amphetamines and ecstasy) can help increase the activity of the central nervous system (CNS). In contrast, opiates (such as heroin) can help reduce the activity of CNS **[6]**. Drug use patterns across different populations reflect such differential effects associated with stimulants and opiates. For example, university students commonly use stimulants to cope with academic pressures to improve concentration and increase alertness; however, individuals who suffer from anxiety symptoms engage in heroin use to reduce stress **[8, 23, 26]**. Therefore, drug use functions can influence the use of specific drugs across different users. In addition, it is noteworthy that perceived drug use functions may vary depending upon the characteristics of the drug users. A previous study found that college women were more likely to use non-medical prescription opioids for self-medication, whereas men were more likely to use them for recreational purposes **[29]**. Despite the critical role of drug use functions in the use of illegal drugs, an absence of research has examined drug use functions across different drug users (e.g., stimulant, heroin and polydrug users) and identified factors that are potentially associated with drug use functions. Insights into this area will help increase the understanding of specific motives behind illegal drug use among different populations. Such insights are likely to inform future interventions, looking into the underlying causes behind certain behaviours exhibited by specific drug users.

Data were collected from illegal drug users in China to explore the perceived drug use functions and the associated factors. Previous studies have found that different users of stimulants like ecstasy and amphetamine have similar motives behind the use of drugs, and some of the reported reasons are 'helping with concentration', 'enhancing an activity','increasing alertness', and 'helping stay awake' **[4, 40]**. Therefore, the participants included in the study who reported having used one or more types of stimulants were regarded as stimulant users. Accordingly, the participants in the current study were categorized into three groups - stimulant users; heroin users, who reported having used heroin only; and combined users, who said having used both stimulants and heroin.

Aims: The objectives of the current study were:

(a) To examine the functions related to illegal drug use, reported by three different drug users (heroin, stimulant and combined).
(b) To determine whether drug use functions are related to demographic factors, such as gender, age and educational attainment.
(c) To find out whether the drug use patterns are associated with specific functions.

2. Methods

2.1. Study site

The data were collected from two compulsory detoxification institutes (one for men and one for women) in Jiangsu Province, China, in 2015. Jiangsu, covering an area of 107,200 square kilometres, is situated in China's relatively populated and economically developed east-central coastal area. By the end of 2018, Jiangsu had a resident population of 80 million, and its GDP was 9,259 billion Yuan (approximately 1,357 billion US dollars) **[19]**. There were seven compulsory detoxification institutes (one for women and six for men) where their families or public safety agencies could send drug users to receive treatment and rehabilitation therapy. The two institutes (one women's and one men's institute) were selected, which had drug users from the same and nearby regions in which police officers maintained supervision over drug users' quarantine and re-education, including drug treatment, psychotherapy, rehabilitation training, health, moral and legal education over a certain period **[41]**.

2.2. Selection of sample and data collection procedure

From a list of registered participants provided by the officials of each of the institutes, 20 per cent of drug users from each of the two institutes were selected using a systematic sampling method **[1]**. Participants were selected based on the following inclusion criteria: (1) age ≥ 18 years, and (2) participants who were physically and mentally fit to complete the survey questionnaire. After procuring informed consent from the participants, a one-on-one, in-person interview was conducted in a private room using a structured questionnaire. The interviewers were trained faculty and graduate students from local universities. Two female participants had limited literacy and difficulty reading, so the interviewers read each question and added their oral responses. Necessary clarifications and instructions were promptly provided whenever required during the survey. The participants were informed about the confidentiality and anonymity of the survey data before the interviews, and no management staff participated in the survey. It took about 30 minutes for each participant to respond to the questionnaire. Upon completing the survey, a small gift was given to the participants as a token of thanks. Nine hundred ten participants were recruited for the survey, and 901 (99 %) participants completed the survey questionnaire. Among the respondents, 827 (91.8 %) reported using MA earlier.

2.3. Measures

2.3.1. Sociodemographic characteristics

Information regarding the participants' sociodemographic characteristics, including age, gender, educational attainment, marital status, occupational status, and household socioeconomic status (SES), was sought from the participants. For statistical analyses, age was divided into four groups, based on the quartiles (i.e.,< 26, 26-30, 31-36, > 36).

2.3.2. Drug use characteristics

Information about the age of drug initiation was sought from the participants, and their responses were divided into four groups based on the quartiles (< 18; 18-20; 21-25; > 25). The investigators used a pre-generated drug list which included heroin, MA, MDMA, Ketamine (in some instances, it is included under the category of new psychoactive substances (NPS)). The participants were asked whether they had ever used any of the drugs **[44]**), Magu pills (which are typically capsules containing a mixture of MA and other drugs such as caffeine), and other synthetic stimulants. Information regarding the overall frequency of drug use (1='a couple times a month', 2='a couple times a week', 3='every day') was also sought from the participants. Based on their responses, the participants were divided into three groups: (1) heroin users who used heroin only; (2) stimulant users who used stimulants only; and (3) combined users who used both heroin and stimulants.

2.3.3. Drug use functions

According to the existing literature **[2-4, 6]**, drug use functions were generally assessed using a 19-item scale. The four sub-scales are sexual effects (e.g., using drugs can help sex last longer (5 items; α=0.92)), socialisation (e.g., using drugs can help gain trust from friends (5 items; α=0.81)), increasing self-confidence (e.g., using drugs makes it possible to do what I do not dare to do usually (4 items; α=0.61)), and changing mood (e.g., using drugs can make me calm down (5 items; α=0.61)). In addition, based on a previous quantitative study among the same population **[46]**, two other sub-scales (killing time and reducing weight) were included. The frequency of using drugs concerning specific motives by each participant was determined. Each item was scored on a 4-point scale with scores ranging from 1 to 4 (1='never'; 2='occasionally'; 3='sometimes'; 4='often'). Average scores on the six sub-scales (i.e., sexual effects, socialization increasing self-confidence, killing time, reducing weight, and changing mood) were determined, with a higher score indicating more frequent use of drugs for a specific motive.

2.4. Statistical Analysis

Firstly, an independent t-test and the chi-square test were performed to compare the three groups' sociodemographic characteristics and drug use characteristics (heroin, stimulant, and combined). Secondly, analysis of variance (ANOVA) was used to determine if the groups' scores differed significantly concerning the six drug use functions (i.e., sexual effects, socialization increasing self-confidence, changing mood, killing time, and reducing weight). Finally, multiple linear regression model analysis was used to assess the differences in drug use functions across the three groups of drug users while controlling sociodemographic variables (i.e., age, gender, educational attainment, family SES, marital status, and occupation), age of drug initiation, and frequency of using drugs. The statistical analyses were performed using SAS 9.4 (Cary, NC).

3. Results

3.1. Demographic characteristics by types of drugs

The current study sample included 901 participants (504 males and 397 females). As shown in **Table 1**, the average age of the participants was 31.3 years (SD=7.5). The majority (84.5%) of the participants were stimulant users. A majority of them (79.7%) completed no more than middle school education, 78.5% were from medium-income families and 59. 5% reported using drugs every day. Nearly half of the participants were unmarried/never married (40.4%) or unemployed (44.8%). Almost three quarters (72.1%) reported using drugs for the first time before the age of 25, and nearly half (47%) said using drugs for the first time before the age of 20.

3.2. Bivariate analysis of drug use functions

As indicated in **Table 2**, male participants usually used drugs for sexual effects (F=497.02; p<.001), while female participants mainly used drugs to 'kill time' (F=22.04; p<.001) and to 'reduce weight' (F=241.48; p<.001). Older participants tended to use drugs for sexual effects (F=8.63; p<.001), while younger ones tended to use drugs to 'reduce weight' (F=30.34; p<.001). Those with greater levels of educational attainment were more likely to use drugs to 'kill time' (F=6.01; p<.01). Those from higher-income families were more likely to use drugs to 'kill time' (F=5.65; p<.01) and 'reduce weight' (F=3.97; p<.05). Those who were unmarried/never married were more likely to use drugs to 'change mood' (F=3.39; p<.05) and 'reduce weight' (F=17.60; p<.001). Those who had been employed in entertainment venues (e.g., night clubs and bars) were more

Table 1. Bivariate comparison of background characteristics concerning types of drugs

	Total	Stimulants	Combined [a]	Heroin
	N=901(100%)	N=761(84.5%)	N=85(9.4%)	N=50(5.5%)
Age (years, M±sd)	31.3±7.5	30.7±7.4	33.8±6.8	35.8±7.4
Gender				
Male	502(56.0%)	408(53.6%)	49(57.6%)	45(90.0%)***
Female	394(44.0%)	353(46.4%)	36(42.4%)	5(10.0%)
Education level				
≤Primary school	169(19.0%)	138(18.2%)	15(18.1%)	16(32.0%)
Middle school	541(60.7%)	470(62.0%)	46(55.4%)	25(50.0%)
≥high school	181(20.3%)	150(19.8%)	22(26.5%)	9(18.0%)
Family economic status				
High-income	82(9.3%)	71(9.4%)	9(10.8%)	2(4.1%)***
Medium-income	695(78.5%)	601(79.8%)	64(77.1%)	30(61.2%)
Low-income	108(12.2%)	81(10.8%)	10(12.0%)	17(34.7%)
Marital status				
Unmarried/never married	356(40.4%)	301(40.2%)	30(35.7%)	25(51.0%)
Married or cohabitating	314(35.6%)	268(35.8%)	34(40.5%)	12(24.5%)
Divorced/separated/widowed	212(24.0%)	180(24.0%)	20(23.8%)	12(24.5%)
Occupation				
Stable jobs [b]	143(16.0%)	110(14.5%)	17(20.5%)	16(32.0%)***
Entertainment [c]	121(13.6%)	112(14.8%)	7(8.4%)	2(4.0%)
Self-employed/family business	228(25.6%)	206(27.2%)	16(19.3%)	6(12.0%)
Unemployed	399(44.8%)	330(43.5%)	43(51.8%)	26(52.0%)
Age (years) of drug initiation				
<18	175(19.6%)	138(18.2%)	24(28.2%)	13(26.0%)**
18-20	244(27.4%)	201(26.6%)	30(35.3%)	13(26.0%)
21-25	224(25.1%)	191(25.2%)	23(27.1%)	10(20.0%)
≥26	249(27.9%)	227(30.0%)	14(28.0%)	8(9.4%)
Drug use frequency				
Everyday	533(59.5%)	427(56.1%)	73(85.9%)	33(66.0%)***
A couple times a week	165(18.4%)	156(20.5%)	4(4.7%)	5(10.0%)
A couple times a month	198(22.1%)	178(23.4%)	8(9.4%)	12(24.0%)

* p < .05; ** p < .01; *** p < .001.
a Combined refers to those who reported having used both stimulants and heroin.
b Stable jobs include government jobs, enterprise/institution jobs, factory workers, chefs, and drivers.
c Entertainment venues include night clubs, bars, etc.

likely to use drugs to 'change mood' (F=5.08; p<.01) and 'reduce weight' (F=2.90; p<.05). Those who initiated drug use at an earlier age, were more likely to use drugs to 'change mood' (F=16.16; p<.001), 'kill time' (F=10.43; p<.001), and 'reduce weight' (F=8.87; p<.001), while those who initiated drug use at a later age, were more likely to use drugs for 'sexual effects' (F=6.16; p<.001). Heroin users were more likely to use drugs to 'change mood' (F=36.00; p<.001), and less likely to use drugs for 'socialisation' (F=3.66; p<.05), increasing 'self-confidence' (F=4.09; p<.05), 'killing time' (F=3.87; p<.05), and 'reducing weight' (F=8.51; p<.001), as compared to the other two groups (stimulant and combined users). Those who reported having used drugs everyday were more likely to use drugs for 'socialisation' (F=11.33; p<.001), increasing 'self-confidence' (F=6.36; p<.01), changing mood' (F=54.21; p<.001), and 'killing time' (F=26.02; p<.001).

3.3. Multiple linear regression analyses

Multiple linear regression analyses (**Table 3**) indicated that after controlling the confounding variables, it was found that heroin users mostly used drugs for changing their mood (β=-0.50; p<.001), while it was found that the stimulant users mostly used drugs for sexual effects (β=0.54; p<.001), socialisation (β=0.41; p<.001), and increasing self-confidence (β=0.38; p<.01). Male participants scored higher than the female participants on the sexual effects (β=-1.21; p<.001) and socialisation dimensions

Table 2. Bivariate comparison concerning drug use functions

	Sexual effects	Socialization	Increasing Self-confidence	Changing mood	Killing time	Reducing weight
Total (M±sd)	2.27±0.96	2.09±0.75	2.19±0.76	2.40±0.71	3.20±0.93	2.30±1.26
Gender						
Male	2.77(0.85)***	2.13(0.75)	2.19(0.75)	2.41(0.72)	3.07(0.95)***	1.79(1.07)***
Female	1.62(0.65)	2.04(0.76)	2.20(0.78)	2.39(0.71)	3.36(0.88)	2.95(1.18)
Age group						
≤ 25	2.00(0.93)***	2.07(0.74)	2.20(0.73)	2.50(0.70)	3.28(0.90)	2.75(1.25)***
26-30	2.28(0.98)	2.12(0.77)	2.21(0.78)	2.32(0.70)	3.20(0.96)	2.55(1.26)
31-36	2.36(0.95)	2.11(0.74)	2.21(0.76)	2.40(0.74)	3.19(0.90)	2.08(1.21)
≥ 37	2.42(0.91)	2.06(0.75)	2.15(0.77)	2.38(0.70)	3.13(0.96)	1.78(1.08)
Education level						
≤ Primary school	2.17(0.91)	2.08(0.75)	2.18(0.81)	2.35(0.73)	2.98(1.04)**	2.30(1.25)
Middle school	2.27(0.96)	2.09(0.74)	2.20(0.74)	2.42(0.71)	3.25(0.88)	2.33(1.26)
≥ high school	2.32(0.98)	2.09(0.77)	2.18(0.77)	2.40(0.72)	3.27(0.95)	2.20(1.25)
Family economic status						
High-income	2.10(0.94)	2.04(0.84)	2.25(0.83)	2.41(0.76)	3.34(0.90)**	2.58(1.27)*
Medium-income	2.27(0.95)	2.09(0.73)	2.18(0.74)	2.39(0.70)	3.23(0.90)	2.30(1.26)
Low-income	2.33(0.97)	2.05(0.79)	2.23(0.80)	2.45(0.79)	2.94(1.08)	2.06(1.20)
Marital status						
Unmarried/never married	2.03(0.91)***	2.09(0.73)	2.18(0.75)	2.47(0.70)*	3.30(0.90)	2.60(1.26)***
Married or cohabitating	2.51(1.00)	2.09(0.76)	2.22(0.78)	2.38(0.74)	3.17(0.94)	2.06(1.20)
Divorced/separated/ widowed	2.28(0.85)	2.06(0.74)	2.18(0.75)	2.32(0.68)	3.12(0.93)	2.18(1.26)
Occupation						
Stable jobs	2.36(0.99)	2.06(0.76)	2.21(0.78)	2.42(0.73)**	3.11(0.99)	2.22(1.31)*
Entertainment	2.11(0.91)	2.22(0.72)	2.36(0.74)	2.46(0.62)	3.21(0.96)	2.61(1.27)
Self-employed/ family business	2.29(0.95)	2.05(0.72)	2.16(0.72)	2.24(0.68)	3.15(0.90)	2.24(1.24)
Unemployed	2.26(0.96)	2.08(0.77)	2.15(0.78)	2.46(0.74)	3.27(0.91)	2.27(1.24)
Drug type						
Heroin	2.20(0.90)	1.82(0.64)*	1.90(0.64)*	2.90(0.65)***	2.94(1.06)*	1.82(1.07)***
Stimulants	2.28(0.96)	2.10(0.75)	2.21(0.77)	2.32(0.68)	3.21(0.93)	2.37(1.27)
Combined	2.20(0.94)	2.15(0.81)	2.26(0.77)	2.84(0.75)	3.40(0.83)	1.94(1.17)
Age (years) of drug initiation						
< 18	2.03(0.95)***	2.13(0.76)	2.22(0.76)	2.61(0.69)***	3.41(0.85)***	2.56(1.29)***
18-20	2.23(0.97)	2.14(0.78)	2.21(0.76)	2.52(0.75)	3.30(0.87)	2.47(1.25)
21-25	2.32(0.99)	2.12(0.78)	2.24(0.81)	2.36(0.69)	3.22(0.94)	2.22(1.26)
≥26	2.42(0.89)	1.99(0.68)	2.12(0.72)	2.18(0.65)	2.95(0.98)	2.02(1.18)
Drug use frequency						
Everyday	2.32(0.98)	2.17(0.78)***	2.26(0.78)**	2.59(0.71)***	3.37(0.86)***	2.30(1.28)
A couple times a week	2.15(0.90)	2.07(0.72)	2.16(0.74)	2.20(0.58)	3.10(0.91)	2.47(1.22)
A couple of times a month	2.23(0.94)	1.88(0.67)	2.04(0.72)	2.06(0.65)	2.84(1.01)	2.16(1.23)

Response option: 1 = 'never', 2 = 'occasionally', 3 = 'sometimes', to 4 = 'often' * p < .05; ** p < .01; *** p < .001

(β=-0.16; p<.01), while female participants reported higher scores on dimensions 'reducing weight' (β=1.02; p<.001) and 'killing time' (β=0.19; p<.01). Results revealed that younger participants used drugs mainly for reducing weight (β=-0.04; p<.001). Those who reported having started to use drugs at an early

Table 3. Multiple linear regression analysis for prediction of drug use functions

	Sexual effects	Socialization	Increasing Self-confidence	Changing mood	Killing time	Reducing weight
Age	-0.00	0.01	0.00	0.00	0.01	-0.04***
Female	-1.21***	-0.16**	-0.02	-0.06	0.19**	1.02***
Education level						
≤ Primary school	Reference					
Middle school	0.04	-0.03	0.01	0.04	0.20*	-0.00
≥ high school	0.02	-0.03	-0.01	-0.01	0.22*	-0.06
Family economic status						
High-income	Reference					
Medium-income	-0.09	0.06	-0.04	-0.04	-0.07	-0.06
Low-income	-0.13	0.08	0.07	-0.02	-0.21	-0.14
Marital status						
Unmarried/never married	Reference					
Married or cohabitating	0.21**	0.00	0.07	0.02	-0.09	-0.14
Divorced/separated/widowed	0.15	0.01	0.05	-0.02	-0.12	-0.06
Occupation						
Stable jobs	Reference					
Entertainment	0.03	0.11	0.09	0.05	-0.05	-0.10
Self-employed/family	-0.06	-0.06	-0.10	-0.11	-0.05	-0.04
Unemployed	0.03	-0.05	-0.12	0.01	0.02	-0.15
Drug type						
Heroin	Reference					
Stimulants	0.54***	0.41***	0.38**	-0.50***	0.20	-0.02
Combined	0.34*	0.36**	0.38*	-0.14	0.17	-0.26
Age of drug initiation						
< 18	Reference					
18-20	0.04	-0.05	-0.05	-0.04	-0.10	0.10
21-25	-0.03	-0.06	-0.00	-0.16*	-0.13	0.08
≥ 26	-0.14	-0.26**	-0.16	-0.28**	-0.32**	0.25
Drug use frequency						
Everyday	Reference					
A couple of times a week	-0.18**	-0.09	-0.10	-0.28***	-0.21*	0.11
A couple times a month	-0.18**	-0.25***	-0.19**	-0.41***	-0.41***	-0.02

* p < .05; ** p < .01; *** p < .001

age, revealed that it was mainly for the purpose of socialisation (β=-0.26; p<.01), to change mood (β=-0.28; p<.01) or to kill time (β=-0.32; p<.01). Those who reported having used drugs everyday reported having used drugs for all purposes (p<.01 & p<.001) except reducing weight.

4. Discussion

In the current study, types of drugs, gender, current age, age at which drug use was initiated, and frequency of drug use were found to be associated with one or more of the drug use functions (i.e., sexual effects, socialization increasing self-confidence, changing mood, killing time, and reducing weight).

Most of the participants used drugs for killing time. The drug users of the three groups did not differ significantly on the 'killing time' dimension, which indicated that regardless of the type of drugs being used, the common motive for using drugs was coping with boredom. In general, 'boredom' refers to an aversive subjective state of dissatisfaction attributed to an inadequately stimulating environment [32]. Previous studies have shown that individuals who scored

higher on measures related to boredom were more likely to engage in risky behaviours, including substance abuse [33, 43, 45]. Previous studies have also highlighted the importance of the impacts of social and cultural environments on boredom. They have reported boredom as a state, which is equated with having too much unstructured free time and is associated with scarce employment and recreation [17]. Boredom is an uncomfortable state, and individuals in the face of such a state may engage in sensation-seeking behaviours, such as drug use [17]. Environmental interventions have been suggested to expand educational and vocational training opportunities, provide income and educational stipends, and low-cost mentorship programmes [45].

The current study found that heroin users mainly used drugs for 'changing mood' compared to stimulant users. Previous studies have shown that psychiatric symptoms (e.g., anxiety, depression) are prevalent among heroin users [27]. However, the purpose behind the use of heroin was still not clear as to whether it was used for controlling negative emotions or for avoiding withdrawal symptoms. It is worth noting that the latter can increase the risk of addiction and reduce abstinence [23, 28]. Some previous studies have reported that compared to the interventions that employ psychological therapy, a combination of psychological treatment and opioid agonist therapy (e.g., methadone) might be more effective, particularly for opiate users [18]. In the current study, compared to the heroin users, the stimulant users reported that they used drugs mainly for sexual effects, socialization or increasing self-confidence. These findings are aligned with the results of some previous review studies that have reported several primary motives behind the use of stimulants, such as increasing sexual capacity, socializing with friends, increasing energy for work and increasing self-confidence [10, 36]. This fact implies that stimulants can serve both as a social lubricant and a sexual stimulant, which may induce risk-taking sexual behaviours, such as having multiple sex partners and engaging in group sex [24]. Keeping in mind that there is no effective pharmacological treatment for stimulant addiction like methadone for heroin, the current treatment of stimulant addiction mainly focuses on behavioural therapy to facilitate cognitive skills and provide psychosocial support [13, 31, 37]. Existing studies have suggested that the Matrix Model of Cognitive Behavioural Therapy has demonstrated efficacy in reducing drug abuse and risk-taking sexual behaviours. The effectiveness increases if other psychosocial factors such as personality patterns, social and cultural circumstances, etc., are accounted for [22, 35, 39].

Multiple linear regression analysis in the current study indicated that frequency of drug use was associated with numerous drug use functions, except the function of 'reducing weight'. Additionally, the present study also found that sociodemographic factors were associated with the motives behind drug use. For example, younger and female participants reported that they used illegal drugs primarily to lose weight, and older and male participants said they used drugs primarily for sexual effects. In addition to the above reasons, those who had initiated drug use at an earlier age reported that they mainly used drugs for changing their mood, killing time, and socializing. Some of the findings of the current study, like differences between males and females concerning some motives behind the use of drugs, are consistent with the results of previous studies [7, 9]. Nevertheless, the current study identified additional sociodemographic factors associated with different motives behind the use of drugs among drug users.

The study also had certain limitations; hence the findings should be interpreted within the context of these limitations. Firstly, the data were self-reported and might be subject to response biases such as recall and social desirability bias. Secondly, the participants were recruited from the compulsory detoxification institutes. The findings may not be generalized to other drug users, such as those who did not attend such treatment programmes. Thirdly, it should be noted that a small number of heroin users may limit statistical power in the current study, and hence there is a need for further exploration. Fourthly, causal inferences cannot be drawn from cross-sectional data. Despite these limitations, this study has important implications that can inform the intervention and suggest treatments and rehabilitation of heroin and stimulant users.

Several interventions for the treatment of drug use, including motivational enhancing therapy (MET), or MET combined with other treatment approaches, have been developed and widely accepted because of their effectiveness in addiction research and opioid addiction [16, 20, 21, 34]. MET has the necessary motivation for drug users to bring about changes by employing cognitive-behavioural therapy techniques like internal ambivalence (e.g., continuing to use drugs vs. making changes in drug use) [15]. Previous review studies have provided strong evidence supporting the effect of MET on reducing alcohol, tobacco, and marijuana use [11]. However, little information is available on the effect of MET on reducing opioid and methamphetamine use [20, 21]. The current study addresses the research gap and offers implications for interventions and treatment strategies (e.g., MET) for heroin and stimulant users. The intervention programmes and treatment strategies should cater to the ordinary motives (e.g., killing time) and the specific functions. It was found that the reasons behind drug use varied across different drug users, and hence intervention programmes should be

tailored according to the drug user characteristics, such as the types of drugs, drug use patterns, and sociodemographic background (e.g., gender and age).

5. Conclusions

Prevention and intervention efforts need to be tailored accordingly to address the needs of different groups based on their specific motives behind the use of drugs because the treatments that help reduce weight or cope with depression are likely to be different **[12]**.

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Contributors

Q. Z. designed the study and conducted the literature review. Y. M. conducted the statistical analysis. Q. Z. and Y. M. wrote the first draft of the manuscript and approved the final manuscript. H. G. collected and interpreted the data and helped reformat the manuscript.

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Conflict of interest

Authors declared 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. The study protocol and consenting procedures were approved by the Institutional Review Board (IRB) of Nanjing Medical University in China.

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New insights from observational retrospective study on tolerability of levomethadone in patients with Opioid Use Disorder

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Summary

Background: Methadone, a racemic mixture of 2 enantiomers, is the gold standard for treating opioid withdrawal syndrome and in the maintenance therapy of opioid addiction. Anyway, the risk of cardiac events, individual variability, and metabolic interferences with other drugs pose a therapeutic challenge in some patients with the need to choose different therapeutic approaches in daily clinical practice. Levomethadone, the laevorotatory enantiomer, can be used at 50% of the racemic preparation with the same therapeutic efficacy. Anyway, data from daily clinical practice are needed regarding the tolerability grade compared to methadone. **Methods**: A single-centre retrospective observation was conducted on 58 patients with Opioid use disorder (OUD) in agonist maintenance therapy with levomethadone over two months to assess tolerability in terms of drug symptoms and patient quality of life. **Results**: After two months of treatment, levomethadone does not need a significant adjustment dose, demonstrating the therapeutic equivalence of racemic methadone and levomethadone at a 2:1 ratio. VAS results revealed a decrease of symptoms related to the presence of constipation, sweating, sedation, sexual dysfunction, and changes in the mood tone, both in the drug naïve subjects and patients previously treated with racemic methadone. In particular, for methadone/buprenorphine subjects, constipation and sweating symptoms decrease in a significant manner ($p<0.05$). PGIC results reveal a reasonable satisfaction of the patients, especially in HIV patients. Results confirmed the tolerability and satisfaction of OUD patients switching from racemic to levomethadone, pointing out the benefits of levomethadone, especially in patients with comorbidity or in polytherapy. In the case of initial treatment, the drug naïve patient's data reveal that levomethadone is well tolerated, and no adverse effects are reported. **Conclusions**: Levomethadone is a safe option over methadone, especially for dedicated subgroups of patients.

Key Words: Levomethadone; Opioid Use Disorder; methadone; Agonist Opioid Treatment

1. Introduction

Patients with Opioid Use Disorder (OUD) are commonly treated with μ-receptor agonist therapy. Methadone is the most frequently used medication. It is recognized as the gold standard for treating opioid withdrawal syndrome and in the maintenance therapy of opioid addiction due to its generally validated and proven efficacy and safety **[3, 10, 15]**. Moreover, it has been placed on the WHO model list of essential medicines.

On the other hand, methadone pharmacokinetics varies significantly from one person to another, consequently impacting the resulting plasmatic concentration and clinical effects **[4, 7]**. Awareness is necessary regarding the drug interaction of methadone. When administered concomitantly with other drug classes, especially the inducers of CYP450 3A4 **[5, 13]** (particularly antiviral drugs and drugs for the central nervous system), a modification of methadone plasmatic concentration can occur. Finally, methadone confers some risk for cardiac adverse events since its use has been associated with arrhythmias **[12]**. In particular, methadone's RCP reported that especially high dose (> 100 mg/day) should be administered under strict medical control to patients at risk for QT prolonga-

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tion, e.g. with a history of QT prolongation, advanced heart disease, concomitant treatment with drugs that can prolong QT.

Methadone is a racemic mixture of 2 enantiomers: the dextrorotatory enantiomer (S-methadone, d-methadone) and the laevorotatory enantiomer (R-Methadone, l-methadone or levomethadone) **[6, 8]**. The two enantiomers have the same chemical-physical characteristics, but they differ in pharmacological parameters. Thanks to the stereoselectivity on the binding of levomethadone to the μ receptors, pharmacological effect is mainly exerted by levomethadone. Indeed, levomethadone has a ten times greater affinity for the μ and δ receptors. The analgesic potency is about ten times higher with a significantly longer half-life than the optical antipode S-methadone **[9, 12, 16]**.

Since methadone has two stereoisomers in a 50:50 ratio, levomethadone could be used at 50% of the raceme dosage, maintaining the same efficacy **[14, 16, 20]**. This fact may improve the tolerability of the treatment **[14, 19]** and, consequently, gives the possibility for clinicians to have an open window dosage, to obtain a reduction in craving and withdrawal symptoms.

Based on the consideration above, it is possible to identify some categories of patients for whom levomethadone is highly recommended, such as all patients with pre-existing structural heart disease to limit the cardiac side effects, since levomethadone is administrated at half the dose, and all those who have comorbidity and need to use drugs that interact with methadone metabolism. Indeed, levomethadone presents a metabolic pathway that guarantees lower interactions with drugs that act on the central nervous system (antipsychotics, antidepressants, and benzodiazepines) and with anti-infective drugs. These drugs are frequently co-administered with opioid agonist therapy; consequently, levomethadone is a safer option for this category of patients.

In light of the preceding, there is still a need to explore levomethadone tolerability and to find out a clinical and recognized consensus, - based on real-world data - about which patients would benefit more from levomethadone than the racemic mixture. This article presents a single-centre retrospective observation conducted on OUD patients in agonist maintenance therapy with levomethadone. The study aimed to report the drug tolerability in daily clinical practice in untreated (drug-naïve) patients or patients who were formerly treated with methadone and to identify patients in opioid maintenance therapy (OMT) who may have more benefit with levomethadone. A secondary aim was an evaluation of the safety profile.

2. Methods

2.1. Subjects and Design of the study

In the screening phase, a group of patients was observed and selected by the investigator accordingly to the following inclusion criteria: age ≥18 years, diagnosis of opioid dependence according to ICD-9-CM criteria, on maintenance therapy with methadone for at least two months in the period between December 2018 and November 2019. Exclusion criteria were the following: age <18 years, pregnancy and/or breastfeeding, not on methadone therapy for a minimum of 2 months in the protocol period specified above. Patients may come from ongoing methadone maintenance therapy or initiate treatment directly with L-methadone from heroin (naïve patients). Fifty-eight eligible patients were selected starting from those diagnosed with opioid dependence according to the above criteria and treated with levomethadone in the planned observation period between December 2018 and November 2019 in the Addiction Pathology Department S.C. SERD ASL AL, Alessandria Italy. Patients have three visits in total (T0, T1, T2), and data were collected at time 0 and after two months (T0 and T2, respectively). Time 0 (baseline visit) is when the patient started levomethadone therapy or switched to this from another opioid agonist drug. At time 0, clinical profile of the patients, tolerability evaluations, posology used, and incidence of adverse reaction and data related to opioid urine test were performed and assessed. Time 1 visit (T1) was based on an assessment on the possible date of interruption of therapy and reasons, registration of current levomethadone posology. In the final visit (T2), tolerability evaluations, posology used, incidence of adverse reaction, and data related to opioid test urine were assessed together with the patient's quality of life measured by the PGIC scale (Patients' Global Impression of Change).

This study was performed according to the ICH E6 guidelines "Good Clinical Practice: Consolidated Guidance". It was a single-centre retrospective observation with stages summarized in the following CONSORT diagram (**Figure 1**).

2.2. Assessment

As primary outcome, drug tolerability was assessed according to

1. the evaluation of levomethadone dosage at different time-points;
2. the assessment of OMT symptoms based on VAS (Visual Analog Scale) on the basis of these parameters:
   - constipation;
   - sweating;

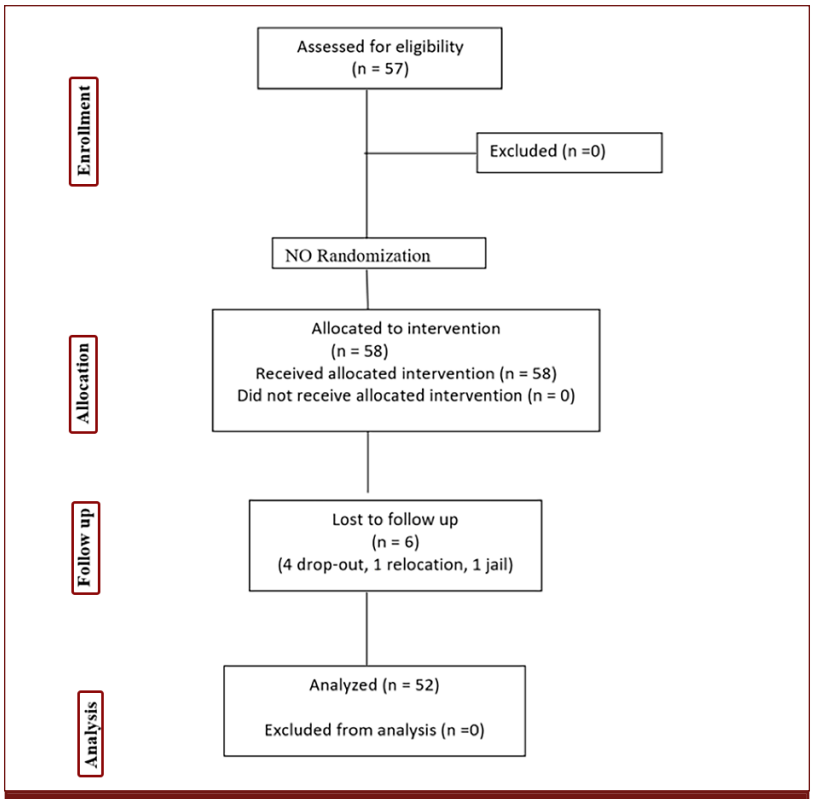

Figure 1: CONSORT diagram

- sedation;
- sexual dysfunction;
- mood changes.

VAS documented drug withdrawal symptoms severity. Participants marked a 10 point line with an increase of number points proportional to the severity of the symptoms from "not at all=0" to "extremely"=9;

3. the collection of the self-report measure Patient Global Impression of Change (PGIC) reflects a patient's belief about the satisfaction of treatment. PGIC is a 7 points scale. Patients rate their change and satisfaction by replying to the question "Since when you started treatment, can you describe your impression of how your condition has changed?" as follows:
   - No change (or even got worse)
   - Always the same, it is difficult to think of an improvement
   - A little better, but not noticeable,
   - Sometimes better, but change is not a fundamental difference
   - Moderately better, a slight and noticeable improvement,
   - Better, a marked improvement that makes a real difference,
   - A significant and decisive improvement that makes a difference.

As a secondary outcome, adverse reactions during treatment were recorded.

2.3. *Data analysis*

Considering the retrospective observational nature of this study, a univariate analysis was applied for each measurement. Mean, median, standard deviation, interquartile range, and min/max values were calculated for the quantitative variables; the absolute and relative frequency distribution were calculated for qualitative variables.

3. Results

3.1. *Primary outcome*

Demographic characteristics of the study sample are reported in **Table 1**.

Table 1. Demographic characteristics of the sample (n =58)

Gender N (%)	
Male	43 (74.2)
Female	15 (25.8)
Age (mean and SD)	43 (11.2)

At the baseline visit, 58 patients were included in the study, 5 (7%) were drug-naïve subjects with heroin dependence, and while (93%) were previously treated with other pure and/or partial opioid agonists; in particular, 53 with racemic methadone and 1 with buprenorphine. The history of drug treatment and the dosage of levomethadone at different time points are reported in **Table 2**.

Table 2. History of drug treatment at baseline and dosage of levomethadone

	Mean (S.D.)
Patients formerly treated with racemic methadone (N=52)	
Last dosage of racemic methadone (mg/day)	58.4 (32.4)
First dosage of levomethadone (mg/day)	28.93 (15.8)
Stabilization dose of levomethadone (mg/day)	30.2 (25.0)
Patients formerly treated with buprenorphine (N=1)	
Last dosage of buprenorphine (mg/day)	24
First dosage of levomethadone (mg/day)	30
Stabilization dose of levomethadone (mg/day)	30
Drug-naïve patients (N=5)	
First dosage of levomethadone (mg/day)	14 (6.5)
Stabilization dose of levomethadone (mg/day)	21.2 (11)

For patients formerly treated with methadone, the last mean dosage of methadone was 58.4 mg/day (SD=32.4) with an interval range from 10 to 150 mg/day, the average initial dose of levomethadone was 28.9 mg/day (SD=15.8) with an interval range from 5 to 75 mg/day. For drug-naïve subjects, the average was 14 mg/day (SD=6.5) with an interval range from 10 to 25 mg/day.

Regarding the need for adjustment stabilization dose, the average was 30.2 mg/day (SD=25) with an interval range from 5 to 100 mg/day for patients formerly treated with methadone and 21,2 mg/day (SD=11) for drug-naïve subjects with an interval range from 5 to 25 mg/day. The observation data demonstrated that in the case of patients formerly treated with methadone, no significant dose variation/adjustment between the initial therapy and the stabilization therapy with levomethadone was necessary, demonstrating the therapeutic equivalence in terms of efficacy of racemic methadone and levomethadone at a 2:1 ratio. These data comply with the scientific literature and the summary of product characteristics. On the other hand, data suggest that in the case of the drug-naïve subjects, the dose adjustment was more relevant, pointing out the possibility of different therapeutic responses of levomethadone between patients drug-naïve and patients already on OMT. In detail, the investigator reported that in total, 4 out 53 patients needed an increase of levomethadone dose, while 5 of them needed a decrease.

Moreover, 10 out of 58 patients presented HIV infection as concomitant pathology at the baseline visit. Characteristics of HIV patients are summarized in **Table 3**. In the case of HIV patients, the trend reveals no need for a relevant adjustment of levomethadone dose, confirming good compliance in patients in polytherapy and comorbidity.

Table 3. Subgroup of HIV patients

Patients with HIV (N=10)	
Last dosage of racemic methadone (mg/day)	58.4 (32.4)
First dosage of levomethadone (mg/day)	28.93 (15.8)
Stabilization dose of levomethadone (mg/day)	30.2 (25.0)

According to the VAS results, during the observation time, the average data demonstrated that all the patients reported a decrease of symptoms related to the presence of constipation, sweating, sedation, changes in the mood tone, sexual dysfunction both in the drug naïve subjects and in patients treated with racemic methadone. In particular, for methadone/buprenorphine subjects observation results revealed that VAS measurement for constipation was 5.25 (SD=2.15) at T0 and 4.51 (SD=1.63) at T2, sweating at T0 was 5.58 (SD=2.24) and at T2 was 4.33 (SD=1.65). Sedation at T0 was 3.69 (SD=2.32) and at T2 was 3.53 (SD=2.17), changes in the mood tone at T0 was 3.29 (SD=2.3) and at T2 was 3.1 (SD=2.22), sexual dysfunction symptoms went from 1.37 (SD=1.53) to 1.25 (SD=1.39). Patients formerly treated with methadone showed a significant decreased of symptoms from baseline to the final visit in constipation and sweating ($p<0.05$) (**Figure 2**). Regarding drug-naïve patients, due to the small sample size (n=5), it was impossible to calculate a significant variation of the VAS measurement between T0 and T2. Anyway, the results demonstrated a lack of variety of symptoms during the treatment, neither positive nor negative (**Figure 3**) confirm the good tolerability of levomethadone over time (2 months). Regarding the subgroup of HIV patients, observation data suggests that in 8 of 10 patients, there was a slight decrease of symptoms. Only one dropout was registered, confirming the tolerability of levomethadone in patients with polytherapy and comorbidity (**Figure 4**).

The Patient Global Impression of Change (PGIC), a self-report measure that evaluates a pa-

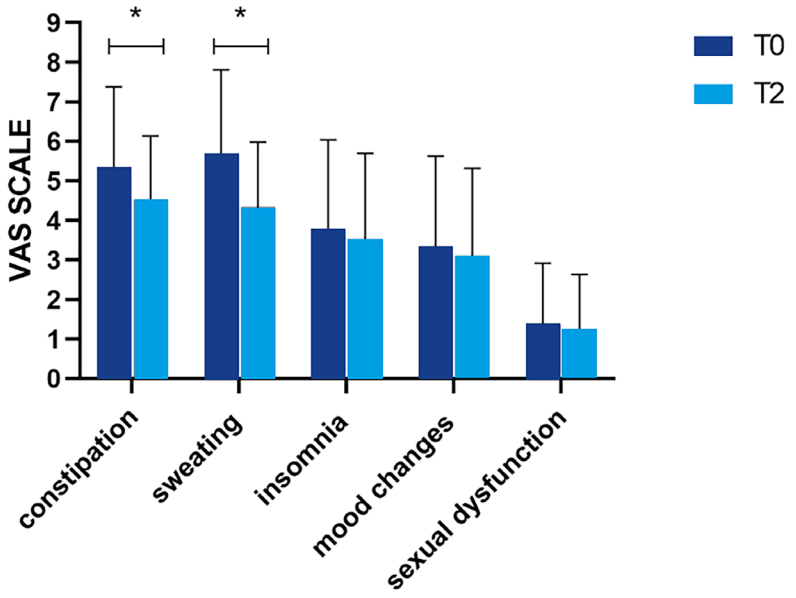

Figure 2. VAS results of methadone/buprenorphine subjects at T0=baseline visit/switch to levomethadone and T2=final visit/after 2 months with levomethadone. Differences were considered statistically significant when p≤ 0.05 (*), p≤ 0.01 (**) or p≤ 0.001 (***)

tient's belief about treatment satisfaction and quality of life (QoL), was performed at T2. Patients formerly treated with methadone/buprenorphine reported good results, so revealing satisfaction with the treatment, and an increased quality of life (5.131; SD=1.27) with respect to the period prior to treatment initiation. The PGIC results for drug naive patients were 4.75 (SD=0.5), suggesting a general acceptance of the treatment. Worth noting that PGIC result of HIV patients was 5.63 (SD=1.8), suggesting good compliance to the treatment in this kind of patients (**Table 4**).

3.2. Secondary outcome

Retention in treatment after two months was 90%. Six patients were lost during follow-up. Four dropouts were reported: one due to poor compliance, one to lousy palatability, one because of adverse events (nightmare during night and irritability), and

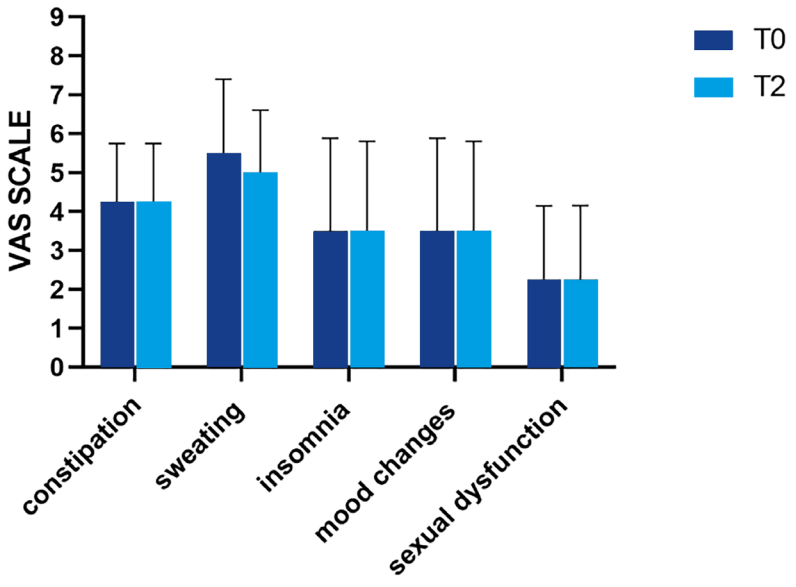

Figure 3. VAS results of Drug naive patients at T0=baseline visit/start of levomethadone and T2=final visit/after 2 months with levomethadone. Differences were considered statistically significant when p≤ 0.05 (*), p≤ 0.01 (**) or p≤ 0.001 (***)

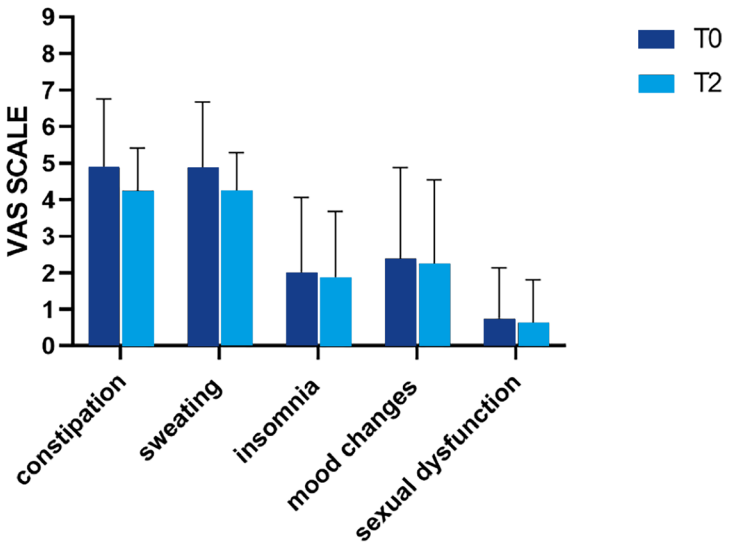

Figure 4. VAS results of subgroup of patients with HIV infection at T0=baseline visit/start or switch to levomethadone and T2=final visit/after 2 months with levomethadone. Differences were considered statistically significant when p≤ 0.05 (*), p≤ 0.01 (**) or p≤ 0.001 (***))

Table 4. PGIC results

PGIC scale	Mean (SD)
Patients all	5.21 (1.06)
Patients formerly treated with methadone/ buprenorphine	5.12 (1.27)
Drug-Naïve patients	4.75 (0.5)
HIV patients subgroup	5.63 (1.18)

one patient left the study as he stopped the treatment (decreasing the dose of levomethadone), as previously planned by clinicians. Two patients discontinued levomethadone due to relocation (one person was imprisoned; one was moved to another Drug Addiction Service). One patient experienced craving, and the investigator provided a higher dose of levomethadone. No other adverse side effects are reported.

4. Discussion

The present study aimed to evaluate the results of a treatment of opioid dependence with levomethadone in some Italian drug addiction services. After replacing methadone with a half-dose of levomethadone, no adverse symptoms were observed; indeed, the VAS scale for symptoms assessment demonstrated good tolerability of the drug. Worth noting that, at the final visit, constipation and sweating were significantly improved in the formerly methadone-treated group, showing a better tolerance to levomethadone than methadone with respect to these two OMT symptoms. These results are extremely interesting since constipation and sweating are common side effects that do not undergo drug tolerance during OMT and are therefore longlasting. VAS assessments are routinely used as they are easy to administer and their simple numerical scoring can be treated as a continuous variable in statistical analyses. **[6]**. These features makes therefore VAS a valuable measure in clinical settings as it facilitates trend analysis during long-term treatments. PGIC score of patients formerly treated with racemic methadone was around 5, which shows satisfaction with the switch to levomethadone. They reported improved physical and mental well-being, satisfaction with the treatment **[3]**, so showing good tolerability of levomethadone.

On the basis of these results, it is worth asking who can benefit from the switch from the racemic formulation to levomethadone **[17, 18]**. Any patient with pre-existing heart disease **[11, 15]** or comorbidity and/or those receiving medications for co-occurring disorders, which may inhibit methadone metabolism, would benefit from (R)-methadone (e.g. HIV patients). These results moreover suggested that the switch from methadone to levomethadone could be safely performed, as long as the dose ratio is kept at approximately 2:1, respectively. The observational data confirmed that switch 2:1 is in line with the efficacy and tolerability expectations. No need for a considerable increase of levomethadone dose was necessary for patients with the last mean methadone dosage of 58.4 ± 32.4 mg/day (min 10 mg/day; max 150 mg/day). A study by Deruvo et al. **[2]** reported that in OMT patients with a last mean racemic methadone dose of 59.08 ± 44.1 mg/die (min 10 mg/die; max 250 mg/die), only 7 out of 49 (14.2%) did not need any dose variation. A study by Consoli et al. **[1]**

reported instead no need for a significant dose adjustment in a group of patients with previous methadone mean dose of 80 mg/day (SD=42.9), in line with the data reported in our study. Based on this, we highlight the importance of collecting real-world data to find out the best indications to achieve the highest clinical awareness in addiction therapy.

On the other hand, drug naive subjects need a dose adjustment, and more time is necessary to find out the optimal stabilizing dose, due to craving symptoms and risk of poor treatment adherence shown by these patients. Of note, results suggest that for HIV patients, the initial dose of levomethadone (25.3 mg/day) is in line with the stabilization dose data (28.13 mg/day). PGIC and VAS results confirmed the excellent tolerability and safety of levomethadone in patients on polytherapy and with a high risk of metabolic modifications.

5. Conclusions

Our data show good tolerability and satisfaction of OUD patients switching from racemic to levomethadone, pointing out the benefits of levomethadone, possibly due to a lower dose with respect to the racemic form. Levomethadone is effective and well-tolerated in the management of OUD patients, in particular in patients with comorbidity or polytherapy since it has less metabolic interference than methadone. As reported above, the therapeutic levomethadone dose is equivalent to half the racemic form. Levomethadone has therefore less risk of QT interval modifications, since this side effect usually occurs at a high therapeutic dose (>100 mg/day). In drug naïve patients, levomethadone is well tolerated, and no adverse effects are reported. No signs of withdrawal symptoms are reported based on VAS and PGIC assessment. From these observational data is, therefore, possible to conclude that levomethadone shows equal and, for some symptoms, more signficant tolerability than methadone. This is particularly important from a therapeutic point of view, in patients with comorbidity and on polytherapy. Finally, we emphasize the importance of a multidisciplinary therapeutic and clinical approach to OUD patients and the need to collect real-world data from clinical practice. Patients, in fact, often do not declare withdrawal or drug symptoms, due to stigma or physiological difficulties. So, the evaluation of a correct therapeutic approach may be more complex.

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Contributors

All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

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Conflict of interest

Authors declared 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 does not require ethics committee approval because it was carried out in a retrospective way on anonymised data. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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Opium use and risk of upper gastrointestinal cancers: A systematic review and meta-analysis

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Summary

Background: This systematic review and meta-analysis was conducted on the most relevant studies to determine any relationship between opium use and upper gastrointestinal (UGI) cancers. **Methods**: A comprehensive search was performed on several electronic databases, i.e. MEDLINE, PubMed, EMBASE, Scopus, Web of Science (ISI), Magiran, and SID, looking for studies that examined the association between opium use and UGI cancers up to August 2020. Q-tests, as well as I2 statistics, were employed to assess the inter-study heterogeneity. Moreover, the random-effects model was utilised to obtain estimates of the pooled crude and adjusted odds ratios (ORs) with their 95% confidence intervals (95% CIs). **Results**: Of 1,378 records, thirteen articles comprised 3,530 UGI cancer cases and 254,219 controls. The meta-analyses obtained from the random-effects model indicated that opium use was associated with an increased risk of UGI cancers, with a crude OR of 1.98 (95% CI: 1.67, 2.35) and an adjusted OR 1.76 (95% CI: 1.41, 2.20). Given the significant heterogeneity value observed in the pooled crude ORs (I2: 48.39% with P= 0.011), subgroup analyses showed that the pooled effect size remained statistically significant in the different strata, except in the strata stratified by type of cancers. Moreover, the findings of meta-regression analyses indicated the date of publication (β=-0.02, P= 0.014) and the total sample size (β=-0.00, P=0.034) might account for the inter-study heterogeneity. Likewise, sensitivity analysis indicated that none of the studies impacted the robustness of the pooled crude ORs. **Conclusions**: We found a significant association between opium use and developing UGI tract cancers, especially in oesophageal cancer.

Key Words: Opium; upper gastrointestinal cancers; oesophageal cancer; meta-analysis

1. Introduction

Cancers have been shown in recent decades to be the most prevalent cause of death worldwide **[28]**, and Iran is no exception. Upper gastrointestinal (UGI) tract cancers, i.e. oral cavity, oesophagus, stomach, liver, and pancreas account for an annual 60 per cent of cancer-caused deaths in Iran **[26]**. According to the previous data, cancer rates are distributed differently in Iran, and the ratios are higher in Golestan and Kerman provinces. For a wide variety of cancers, some risk factors are considered causative, of which the most significant is long-term opium or other opioids consumption **[6, 17, 19]**. Admittedly, a case-control study performed in Rafsanjan (a region in Kerman) indicated that opium consumption is positively associated with an increased risk of UGI tract cancers **[42, 46]**. Likewise, previous reports have shown that larynx and bladder cancers are similarly caused by opium use as it affects UGI cancers through their mutagenic role **[13, 25, 39]**. Furthermore, in a comprehensive cohort study undertaken in Golestan province, 1,833 cancer-diagnosed patients were evaluated for ten years, revealing a strong association between

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opium use and the risk of developing all kinds of cancers such as gastrointestinal and respiratory **[18, 38]**. It seems that these differences are reflective of many factors that are effective in the distribution of cancer patterns in each country **[3, 14, 21, 34]**. For example, opium is approximately the most destructive substance used worldwide and is the leading cause of economic losses and diseases like cancers in many countries **[20, 22]**.

Opium was first used in prehistoric sites across western, southern, and central Europe from the early Neolithic period **[45]** until south-central Asian countries, especially Iran, Pakistan, Afghanistan, and India **[16, 23, 37]**. Nowadays, given the common misconception that opium use can alleviate chronic diseases like cancers due to its pain-relieving feature, opioid and their derivatives have broad therapeutic applications **[1, 2, 12, 17, 43]**. Additionally, there is still controversy as to the relationship between cancer and misuse of some other substances like hookah (water pipe), cigarette **[9, 36]**, and 'nass' (a chewing product containing tobacco, ash, and lime) **[32]**. In sex- and age-matched case-control study, hookah smoking and opium consumption were shown to be related to oesophageal cancer; however, the same finding was not significant for cigarette smoking, pipe smoking, drug withdrawal, and alcohol consumption **[31]**. On the other hand, the ways opioids are misused, affect the human body differently. Yet, there is not insufficient information about whether opioids use correlated with carcinogenic metabolites, by-products, and bioavailability **[27, 36]**.

Previous studies have shown the possible association between opium use and oesophageal **[27]**, gastric **[37]**, and pancreatic **[35]** cancer. Nevertheless, given these studies' case-control methods and confounding factors, such an association could not be adequately confirmed. Thus, this systematic meta-analysis was conducted on the most relevant studies to see if opium use is associated with any UGI tract cancers.

2. Methods

The MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists were used for conducting and reporting our meta-analysis.

2.1. Literature Search

Several electronic databases including MEDLINE, PubMed, EMBASE, Scopus, Web of Science (ISI), Magiran (http://www.magiran.com/), and SID (http://sid.ir/) were systematically searched. Moreover, the reference lists for previous reviews, relevant articles, and Google Scholar were also searched as an advanced search function for studies investigating the association between opium use and UGI cancers until August 2020. Comprehensive searches in the literature were also performed through a combination of the following MeSH terms (Medical Subject Heading) and relevant keywords: exposures ("Opium" OR "Papaveretum" OR "Omnopon" OR "Pantopon" OR "Opiate" OR "Poppy Tears" OR "Lachryma Papaveris" OR "Opium Poppy" OR "Laudanum" OR "Shireh" OR "Tariak" OR "Teryak" OR "Aunti Emma" OR "Big O" OR "Black Pill" OR "Chandu" OR "Chinese Tobacco" OR "Dreams" OR "Fi-do-nie" OR "Great Tobacco" OR "Guma" OR "Hop/hops" OR "Ope" OR "Pox" OR "When-Shee" OR "Ze") AND outcomes ("Mouth Neoplasms" OR "Mouth Neoplasm" OR "Oral Neoplasm" OR "Oral Neoplasms" OR "Neoplasms, Mouth" OR "Cancer of Mouth" OR "Mouth Cancers" OR "Oral Cancer" OR "Oral Cancers" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Esophageal Neoplasms" OR "Esophageal Neoplasm" OR "Esophagus Neoplasm" OR "Esophagus Neoplasms" OR "Cancer of Esophagus" OR "Cancer of the Esophagus" OR "Esophagus Cancer" OR "Esophagus Cancers" OR "Esophageal Cancer" OR "Esophageal Cancers" OR "Stomach Neoplasm" OR "Stomach Neoplasms" OR "Gastric Neoplasms" OR "Gastric Neoplasm" OR "Cancer of Stomach" OR "Stomach Cancers" OR "Gastric Cancer" OR "Gastric Cancers" OR "Stomach Cancer" OR "Cancer of the Stomach" OR "Liver Neoplasms" OR "Liver Neoplasm" OR "Hepatic Neoplasms" OR "Hepatic Neoplasm" OR "Cancer of Liver" OR "Hepatocellular Cancer" OR "Hepatocellular Cancers" OR "Hepatic Cancer" OR "Hepatic Cancers" OR "Liver Cancer" OR "Liver Cancers" OR "Cancer of the Liver" OR "Pancreatic Neoplasms" OR "Pancreatic Neoplasms" OR "Pancreas Neoplasm" OR "Pancreas Neoplasm" OR "Cancer of Pancreas" OR "Pancreas Cancers" OR "Pancreas Cancer" OR "Pancreatic Cancer" OR "Pancreatic Cancers" OR "Cancer of the Pancreas" OR "Upper gastrointestinal cancers" OR "Oesophageal squamous cell carcinoma" OR "Oesophageal adenocarcinoma" OR "Gastric Cardia Adenocarcinoma" OR "Gastric Noncardia Adenocarcinoma" OR "Oesophageal Adenosquamous Carcinoma" OR "Gastric Lymphoma" OR "Familial Primary Gastric Lymphoma" OR "Primary Gastric Lymphoma" OR "Gastric Lymphoma" OR "Duodenal Adenocarcinoma" OR "Oesophageal Squamous Cell Cancers" OR "Oesophageal Adenocarcinomas"). All search findings were managed using EndNote X8 software.

2.2. Study selection

Two researchers (SH and SMAK) made an independent evaluation of the findings of the literature searches based on our inclusion criteria. After the du-

plicates and irrelevant citations were removed when titles, abstracts, and full texts were investigated, the relevant studies were identified.

Studies were selected if they:

1) were an original observational human study with a cohort, nested or case-control, and cross-sectional design;
2) investigated the association between opium use and risk of UGI cancers (oral cavity, oesophagus, stomach, liver, and pancreas) **[10]**;
3) were published in English or Persian languages
4) and finally reported sufficient data on risk estimates (relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs)) that could be calculated or transformed into odds ratios with their 95% confidence interval (CIs).

However, the PICOS tool in the present study stands for: Population: opium users, Intervention: not applied, Comparison: non-opium users, Outcomes: UGI cancers, study: observational designs.

2.3. Data extraction and quality assessment

Two independent researchers (SO and SMAK) extracted the required data from all the eligible studies. The data was then entered into a predefined form in an Excel spreadsheet. A third author (HA) also checked the data extraction forms to improve accuracy. The following items were collected: first author's last name, year of publication, the place where the study was conducted, study design, the participants' basic characteristic, opium use assessment, the definition of opium use, duration and dosage of opium use, type of cancer, outcome assessment, matching status, adjusted variables, the total sample size in exposed/unexposed groups, number of cigarette smokers, tobacco users, and alcohol drinkers in each group, and crude and adjusted risk estimates with their 95% CIs. It is noteworthy that only studies published with overlapping data and recent articles with comprehensive information were included. The Newcastle–Ottawa Quality Assessment Scale (NOS) **[30]** was used to assess the quality of the included studies. Each study takes a NOS score ranging from 0 to 9, and those that obtained the score of 7 or greater were considered a high-quality study.

2.4. Statistical analysis

All the statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) software (version 2; Borenstein, Hedges, Higgins, & Rothstein, 2005). The association between opium use and the risk of UGI cancers were examined based on the crude and adjusted effect OR estimates and corresponding 95% CI in each included study. Since the ORs across the included studies were the most common effect measure, all other effect measures such as hazard ratios (HRs) and relative risks (RRs) were transformed into OR. The following formula was used to change measures from RR to OR: ((1-r)×RR)/(1-RR×r) and from HR to OR: ((1-r)×(1-eHR×ln(1-r)/r)/(1-(1-eHR×ln(1-r)/r)×r) where RR is the relative risk, HR is the hazard ratio, and r is the risk for the control group **[40, 47]**. The random-effects model was also used to pool the effect sizes. In addition, the Cochran Q and I2 statistics were used to evaluate the inter-study heterogeneity across included studies. A $P< 0.1$ for Q-test and I2 scores higher than 50% indicated significant heterogeneity **[11]**. Leave-one-out sensitivity analyses were performed by excluding studies, one at a time, to assess the stability of the pooled ORs and to examine the potential source of inter-study heterogeneity if the presence of heterogeneity was considerable. Subgroup analyses for suspected interactions with categorical variables including study design (case-control vs. cohort), city (Golestan vs. Tehran vs. another town), type of cancer (oesophageal vs. gastric vs. oral cavity vs. pancreatic vs. liver), alcohol status (Non-significant association (Non-SA) vs. Not reporting (NR) vs. significant association (SA)), cigarette status (Non-SA vs. NR vs. SA), and tobacco status (Non-SA vs. NR vs. SA), quality status (high vs. low) and meta-regression analyses for continuous variables including total sample size and year of publication among each study were conducted to explore heterogeneity. Evidence of publication bias was assessed visually via funnel plot asymmetry, and also Egger's and Begg's tests were used to evaluate the included studies quantitatively **[5, 7]**. The protocol for the review was registered with PROSPERO (Provisional registration number: CRD42020208315).

3. Results

3.1. Characteristics of the selected studies

Our electronic and manual searches in the literature identified 1,378 records, of which 1,183 were excluded after the screening was performed following the titles and abstracts were considered duplicate or irrelevant. Then, a total of 204 full-text articles were assessed based on our inclusion criteria. Of these articles, 13 (or 18 studies) observational articles **[4, 8, 14, 15, 24, 27, 31, 33, 35-38, 44]** were finally included in the current meta-analysis (**Figure 1**).

Likewise, out of these studies, 13 cases **[4, 8, 14, 15, 27, 31, 33, 35-37, 44]** were conducted with a case-control design and five with a cohort design **[24, 38]**. According to the type of cancer, eight, four, three, two, and one studies have reported that opium use was associated with oesophageal cancer **[4, 14, 15, 27, 31, 36, 38]**, gastric cancer **[14, 37, 38, 44]**, pancreatic cancer **[24, 35, 38]**, oral

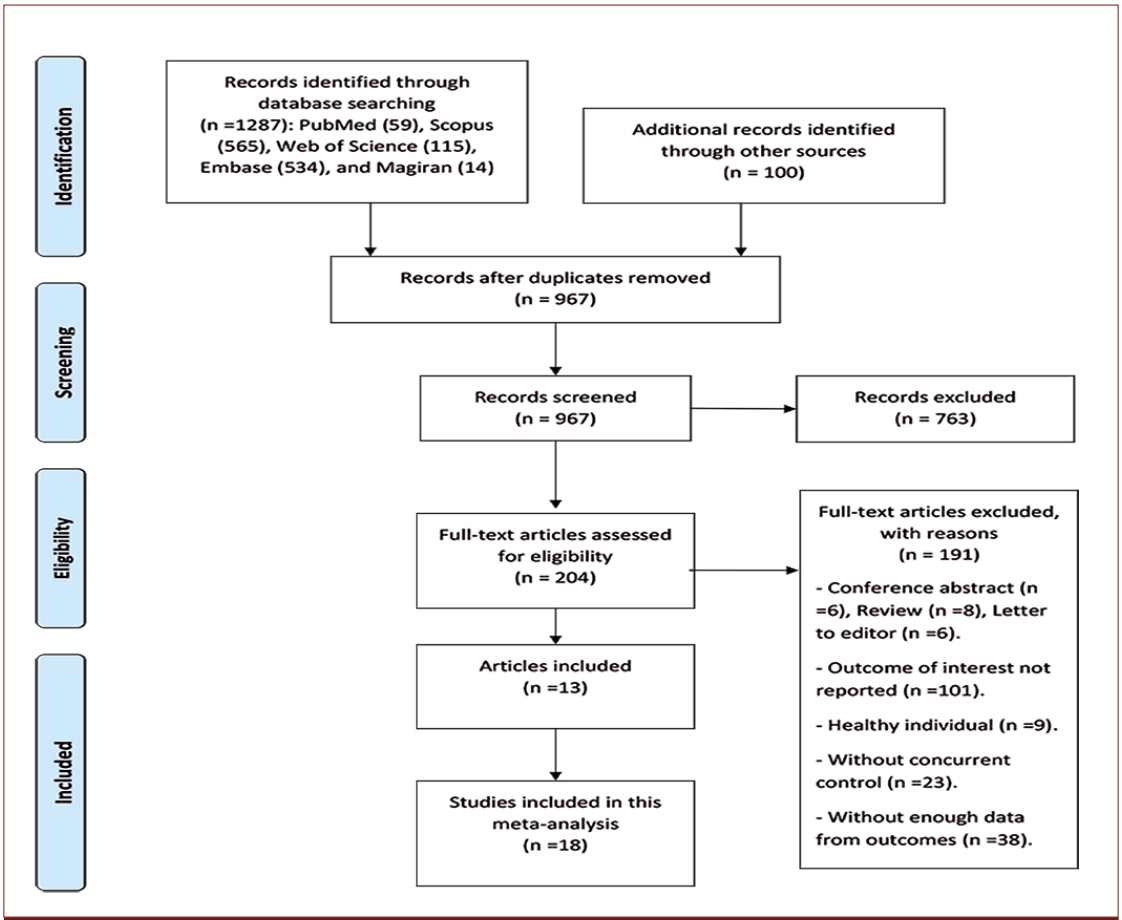


Figure 1. Articles' selection

cavity cancer **[8,33]**, and liver cancer, respectively **[38]**. Seven of the included articles (or 11 studies) reported adjusted effect estimates of ORs **[24, 27, 35-38, 44]**. In addition, a total of 3,530 patients with UGI cancer cases were compared with 25,4219 healthy controls across the included studies published from 1983 **[8]** to 2020 **[38]**. Besides, the quality scores ranged from 5 to 8 according to the NOS tool. A summary of the basic characteristics of the included studies was presented in **Table 1 A, B.**

3.2. The main outcomes of opium use and UGI cancers risk

Of the studies included in the present meta-analysis, 18 and 11 addressed, respectively, the summary effect estimation of crude OR and the adjusted OR regarding the association between opium use and UGI cancers risk. The pooled results obtained through the random-effects model indicated that the opium use was associated with an increased risk of UGI cancers with a crude OR 1.98 (95% CI: 1.67, 2.35) and an adjusted OR 1.76 (95% CI: 1.41, 2.20) (**Figure 2 A-B**). There was significant evidence of the inter-study heterogeneity among the included studies in a meta-analysis of crude ORs (I2: 48.39% with P= 0.011).

3.3. Additional Analyses for Unadjusted ORs

Given the existing significant heterogeneity in the pooled crude ORs, the subgroup analyses were performed concerning the study design, city, type of cancer, alcohol, cigarette and tobacco status, and quality scores. **Table 2** depicts the findings of subgroup analyses about the association between opium use and the risk of UGI cancers based on the pooled crude ORs. The pooled crude ORs remained statistically significant in different strata such as study design, city, alcohol, cigarette and tobacco interactions, and quality scores. When stratified by the type of cancers, a significant association was found between opium use and oesophageal cancer (crude OR= 1.74; 95%CI: 1.48, 2.05; I2: 0.00%, P=0.748), gastric cancer (crude OR= 2.22; 95%CI: 1.57, 3.14; I2: 62.61%, P=0.046) and oral cavity cancer (crude OR= 4.83; 95%CI: 2.93, 7.96; I2: 0.00%, P=0.740); however, no such a significant association was observed between opium use and pancreatic cancer (crude OR= 1.76; 95%CI: 0.98, 3.14; I2: 50.30%, P= 0.134). Moreover,

Table 1 A. Summary of basic characteristics of the included studies

Authors	Year	No. of cases/ controls	Country/city	Study design	Control setting	Type of cancer
Bakhshaee [4]	2017	95/14	Iran/Mashhad	CC	hospital-based controls	Oesophageal
Fahmy [8]	1983	381/1,000	Iran/Fars	CC	NR	Oral Cavity
Islami [15]	2009	300/571	Iran/Golestan	CC	neighborhood controls	Oesophageal
Islami #a [14]	2004	156/260	Iran/Golestan	CC	noncancer patients	Oesophageal
Islami #b[14]	2004	82/260	Iran/Golestan	CC	noncancer patients	Gastric
Naghibzadeh Tahami [44]	2014	89/178	Iran /Kerman	CC	healthy controls	Gastric
Nasrollahzadeh [27]	2008	300/571	Iran/Golestan	CC	healthy controls	Oesophageal
Pournaghi [31]	2018	96/187	Iran North Khorasan	CC	healthy controls	Oesophageal
Razmpa [33]	2014	80/80	Iran/Tehran	CC	healthy controls	Oral Cavity
Shakeri #1 #a [36]	2012	130/260	Iran/Golestan	CC	Hospital-based controls	Oesophageal
Shakeri #1 #b [36]	2012	300/571	Iran/Golestan	CC	Neighbourhood of residence	Oesophageal
Shakeri #2 [37]	2013	309/613	Iran/Golestan	CC	healthy subjects	Gastric
Shakeri #3 [35]	2016	357/328	Iran Tehran	CC	healthy controls	Pancreatic
Sheikh #a [38]	2020	342/49,692	Iran/Golestan	Cohort	cohort participants	Oesophageal
Sheikh #b [38]	2020	308/49,726	Iran/Golestan	Cohort	cohort participants	Gastric
Sheikh #c [38]	2020	78/49,956	Iran/Golestan	Cohort	cohort participants	Pancreatic
Sheikh #d [38]	2020	73/49,961	Iran/Golestan	Cohort	cohort participants	Liver
Moossavi [24]	2018	54/49,991	Iran /Golestan	Cohort	healthy individuals	Pancreatic

Abbreviations: CC, case-control; NOS, Newcastle-Ottawa Scale.

the results of meta-regression analysis indicated that the publication year (β= -0.02, P= 0.014) and the total sample size (β= -0.00, P= 0.034) might account for the inter-study heterogeneity across the included studies.

The sensitivity analysis results were seen in a study conducted by Fahmy et al., **[8]** as a source of heterogeneity in our meta-analysis. After removing this study, the statistical heterogeneity decreased across the included studies (I2: 48.39 P= 0.001 vs. I2: 24.48% with P= 0.171). Sensitivity analysis also indicated that none of the studies effected the pooled crude ORs robustness after the studies were excluded one by one.

3.4. Publication bias

It should be noted that the funnel plot and Egger's and Begg's tests were employed to assess the potential publication bias visually and quantitatively, respectively. As demonstrated by **Figure 3**, the funnel plot showed a symmetrical distribution shape. In contrast, the Egger's test (P=0.77) and Begg's test (P=0.34) reported no evidence of statistically potential publication bias across the included studies in our meta-analysis.

4. Discussion:

Given that opium use has a crucial impact on health and cancer development, there is a deep concern regarding the exact relationship between opium

Table 1 B. Summary of basic characteristics of the included studies

Authors	Outcome assessment	Adjustments	NOS score**
Bakhshaee [4]	Proven through biopsy	N adjustment	7
Fahmy [8]	Biopsy examination	N adjustment	6
Islami [15]	Histopathological diagnosis	N adjustment	7
Islami #a [14]	Physical examination followed by oesophago-gastro-duodenal videoendoscopy	N adjustment	8
Islami #b[14]	Physical examination followed by oesophago-gastro-duodenal videoendoscopy	N adjustment	8
Naghibzadeh Tahami [44]	based on the pathological data records	Adjusted for Smoking	6
Nasrollahzadeh [27]	Physical examination followed by oesophago-gastro-duodenal videoendoscopy	Adjusted for education and ethnicity	5
Pournaghi [31]	Pathologic report	N adjustment	6
Razmpa [33]	Pathology specimens	N adjustment	7
Shakeri #1 #a [36]	Upper gastrointestinal endoscopy	Adjusted for education, ethnicity and consumption of cigarette, hookah, Nass and opium (for those analyses these were not the main independent variable)	7
Shakeri #1 #b [36]	Upper gastrointestinal endoscopy	Adjusted for education, ethnicity and consumption of cigarette, hookah, Nass and opium (for those analyses these were not the main independent variable)	7
Shakeri #2 [37]	Upper GI endoscopy	Adjusted for age, ethnicity, education, fruit consumption, vegetable consumption, socioeconomic status, and in each case for the other three main variables (e.g. opium use was also adjusted for cigarette, hookah and nass use, etc.)	8
Shakeri #3 [35]	Esophago-gastro-duodenal endoscopy	Adjusted for age, sex, residence, alcohol use, and ever use of any type of tobacco	8
Sheikh #a [38]	Medical reports reviewed separately by two expert physicians	Adjusted for sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartiles, and regular alcohol drinking (never/ever)	7
Sheikh #b [38]	Medical reports reviewed separately by two expert physicians	Adjusted for sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartiles, and regular alcohol drinking (never/ever)	7
Sheikh #c [38]	Medical reports reviewed separately by two expert physicians	Adjusted for sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartiles, and regular alcohol drinking (never/ever)	7
Sheikh #d [38]	Medical reports reviewed separately by two expert physicians	Adjusted for sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartiles, and regular alcohol drinking (never/ever)	7
Moossavi [24]	Based on reported clinical signs and symptoms, imaging findings, histopathology report, and clinical follow up	Adjusted for age, sex (model 1)cigarette smoking status (never, ever) and alcohol consumption (never, ever) (model 2)	7

Abbreviations: CC, case-control; NOS, Newcastle-Ottawa Scale.

Table 2 . Findigs of subgroup analyses

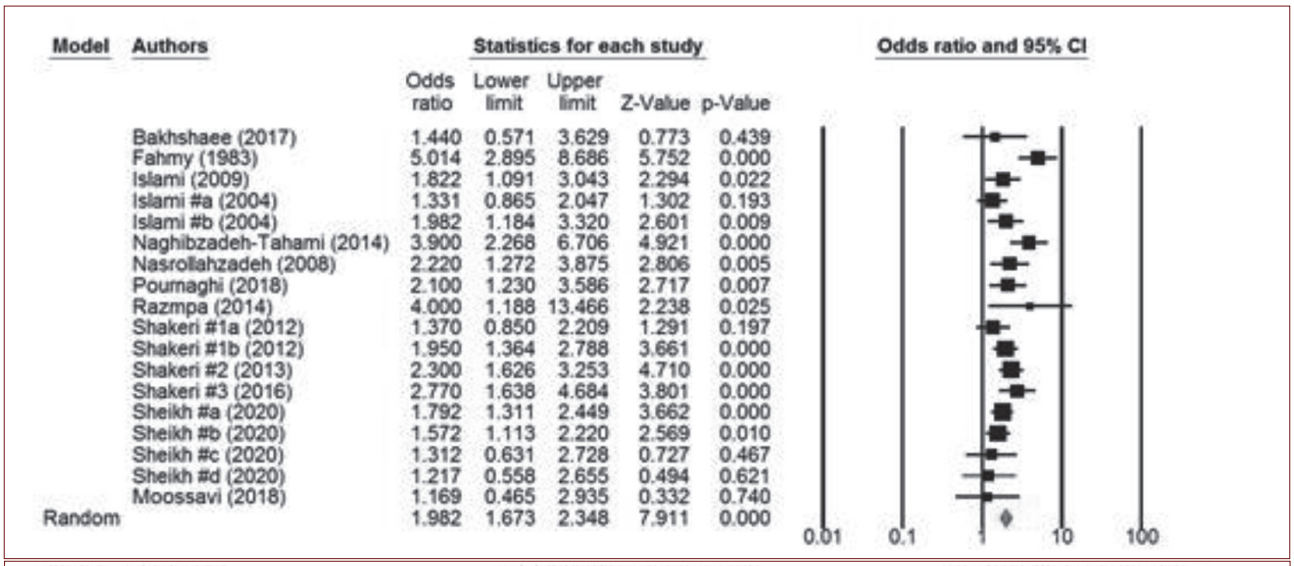
Outcomes		Number of studies	OR (95% CI)	I2 and P-value
Total		18	1.98 (1.67, 2.35)	48.39%, P= 0.011
Study design	Case-control	13	2.20 (1.78, 2.71)	52.97%, P= 0.013
	Cohort	5	1.59 (1.29, 1.95)	0.00%, P= 0.788
City	Golestan	12	1.74 (1.53, 1.98)	0.00%, P= 0.640
	Tehran	2	2.94 (1.81, 4.75)	0.00%, P= 0.586
	Other city	4	2.96 (1.77, 4.92)	63.88%, P= 0.040
Type of cancer	Oesophageal	8	1.74 (1.48, 2.05)	0.00%, P= 0.748
	Gastric	4	2.22 (1.57, 3.14)	62.61%, P= 0.046
	Pancreatic	3	1.76 (0.98, 3.14)	50.30%, P= 0.134
	Oral cavity	2	4.83 (2.93, 7.96)	0.00%, P= 0.740
	Liver	1	1.22 (0.56, 2.66)	-
Alcohol status	Non-SA	7	2.51 (1.71, 3.68)	68.85%, P= 0.004
	NR	9	1.73 (1.49, 2.01)	0.00%, P= 0.596
	SA	2	2.34 (1.62, 3.38)	0.00%, P= 0.373
Cigarette status	Non-SA	9	1.84 (1.53, 2.20)	8.87%, P= 0.361
	NR	5	1.64 (1.35, 2.00)	0.00%, P=0.836
	SA	4	3.19 (2.15, 4.75)	55.05%, P=0.083
Tobacco status	Non-SA	6	1.69 (1.43, 1.99)	0.00%, P= 0.820
	NR	7	2.10 (1.45, 3.04)	56.21%, P= 0.033
	SA	5	2.40 (1.61, 3.50)	60.71%, P= 0.037
Quality status	High	14	1.78 (1.57, 2.02)	0.00%, P= 452
	Low	4	3.09 (2.03, 4.69)	57.41%, P= 0.070

*Non-SA, Non-significant association; NR, Not reporting, SA, significant association.

use and UGI tract cancers, though it is still unproven. Therefore, we collected and combined relevant studies and their findings to see if this association exists. Comprising 18 studies, the present meta-analysis found a significant association between opium use and an increase in the rate of UGI tract cancer, especially oesophagus cancer, in some Iranian populations, .

A review of the related literature shows a strong theory about the mechanism of morphine, as a significant opium alkaloid, and its effect on the human body's cells, since they are highly mutagenic in bacteria and, after metabolic activation, induce sister-chromatid exchanges in mammalian cells. The study by Friesen et al. **[9]** reported six abundant mutagenic compounds that were extracted from morphine pyrolysate, along with its proven correlations with oesophageal cancer. Overall, the carcinogenic mechanism of opium has a lot of aspects as indicated by many studies. Indeed, the administration of pyrolycate-derived thermal decompositions of opium (morphine) through topical, subcutaneous, intra-tracheal, and intra-gastric pathways was shown to cause cancerous activity in mice **[9, 29]**.

In the present study, it was overall found that opium is significantly associated with UGI cancers development. The eight studies about oesophageal cancer included in this meta-analysis showed that opium use leads to an approximately two-fold increase in the odds of developing UGI cancer. Also, given the study's low heterogenicity in relevant studies, the observed association between opium use and UGI cancer development was more trustworthy. Definitely, not only was opium use found to increase the likelihood of developing oesophageal cancer, but it also led to an oral cavity, gastric cancer, pancreatic cancer, and liver cancer. Therefore, it became clear that opium significantly increased the risk of all UGI cancers, except for the pancreas. In contrast, Shakeri et al. **[35]** showed that opium was associated with pancreatic cancer with an OR of 1.91, which might be due to the few numbers of studies that were included. Shakeri and his colleagues **[37]** presented a proven association between opium and gastric adenocarcinoma as a public health significance. Moreover, according to four studies in this meta-analysis, we found significant odds of developing gastric cancer and opium use (OR= 2.2). As the first and the most in contact with inhaled substances, the oral cavity is affected by



Figures 2A (up) and 2B (down). Forest plots of studies evaluating the crude ORs and adjusted ORs of UGI cancers associated with opium use

opium, as shown by two studies with odds of 4.8 **[33]**. Nevertheless, it is suggested that more studies with a larger sample size be conducted in the future.

On the other hand, tobacco smoking, cigarette smoking, and alcohol consumption are frequently observed in individuals who tend to use opium in their free time **[27, 31, 35]**. The relevant articles have shown a significant association between cancer development and maintaining the three habits mentioned above since they result in cancer development, especially in the UGI tract in a synergistic pathway **[27, 31]**. Likewise, our meta-analysis reported that opium use interacts with these three confounding factors, with cigarette smoking highly associated with cancer (OR = 3.19). Although in the subgroup analysis of case-control studies, a significantly higher likelihood of opium use was observed in the presence of smoking and tobacco in patients with UGI tract cancers, there was no strong relationship between simultaneous opium and alcohol use and an increased risk of cancer. Given that tobacco smoking, cigarette smoking, and alcohol consumption and their destructive effects on society have had an unprecedented rise, their association with cancers could be independently examined in a more prominent number of studies.

UGI cancers are the most common cause of death in Iran, with pancreatic cancer as the most lethal **[41]**. Hence, given its importance, it is of utmost urgency to policymakers to identify the principal risk factors and environmental causes that could lead to an increased rate of this disease. In the present study, the crude and adjusted OR values for developing UGI tract cancer through opium consumption were 1.98 and 1.76, respectively. Thus, it can be concluded that not only would opium use be a socially dangerous problem for any age group, but it is also definitely known as a risk factor for developing UGI cancers, especially oesophageal and oral cavity ones.

Considering the limitations of this study, i.e. few numbers of studies included in our meta-analysis and lack of fully adjusted analyses, it is highly recommended that further studies with fewer limitations and more significant numbers of qualified studies be undertaken. Concerning the aim of the current

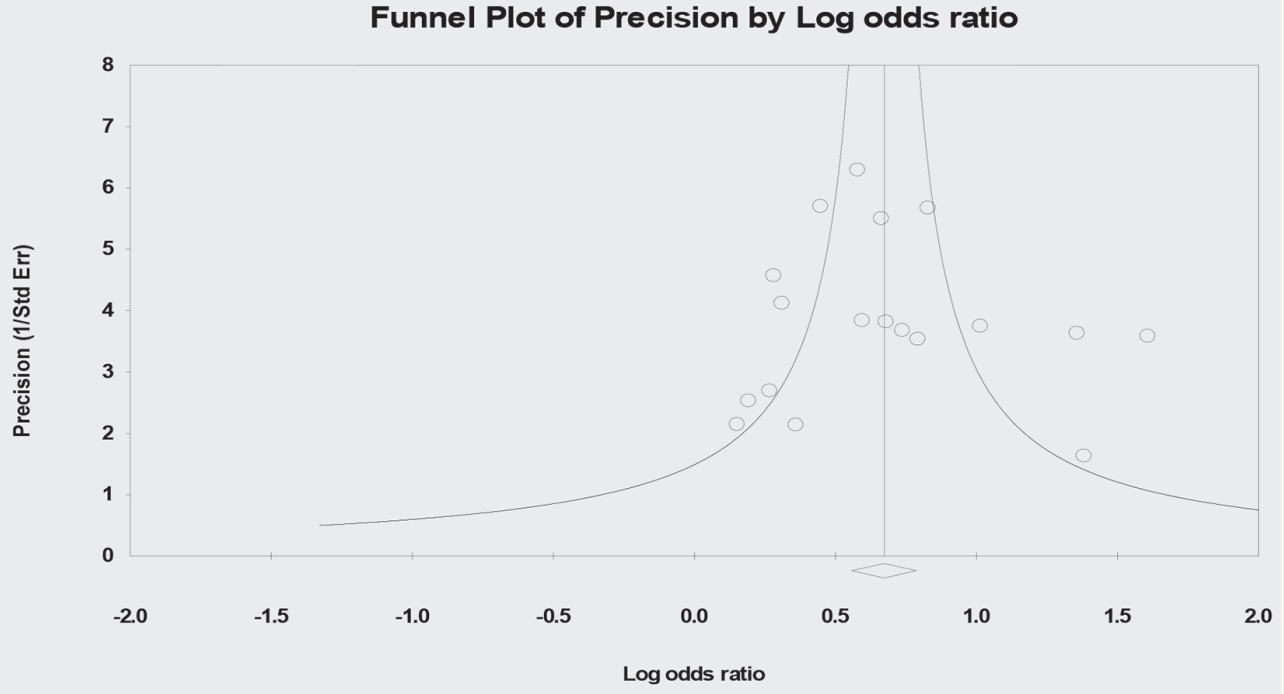


Figure 3. Funnel plots of studies evaluating the risk of UGI cancers associated with opium use

research, many studies were eliminated due to the inclusion and exclusion criteria, leading to the selection of some case-control and cohort studies with Iranian populations. It should be noted that studies conducted outside of Iran were not included in this meta-analysis. Moreover, we did not consider various ways of opium use due to the widespread and non-homogeneous data. It is, accordingly, suggested that this variable, i.e. different ways of misusing opium, be considered in future studies.

5. Conclusions

The present meta-analysis revealed that opium use is significantly associated with the development of UGI tract cancers, especially oesophageal cancer. Considering Iran's particular geographical location as a gateway for transporting enormous amounts of opium consignments, planning some deterrent policies in the country assumes crucial significance. Thus, based on the results of this review, it is strongly recommended that opium use is prevented, and opium users are punished through an appropriate cycle of management so that its detrimental effects and huge costs on society and people could be eliminated.

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Image Rehearsal Therapy (IRT) as a treatment for nightmares within substance-dependence populations

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Summary

Nightmares are perhaps one of the most overlooked symptoms of sleep disorders. These dreams have been found to be associated with increased awakenings during the night as well as intensified symptoms of distress. Nightmares are common in substance dependence populations that have endured significant trauma prior or during their addiction. Imagery Rehearsal Therapy has demonstrated substantial results in decreasing nightmare frequency and improving overall mental health. In comparison to medications, results achieved with IRT were maintained at long-term follow-up. Given the co-morbidity between sleep disorders and substance-dependence disorders, the additional benefits of this treatment may aid patients in overcoming their sleep issues while supporting their recovery from addiction. The flexibility of IRT therapy opens the opportunity for it to be applied to a variety of patient settings and populations. Future studies focusing on this therapy are currently paving the path for the incorporation of virtual technology into its delivery to further accommodate the patient's comfort needs.

Key Words: Imagery rehearsal therapy(IRT); Nightmares; Substance Use Disorder population; Post-Traumatic Stress Disorder

1. Introduction

Sleep disturbances have long been recognized as both a symptom and cause of substance-dependence disorders. The bi-directional relationship that exists between addiction and sleep disturbances highlights the need to investigate how the treatment of one illness may impact the progression of underlying disorders. Given the increased occurrence of abuse and PTSD among the substance dependence population **[4, 9, 10, 12, 14, 20-22, 25]**, it is likely that trauma-related symptoms such as nightmares, anxiety-provoking dreams, and difficulty staying asleep may be contributing to a large portion of the sleep disturbances exhibited among patients with addictions.

Among the PTSD population, 71%-96% of sufferers report disturbing dreams highlighting nightmares as one of the most common symptoms of the disorder **[30]**. The resulting sleep deprivation has been correlated with adverse effects on mood, memory, physical healing, and stress levels **[29]**, each potentially preventing the successful resolution of trauma and addiction symptoms. The co-morbidity between addiction and PTSD symptoms indicates that nightmare treatment may provide an avenue through which patients could regain the cognitive faculties necessary to remain on their path of recovery **[12]**. In recent years, Imagery Rehearsal Therapy has emerged as the leading evidence-based therapy to address nightmares and improve sleep quality **[16]**.

2. Nightmares

Nightmares are characterized as disturbing dreams that could present themes related to failure, accidents, injury, death as well as other fear-inducing topics. Nightmares are often vivid and cause the sufferer to awaken in an anxiety-induced state. This

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increase in sympathetic arousal may involve an accelerated heart rate, elevated blood pressure and sweating [26]. The resulting sleep fragmentation and deprivation could prompt the individual to self-medicate or avoid sleep, each of which may aggravate the intensity of the nightmares [18]. These dreams could occur independently or under the umbrella of a psychological disorder such as PTSD, depression, anxiety, and schizophrenia [28]. Repeated occurrences of nightmares have been correlated with exacerbation of these psychopathologies [19] as well as disruption of daily functioning leading to lack of energy, difficulties concentrating, and poor academic performance [11]. Successful treatment of nightmares has been demonstrated to enhance sleep quality and improve functioning after awakening. Unfortunately, nightmares remain largely untreated. Although over 70% of patients in psychiatric samples experience nightmares, less than a third of patients are aware that their condition is treatable. Moreover, it is rare for sleep centers to offer nightmare screenings and most patients do not report their nightmares to health-care providers [11].

Some authors have described drug dreams and nightmares as a signal of drug craving persistence in time. Patients who reported drug dreams, may present a stronger drug craving, of which the higher mesolimbic-mesocortical dopamine tone is the neurobiological correlate. The association between the greater limbic DA tone and the occurrence of drug dreams appears consistent with the results of clinico-anatomical studies of dreaming on the crucial role of the mesolimbic-mesocortical dopamine system in the instigation of dream [5, 6].

3. IRT description

Current non-pharmacological treatments to trauma-related nightmares include eye-movement desensitization and reprocessing, hypnosis, lucid dreaming and Imagery Rehearsal Therapy (IRT) [16]. Of these approaches, IRT is supported by the best available empirical evidence and is thus considered a Level A approach for nightmare disorder [3].

In controlled treatment studies, IRT has been demonstrated to decrease nightmare frequency and PTSD severity as well as improve sleep quality and daytime anxiety [3, 11, 16]. IRT has also been found to decrease the number of awakenings caused by nightmares as well as distraction the following day. IRT is defined as a cognitive-behavioral technique in which participants are asked to write down the content of their nightmare and change the storyline to a positive one. This scenario is rehearsed 10 to 20 minutes a day until the participants experience less anxiety-provoking dreams [3].

Prior to the application of IRT, the therapist may choose to engage the patient in cognitive restructuring sessions to remedy any maladaptive beliefs that may inadvertently reinforce the occurrence of their nightmares. The first component consists of sessions that educate subjects to view nightmares as a learned sleep disorder alike insomnia. This helps to place the focus on the effects of poor sleep quality instead of the patients' trauma. During this time, patients discuss the possibility of their dreams serving as an emotional response to traumatic events that could be facilitating their ability to recall meaningful details of the experience and make necessary lifestyle changes to avoid similar events. During these sessions, subjects reflect on the possible consequences of eliminating nightmares. They examine their beliefs regarding the processing of difficult emotions such as anxiety and depression, and the manner in which symptoms may present in the body in the absence of such dreams. They also reflect on the belief that nightmares could present as trauma that has been "stuck" on their mind. These sessions set the stage for participants to view their nightmare disorder as a phenomenon that is separate from their trauma and can be successfully targeted with sleep therapy. These shifts in perception may aid in minimizing any possible resistance to the treatment, in this way ensuring that patients experience the full results of IRT. This discussion also provides the opportunity for researchers to present evidence-based research that demonstrates how mental health generally improves after treatment [16].

During the second component, patients are led through a discussion of imagery techniques. They are educated to see daytime imagery as a natural part of mental functioning that may affect the content of their dreams at night. Patients with imagery deficiencies or who readily imagine unpleasant stimuli are provided with special techniques to prevent anxiety upon encountering these difficulties. These may include breathing deeply and exhaling the image away, acknowledging the unpleasant image and choosing to imagine a more positive image and maintaining the feet grounded on the floor while focusing on the environment. During these meetings, patients are guided to see pleasant imagery as a process that most individuals employ prior to falling asleep. They are asked to practice the skill daily to facilitate their upcoming IRT sessions [16].

As the treatment begins, the focus shifts to ensuring the patient is at ease in the psychotherapeutic environment and feels well-prepared with grounding strategies to minimize their anxiety. The patient's nightmares are discussed as the therapist provides suggestions as to how to rescript the content. At each meeting, the therapist reviews the client's progress to determine if there is improvement in the quality of their dreams. The therapist provides revisions to

Table 1. Suggested guidelines for IRT therapeutic sessions

Session 1: Introduce patients to the therapeutic environment and provide an overview of the IRT process. Discuss evidence-based research that supports the application of IRT and its impact on mental health. Provide psychoeducation on the etiology of nightmares and its relation to sleep disorders. Encourage patients to discuss their beliefs about nightmares. Emphasize that future sessions will shift the attention from the traumatic content of nightmares to promoting the experience of a more positive dream.
Session 2: Introduce patients to imagery techniques. Review the role of imagery techniques in mental-functioning and dream content. Ask patients to practice imagery by providing a list of suggested objects or situations to imagine. Provide special imagery techniques to patients with imagery difficulties. Ask patients to practice imagery techniques daily for approximately five to ten minutes.
Session 3: Examine the role of the "nightmare sufferer". Encourage patients to describe how nightmares have affected their life and reflect on how their experience may change after treatment. Instruct patients to utilize imagery to imagine a new identity that does not experience these dreams. Discuss how rehearsing this new identity may ease their transition into treatment. Ask patients to incorporate the image of their new identity into their imagery practice.
Session 4: Obtain a history of the patients' difficulties with sleeping and nightmares. Ask the patient to choose a nightmare to modify and write down the plot. Prompt patients to brainstorm positive alterations to their dream. Provide advice as to how to rescript the content of the dream. Ask patients to reflect on how they usually feel after experiencing a nightmare. Discuss de-arousal and grounding strategies to utilize upon waking from a nightmare. Distribute pamphlets or digital media to facilitate patients with practicing meditation, progressive-muscle relaxation and breathing techniques.
Session 5: Review the patients' progress with their imagery and relaxation practice. Give advice as to how to improve their experiences. Review the patients' modified dream content and revise the plot as necessary. Ask patients to utilize imagery to rehearse their dream content for ten to twenty minutes daily at home. Remind patients that imagery works best in an environment that is quiet and free of distractions.
Session 6: Review the patients' experience with rehearsing the dream. Ask patients to reflect on the effects of imagery on their dream content. Provide additional revisions to the script as necessary. Discuss obstacles that may have arisen during the treatment practice. Brainstorm possible solutions to these obstacles with the patients. Ask patients to continue their imagery practice.
Session 7: Review the patients' progress with the treatment. Encourage patients to make any additional modifications to their script if necessary. Ask patients to reflect on possible stressors that may prevent their continued participation in the treatment. Summarize the results of the therapy.

the script as necessary. Recommended guidelines for conducting these sessions are provided in **Table 1 [7]**.

4. Discussion

The connection between sleep disturbances and substance disorders is one that is progressively gaining consideration within the field of psychiatry. The various effects of sleep quality on mental and physical health suggests a pathway that could facilitate patients in overcoming their addictions and retaining their recovery. The impact of substances on sleep health is one that should be noted, as it in turn can feedback to influence the patient's withdrawal. For example, substances such as alcohol, marijuana, nicotine, cocaine and caffeine have been demonstrated to influence the intricate neural networks involved in sleep maintenance. These effects contribute to alterations in neurotransmitters such as GABA, orexin and dopamine that may promote the development of insomnia and sleep apnea among other disorders **[1]**. Such alterations may impair brain regions associated with wakefulness such as the locus coerulus and the raphe nuclei thus prolonging cognitive dysfunction and aggravating stress triggers underlying drug cravings **[31]**. Additionally, the sleep disorder could arise during the process of drug detoxication. Disorders such as sleep insomnia have been shown to arise during opiate and cocaine withdrawal, pointing to the importance of underlining these symptoms as a vital component of the patient's recovery plan **[1]**.

Sleep disorders may arise through a variety of reasons including medical conditions such as heart failure, stroke and asthma as well as psychiatric conditions such as depression and anxiety **[2]**. Even in the absence of drug usage at the onset of the sleep disorder, the afflicted individual may self-medicate their symptoms with substances such as alcohol **[18]**. These behaviors could serve as a risk factor for the development of an addiction that may exacerbate the underlying symptoms.

Nightmares are perhaps one of the most overlooked symptoms of sleep disorders. These dreams have been found to be associated with increased awakenings during the night as well as intensified symptoms of distress. Nightmares are common in substance dependence populations that have endured significant trauma prior or during their addiction. While there are multiple approaches to treating nightmares, the majority have not been supported by sufficient evidence. Moreover, therapies such as lucid dreaming, desensitization and exposure therapy have

demonstrated trauma symptoms that remained the same or worsened due to exposing patients to triggering stimuli during sessions **[11, 27]**.

Of these treatments, Imagery Rehearsal Therapy has demonstrated substantial results in decreasing nightmare frequency and improving overall mental health. The therapy involves asking patients to write the plot of their nightmares as a script, revise the script to a more positive one, and rehearse it until sleep quality improves. While the method is comparatively straightforward in its application, there are possible obstacles that are worth addressing to ensure the patients receive the best outcome. Prior to starting therapy, patients may have become accustomed to these dreams to the extent that a "nightmare sufferer" identity is created. This identity revolves around the belief that their condition is untreatable. Over time, it can integrate into their sense of self such that patients could experience anxiety at the thought of living a life without these dreams. Similar to the IRT process itself, patients could utilize imagery to rehearse a new identity and ease the transition to new behavioral patterns. In addition, it is suggested for patients to choose a nightmare that has little emotional intensity as they are learning the IRT technique. This reduces exposure to traumatic stimuli as they gain confidence in their abilities to confront more frightening dreams. During the therapy sessions, it is important to remind patients that nightmares often share common themes. Therefore, it is many times sufficient to work on a couple of nightmares at a time and allow the shared elements of the dreams to remedy themselves **[16]**.

Among the pharmacological approaches to nightmares, Prazosin has demonstrated significant reductions in trauma-associated dreams during placebo-controlled studies **[3]**. Although the medication is generally well tolerated, patients have reported a reemergence of nightmare symptoms once treatment was discontinued **[17]**. In comparison, results achieved with IRT were maintained at long-term follow-up **[15, 28]**.

While Imagery Rehearsal Therapy has demonstrated its efficiency in improving dream quality, its most long-standing benefits extend beyond the realm of sleep disorders. The nature of the technique equips patients with vital tools to allow them to build the foundation for a healthy lifestyle. This opens the window for IRT to be considered for a wide variety of patient populations that suffer from nightmares. Given the co-morbidity between sleep disorders and substance-dependence disorders, the additional benefits of this treatment may aid patients in overcoming their sleep issues while supporting their recovery from addiction. For example, the IRT technique involves the patient's continued motivation and participation, both of which provide patients with feelings of accomplishment as they take on active roles in the treatment process. The therapist may choose to create meetings that are more interactive with the use of worksheets, pamphlets and digital media. Such tangible materials could facilitate the patient through the scripting procedure and provide guidance for practicing relaxation techniques **[28]**. These meetings enhance the patient's self-efficacy as they engage their critical thinking skills to brainstorm possible conflict solutions to embed into their scripts **[16]**. This feeling of empowerment has been demonstrated to be associated with an increased sense of self-worth. This encourages the patient to feel in control of making informed decisions regarding their physical and mental health **[8]**.

Moreover, the therapy connects patients with the mind's inherent ability to visualize and manipulate images. As the patient strengthens this skill, it is often only necessary to work with a few dreams at a time. The practice awakens a latent healing system such that other similarly themed dreams are positively changed **[16]**. Among the substance dependence population, the use of imagery could have enduring advantages. Studies have examined the impact of vivid imagery prior to athletes' performance. Such data suggests that imagery provides the direction and incentive to overcome obstacles that may arise during goal formation. According to the Elaborate Intrusion theory, the image generates a host of cognitive activity that could support the individual in developing healthy skills and disengaging from dysfunctional habits **[23]**. The current development of Functional Imagery Training hopes to combine brief motivational interviewing with imagery. The treatment shows promise in helping patients to self-motivate by visualizing previous successes during their battle with addiction and imagining detailed images to map their future actions **[13]**.

One of the most notable features of IRT is its intrinsic flexibility and cost-effectiveness. The treatment offers therapists the option to apply it within self-help or group environments depending on the patient's comfort needs **[16]**. The duration of the therapy can be varied as well as the materials the therapist chooses to incorporate into the technique. This allows the provider to utilize a creative and personalized approach in treating each individual patient. With the advent of new technology, the versatility of IRT is only expected to increase. Recent studies have examined the use of virtual reality in facilitating patients' abilities to rehearse dream scripts. This technology permits patients with imagery-generation difficulties to alter nightmare-like images to less-threatening ones and rehearse their scripts in an immersive environment **[24]**.

5. Conclusion

In the current substance-dependence population, patients exhibit considerable co-morbidities with sleep disorders. The bridging of the two fields is an exciting notion that could inspire health-care providers with an array of new treatment options. Through the application of methods such as Imagery Rehearsal Therapy, patients will be exposed to an approach that is non-threatening and palatable. This therapy reconnects patients with the body's natural ability to use imagery as a method to map and achieve their goals. The benefits of solidifying this skill extend beyond the therapy sessions. Patients will realize their abilities to heal their illness while gaining confidence in reaching their desired ambitions. The treatment provides patients with the opportunity to create long-lasting changes to their mind's chemistry as they avoid the potential side effects of pharmacological medication such as Prazosin. As they participate in IRT, they will discover and refine personal skills that will empower them to tackle life-challenges and take self-directed steps towards their greatest potential.

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Problem Tree Force Field analysis of injection of agonist opioid medications and benzodiazepines in North Macedonia

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Summary

Background: The aim of this paper is to analyse the roots and effects of injection of agonist opioid medication (AOM) and benzodiazepines by many patients participating in an agonist opioid treatment (AOT) programme and the factors involved both for and against the proposed change for solving this problem. **Methods**: For this purpose, we used Problem Tree Force Field analysis. "Problem Tree" was used to identify the focal problem and the associated causes and effects with the aim of identifying solutions to the problem by mapping out the anatomy of these causes and their effects. By rephrasing each of the problems into desirable outcomes, root causes and consequences are turned into solutions. Goals for change were then set in the "Force Field Analysis" to identify the factors and subsequent pressures for and against the proposed change. **Results**: The analysis showed that the black market near the AOT service and the opportunity to sell take home therapy providing both financing and "borrowed therapy" with "interest", aggravating poverty, unemployment, non-integration into the community, lack of social support, incoherent harm reduction interventions, exchange of injection equipment in front of the service, lack of education of out-reach workers and lack of staff are just some of the reasons for abuse and diversion of the AOM. This leads to a poor treatment outcome with the resulting consequences for patient health, staff, and the environment and which contributes to violence and stigma making recovery unlikely. Drivers and resistors are also analysed, which help in visualizing the possibilities for achieving the proposed change and to determine which decisions and actions are needed and available. **Conclusions**: This tool shows the reality and helps to find solutions. New formulations of AOM can be one of the solutions to the diversion and abuse of AOM.

Key Words: Abuse; Diversion; New Formulation of AOM

1. Introduction

Although the effectiveness of agonist opioid treatment (AOT) has been proven by many studies **[8, 10, 16, 18, 23]**, there is concern about the possibility of risks of abuse and diversion of drugs to the black market **[1-3, 22]**. The reasons for selling agonist opioid medications (AOM) by patients in AOT programmes on the black market are different, such as that of providing money for living necessities or, according to one study **[7]**, deeper major motives for selling prescribed drugs such as to raise funds to buy other, preferred, drugs and/or to pay for a private prescription. Some of the buyers on the black market can be patients who once sold their therapy and became destabilised and started injecting opioids together with benzodiazepines, so they need more therapy than prescribed, i.e., they want to supplement their therapy. Prices on the black market vary, but of course you get less when you sell, and you need more when you buy. Republic of North Macedonia faces many challenges in treatment responses that are complicated by abuse and diversion of AOM, lack of resources **[11]** and incoherent or unrelated activities. According to the data of the 2017 bio-behavioural study, people who are injecting drugs most commonly have inject-

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ed methadone in combination with diazepam (60.0%; CI95%=51.6-71.3%). Additionally, 22.0% of people who are injecting drugs had injected methadone only in the last month [20]. In AOT programmes the situation is similar and most people who inject drugs inject methadone, which is for oral use, in combination with benzodiazepines [19]. Rarely does a patient only inject methadone. This situation is worrying and requires an analysis of the situation that contributes to this to find a strategy that will improve it. The aim of this paper is to analyse the roots and effects of the injection of AOM and benzodiazepines by many patients on an AOT programme and the factors for and against the proposed change for solving this problem.

2. Methods

For this propose we used Problem Tree force field analysis [17]. The Problem Tree was used to identify the focal problem and the associated causes and consequences. The Problem Tree is a tool for situational analysis of a specified problem. It was used with the aim to identify solutions to the problem by mapping out the anatomy of root causes and effects associated with an identified problem. Problem Tree was used to develop an Objectives Tree by rephrasing each of the problems into positive desirable outcomes. It enables one to turn root causes and consequences into solutions, and to identify key points of influence. The established objectives were translated into objectives for change. Objectives for change then were used in the Force Field Analysis. Force Field Analysis uses the outcome established under the Objectives Tree to identify the factors and subsequent pressures for and against the proposed change.

3. Results

Injecting of AOM and benzodiazepines by many patients on an AOT programme was identified as a specific problem for analysis in North Macedonia. From mapping out the anatomy of the root causes associated with injection of AOM and benzodiazepines with the Problem Tree tool several root causes have emerged. Poverty among patients, unemployment, non-integration into the community, and lack of social support pushes patients to sell their AOT medications to provide finances for travel, food, clothing, housing or financial refer effects. The presence of the black market in front the AOT service and the opportunity to sell "take home therapy" on the black market together with patients' poverty are among the root causes. In addition, the opportunity to "borrow" therapy with "interest" on the back market is listed as a cause, i.e., for each borrowed therapy two therapies, or a certain amount of money that rises with interest, would be charged. Incoherent harm reduction intervention, exchange of injection equipment in front of the service facility (more supply than exchange) and lack of education among the CSO's out-reach workers who give misinformation to patients such as that they have been on AOT for too long, which encourages patients to reduce or even try to stop therapy, are among other root causes. In addition, lack of staff is seen as another root cause for diversion and abuse of the AOM. A small number of unprotected, mainly female staff suffer aggression from patients if attempts are made to provide supervised administration of the AOM. These root causes lead to an inadequate dose of AOM which then leads to the injection of AOM with benzodiazepines, and which is the main problem in a large number of patients.

On the other hand, the effects of the injecting AOM with benzodiazepines causes a vicious circle, i.e. leading to insufficient duration of the therapy – less than 24 hours –, the need for more frequent use and a larger quantity of AOM (methadone), buying methadone on the black market, aggression and violence towards those patients who own methadone or many selling on the black market, high levels of stress for patients, increasingly low prospects for recovery and poor response to treatment. Patients with poor treatment response and who owe money or methadone to the black market are aggressive and violent towards the staff in order to take a larger quantity of methadone and take-home therapy which then leads to higher stress for the staff and resulting eventually in a lack of staff due to the risks of working in unsafe and unhealthy conditions because no one wants to work in unsafe and unhealthy conditions.

Unstable patients, suffering and shortages of staff, dirty environments with used needles and syringes and incidental injuries to employees and visitors with used needles left on the ground all increase the stigma towards people who use drugs, AOT programmes, drug treatment facilities and staff. Related to this stigma, dissatisfied residents from the neighbourhood want the service facility moved from their municipality because nobody wants to live in an unsafe and unhealthy environment.

Other effects of injecting AOM and benzodiazepines are manifested as patients' health consequences with a high percentage of hepatitis C, specifically 72% according to the data of the 2017 bio-behavioural study [20]. Also indicated were increased cases of thrombophlebitis, inflammations, ulcerations, skin infections, and other somatic consequences such as endocarditis, thromboembolism, febrile conditions, bacteraemia, sepsis, and mortality.

Another consequence of the main problem, namely that of injecting AOM and benzodiazepines resulting in poor treatment outcomes and harm reduction, are overdoses of persons near the service facility for which insufficient staff either administer an opioid

antagonist or call an ambulance which further adds to the stress on staff personnel. Loss of productivity, health expenses, costs of cleaning up unsafely discarded injection equipment and dealing with related injuries as well as disability and premature deaths are all consequences of the burden posed by the main problem and which further contribute to poor treatment outcomes and harm reduction within the programme (**Table 1**).

The desired result within the Objective Tree was to reduce the injection of methadone and benzodiazepines by patients on AOM resulting in a better treatment outcome; less cases of C and B hepatitis, other infections, overdoses, and mortality; safer service for patients and staff; a safe clinical environment; a reduced level of dissatisfaction in the neighbourhood; a decrease in stigma; attraction and recruitment of staff to treatment centres and reduced health expenses. With Force Field Analysis which uses the outcomes established under the Objectives Tree as a guide, several drivers and resistors were identified for proposed change. Identified resistors were: the black market; existing organisational structures; financial implications; legislation and anxieties regarding coherent harm reduction activities such as consumption rooms, and not competent/uneducated CSO's outreach workers as unintended resistors. The identified drivers were: staff from treatment service; the Ministry of Health; CSO's executive management; patients/parents; the neighbourhood community and public sector; the municipality where the service is located and the pharmaceutical industry with new depot formulations of the AOT programme which can prevent abuse and diversion of the therapy. Drivers and resistors were also analysed, and the highest rated drivers were the staff working with AOM as well as AOM depot preparations, while the highest rated resistance was found to be in the black market. Other factors pertaining to resistance are much less influential according to the author (**Table 2**).

4. Discussion

Selling their therapy because of the social challenges which patients face as well as borrowing therapy with interest leads to below standard and in-

Table 1. Problem Tree Analysis

Effects:
1. Inadequate dose of AOM and insufficient duration of methadone therapy
2. Need for more frequent use and larger quantity of methadone
3. Borrowing AOM (methadone) from the black market
4. Aggression and violence towards patients who own AOM or money to the black market
5. Increased stress for patients, unlikely recovery, and poor response to treatment
6. Aggression and violence from patients towards the staff in order to take larger quantity of AOM
7. Increased stress for the staff and lack of staff
8. Unsanitary environment with needles and syringes and incidental injuries with needles
9. Stigma towards people who use drugs, AOT, drug treatment facilities and staff
10. Dissatisfied residents from the the surrounding neighbourhood who want to move the service facility from their municipality
11. High percentage of hepatitis C and other other negative health consequences
12. Overdoses of persons near the service facility
13. Health expenses and premature deaths
14. Costs of cleaning up unsafe discarded injection equipment and dealing with related injuries
Focal Problem
Upstream or Root causes:
1. Black markets with AOM, drugs, benzodiazepines-ampoules, in front of the AOT services.
2. Opportunity to sell "take home therapy" at the black market to provide finance for travel, food, clothing, housing, or financial support for other needs.
3. Poverty among patients, unemployment, non-integration into the community, lack of social support for patients.
4. Opportunity to "borrow therapy"at the black market where, for each borrowed therapy two therapies are owed or, alternatively, a certain amount of money, with interest, is to be returned
5. Incoherent harm reduction intervention, exchange of injection equipment in front of the service facility and lack of education of the CSO's out-reach workers who give misinformation to the patients about duration of AOT.
6. A small number of unprotected, mainly female staff suffer aggression from patients if attempts are made to provide supervision while taking AOM

Table 2. Force Field Analysis

Drivers	Score	Objectives	Resistors	Score
Staff from treatment service	5	Reduce injecting of methadone and benzodiazepines by patients on AOT.	Black Market	5
Ministry of Health	3	Better treatment outcome (less C, B hepatitis, other infections, overdoses, mortality).	Existing organisational structures	3
CSO's executive management	2	Safe service for patients and staff.	Financial implications	3
Patients/Parents	2	Clinic	Legislation and fears (regarding consumption rooms)	3
Neighbourhoods (public)	2	Reduced dissatisfaction of neighborhood Decreased stigma	Incompetent, uneducated CSO outreach workers	2
The municipality were the service is located	2	Reduced health expenses		
Extended-release buprenorphine	5			

adequate dosing because patients do not take the prescribed standard dose which is usually 100-120 mg for methadone, and 16 mg for buprenorphine **[14]**, so as to return some of the therapy to the black market where they owe debt. Misinformation from CSO's out-reach workers about duration of AOT leads to self-reduction of therapy by patients with the consequences of non-standard dosing once again. Some individuals receiving under pressure to divert due to the threat of violence and in order to cope with that pressure they then exert pressure, threats and violence on staff which leads to a lack shortage of staff in the services for AOT **[11]** and the absence of supervised delivery of therapy leading to inadequate dosing as well.

Patients receiving sub-optimal doses of OMT either diverted or misused their opioid medication at some stage, which may have diminished the benefits they would have gained from therapy. They may have self-medicated either by misusing their medication via the parenteral route to increase bioavailability, or by using other medications or illicit drugs **[5, 6, 13, 15]**.

Incoherent harm reduction policy where the facilities for activities most difficult to carry out are missing, such as consumption rooms **[12]**, and the exchange of needles and syringes taking place in the open, in full view of the neighbourhood and public citizens, causes damage and stigma to AOT services when these activities are taking place in their immediate vicinity. Unsanitary environment and the risks posed by the used needles on the ground motivate the citizens to seek the closure and removal of the AOT services from their neighbourhood, which does nothing to solve the problem but just moves it elsewhere or disperses it to many other places.

When patients take home methadone or buprenorphine the risk of abuse, diversion, sale or supplying it to another person is possible, but with the new buprenorphine formula there is no need for such take home therapies because buprenorphine is given in the form of injection weekly, monthly or even for 6 months periods in the form of an implant **[9]**.This avoids the stigma, the threat to the reputation of treatment services, the compromised public acceptance of AOT **[4]**, overcrowding in front of the services and any dissatisfaction within the neighbourhood which dislikes the services being so near them. However, depot preparations are much more effective in preventing diversion and misuse of AOM **[21, 24]** than measures such as supervised drinking, patient registries, professional licensing, and other similar measures which are unable to fight the black market.

5. Conclusion

The Force Field Analysis sheds light on the reality and the possibilities for implementing the proposed change and to reach a conclusion as to which actions are needed and possible. This analysis helps to guide treatment policy and practice. Luck of staff, poor outcome, the quality of life of both patients and staff can be improved with extended-release buprenorphine as an additional treatment option if it is available in the country. Stigma, violence, and aggression can therefore be decreased as well over time.

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Authors declared 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.

Note

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