A STUDY OF COMORBIDITY BETWEEN OPIOID ADDICTION AND MAJOR DEPRESSIVE DISORDERS IN EL HUSSEIN UNIVERSITY HOSPITAL

By

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ABSTRACT

Background: Comorbidity of substance abuse and mental disorders is a major issue in psychiatry that notably associates with more severe symptoms, longer illness duration, and higher service utilization. Therefore, identifying key clusters of comorbidity represent important steps toward improving mental health care.

Objective: To assess the relationship between opioid addiction and the comorbidity of major depressive disorders, explore the characteristics of patients using different types of opioids, and assessment of the severity of addiction and depression.

Patients and Methods: The sample consisted of 229 patients diagnosed with opioid use disorder according to DSM -IV, and their ages ranged from 15-50 years old. They were subjected to a semi-structured interview sheet, a structured clinical interview for DSM-IV (SCID-I) to diagnose psychiatric disorders, the addiction severity index scale, urine drug screening, and Hamilton depression scale.

Results: The most common psychiatric comorbidity was major depressive disorder representing 32.8% of the total sample. Patients with comorbid major depressive disorder had statistically significant higher history of suicidal attempt, history of overdose, number of treatment trials, and previous admission for addiction problems as compared with patients with no comorbidity. The prevalence of MDD comorbidity was 55% among tramadol users, 26.2% in heroin users, and 18.8% in Nalbuphine users.

Conclusion: There was a significant relation between opioids addiction and major depressive disorder, between the severity of addiction and psychiatric comorbidity.

Keywords: Opioid abuse, Comorbidity, Depression.

INTRODUCTION

According to *Bewley-Taylor and Nougier (2018)*, 53 million people worldwide had used opioids in the previous year; these estimates are 56% higher than the previous estimated. Opioid dependence involves a cluster of symptoms, including impaired control over use, prominence of use of a substance in a person's life, and physiological symptoms such as tolerance and withdrawal. Major depressive

disorder (MDD) is one of the most prevalent mental disorders worldwide, as well as one of the most disabling. According to the global burden of disease study, depression is the fourth leading cause of disability and it is expected to be the second by 2020 *(Gutiérrez-Rojas et al., 2020)*. Opioid dependence, have more than four times the expected risk of mortality, with life expectancies reduced by more than nine years compared to national norms *(Hayes et al., 2011)*.

A 2016 study in the Annals of family medicine found that about 10 % of people prescribed opioids developed after a month of taking drugs. The longer they use opioids, the greater risk of developing depression become *(Scherrer et al., 2016)*. The relationship between opioids and depression is close, complex, and multifaceted; depression is associated with endogenous opioid dysfunction and depression associated with opioid abuse *(Sullivan, 2018)*. Patients with major depressive disorder who experienced social rejection shows reduced endogenous opioid release in the brain regions that regulate mood and motivation and show slower emotional recovery compared to healthy controls *(Hsu et al., 2015)*.

The present work aimed to assess the relationship between opioid addiction and the comorbidity of major depressive disorders, explore the characteristics of patients using different types of opioids, and assessment of the severity of addiction and depression.

PATIENTS AND METHODS

This study was a cross-sectional study using a convenience sample of patients diagnosed with opioid dependency. All patients were selected from the outpatient clinic and inpatient department at psychiatry and addiction unit at Al-Hussein university hospital. Selected patients were fulfilling the diagnosis of opioid dependency according to DSM-IV. The time frame of the study was between March 2017 and September 2018.

Inclusion criteria: Age: 15-50 years, both sexes, and patients fulfilling the diagnosis of opioid addiction according to DSM-IV.

Exclusion criteria for the patients: Patients using opioids for medical indication and under medical supervision (e.g. cancer), and patients with below-average intelligence (e.g. Mental retardation).

The requirements of Al-Azhar University Ethics Committee were fulfilled, and informed oral consent has been obtained from every patient before participating in the study. Using a semi-structured interview, starting with socio demographic characteristics of the patients, family history and substance use pattern, type, onset, reason, relation to symptoms severity or relief, relapse rates, and treatment trials if any.

Structured Clinical Interview for DSM-IV (SCID I): The semi-structured diagnostic interview begins with a section on demographic information and clinical background. Then, there were 7 diagnostic modules, focused on different diagnostic groups: mood, psychotic, substance abuse, anxiety, somatoform, eating, and adjustment disorders. It was considered the standard interview to verify the diagnosis in clinical trials and was extensively used in other forms of psychiatric research. Hamilton Depression

Scale (HAM-D) scale was used for the assessment of depressive status as each of the nine DSM IV items has a score in the test. This scale was used for patients with the diagnosis of major depressive disorder. The 17 points scale was used with the following cut-off points: 0-11 for minor or no depression (mild), 12-18 for less than major depression (moderate), 19-24 for major depression (severe), and 25 or =more for severe depression (very severe). The Addiction severity index (ASI) version 5 was based on a structured interview that provides extensive information on substance use and psychosocial functioning in seven domains: medical, employment, alcohol abuse, drug abuse, legal, family/social and psychological. ASI was a reliable valid tool for the assessment of drug use and has shown excellent capabilities for characterizing severe addiction problems with multiple areas of dysfunction. Urine screening for drugs to confirm the diagnosis, urine drug screening was done for tramadol HCL, opioids, benzodiazepines, and cannabinoids.

Statistical analysis:

Demographic characteristics, psychiatric assessment and addiction history of the patients is summarized using the mean, standard deviation, median and quartiles for numeric data and frequency distribution for categorical data. Comparison of categorical data between patients with major depressive disorder and patients without co-morbidity was done using chi-square test and Fisher's exact test, while comparison of numerical data was done using independent t-test and Mann Whitney U test. All analyses were done using SPSS version 26 (USA). A p-value of 0.05 or less was considered significant.

RESULTS

The study sample consisted of 229 patients who were opioid-addicted. 61.1% of them were interviewed at outpatient settings while the others were inpatients. Female patients were only 32 representing 14% of the study group. The highest prevalence of MDD comorbidity was observed among tramadol users (55.0%), followed by heroin (26.2%), and the least was in Nalbuphine users (18.8%). The mean age was 28.2 (SD=8.6) years. 47.6% of the patients were living in rural areas, while 52.4% were living in urban areas. Patients had different levels of education: Non-educated were 18.3%, those with primary education were 30.1%, secondary education were 29.3%, while those with university degree were 22.3%. The employment status was: unemployed 14.4%, worker 25.8%, student 21.0%, employee 18.8%, business owner 15.3% and housewives 4.8%. 45.4% of the participants said that they had an irregular occupation in the last 3 years and 44.1% said that they are receiving financial support from their families. Almost half of the participants were single 48.5%, the married patients are 38.0%, and the divorced are 10.9% while the widows are 2.8%. The highest percentages of participants (56.8%) are from the middle social class, 21.8% are from the high class and 21.4% are from the low class. There was a positive family history for psychiatric disorders in 37.1% of patients and a positive family history of substance abuse in 41.5% of them. 56% of the patients have psychiatric co-morbidities **(Figure 1)**.
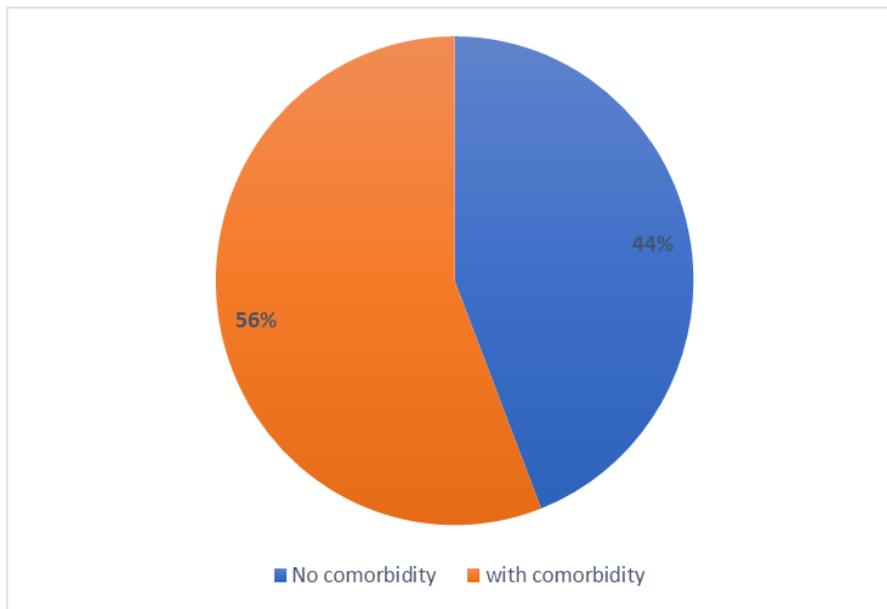
Figure (1):   **Prevalence of psychiatric co-morbidities among opioid addicts**

The most common psychiatric comorbidity was the major depressive disorder, found in 75 patients representing 32.8% of the total sample, followed by anxiety disorder in 7% of patients. Other comorbidities were found at lower frequencies **(Figure 2)**.
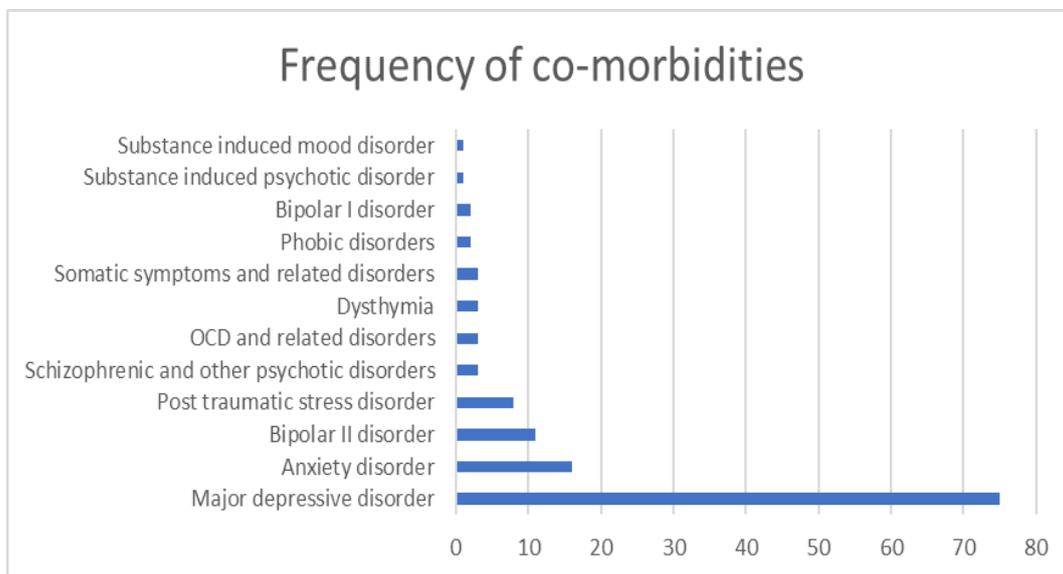
Figure (2):   **Psychiatric co-morbidities distribution in the sample**

The addiction severity index was assessed in all patients and was given a score from 1 to 5 according to severity. In the medical, employment family and social aspects the most frequent category was moderate followed by mild with few cases in the extreme category. For the psychiatric aspect, the most common category was the severe 44.5%, and for the legal aspect, most cases (66.8%) had no legal consequences **(Table 1)**.

Table (1): Scores for the addiction severity index of the patients

Addiction severity index	Medical N (%)	Employment N (%)	Drug N (%)	Family N (%)	Social N (%)	Psychiatric N (%)	Legal N (%)
No	44 (19.2)	38 (16.6)	19 (8.3)	30 (13.1)	38 (16.6)	21 (9.2)	153 (66.8)
Mild	55 (24.0)	46 (20.1)	51 (22.3)	45 (19.7)	46 (20.1)	34 (14.8)	21 (9.2)
Moderate	69 (30.1)	84 (36.7)	83 (36.2)	90 (39.3)	87 (38.0)	58 (25.3)	34 (14.8)
Severe	57 (24.9)	53 (23.1)	63 (27.5)	57 (24.9)	52 (22.7)	102 (44.5)	19 (8.3)
Extreme	4 (1.7)	8 (3.5)	13 (5.7)	7 (3.1)	6 (2.6)	14 (6.1)	2 (0.9)

Comparison of the sociodemographic factors between patients with major depressive disorder and patients with no co-morbidity showed that the only significant difference was observed in the educational level **x** A higher percentage of patients with MDD (35%) are not educated as compared to the percentage of those who are not educated in patients with no co-morbidity (9%). **(Figure 2)**.

Table (2): Comparison of patients with MDD versus of opioid addicts with no comorbidity in Sociodemographic characteristics

Parameters	Comorbidity	No comorbidity N=101	MDD N=75	Total	P-value
Sex	Male	91 (90.1)	61 (81.3)	152 (86.4)	0.094
	Female	10 (9.9)	14 (18.7)	24 (13.6)	
Residence	Rural	47 (46.5)	37 (49.3)	84 (47.7)	0.713
	Urban	54 (53.5)	38 (50.7)	92 (52.3)	
Education	Not educated	9 (8.9)	26 (34.7)	35 (19.9)	**< 0.001**
	primary	32 (31.7)	16 (21.3)	48 (27.3)	
	secondary	35 (34.7)	18 (24.0)	53 (30.1)	
	university	25 (24.8)	15 (20.0)	40 (22.7)	
Employment	unemployed	10 (9.9%)	13 (17.3)	23 (13.1)	0.564
	worker	28 (27.7)	17 (22.7)	45 (25.6)	
	student	20 (19.8)	17 (22.7)	37 (21.0)	
	employee	24 (23.8)	12 (16.0)	36 (20.5)	
	business owner	15 (14.9)	12 (16.0)	27 (15.3)	
	house wife	4 (4.0)	4 (5.3)	8 (4.5)	
Occupation in last 3 years	regular	62 (61.4)	37 (49.3)	99 (56.3)	0.111
	irregular	39 (38.6)	38 (50.7)	77 (43.8)	
Family support patient financially	Yes	51 (50.5)	33 (44.0)	84 (47.7)	0.394
	No	50 (49.5)	42 (56.0)	92 (52.3)	
Marital status	Single	49 (48.5)	34 (45.3)	83 (47.2)	0.058
	Married	42 (41.6)	23 (30.7)	65 (36.9)	
	Divorced	9 (8.9)	14 (18.7)	23 (13.1)	
	Widow	1 (1.0)	4 (5.3)	5 (2.8)	
Social class	Low	17 (16.8)	20 (26.7)	37 (21.0)	0.188
	middle	64 (63.4)	38 (50.7)	102 (58.0)	
	High	20 (19.8)	17 (22.7)	37 (21.0)	
Family history of psychiatric disorder	No	65 (64.4)	47 (62.7)	112 (63.6)	0.818
	Yes	36 (35.6)	28 (37.3)	64 (36.4)	
Family history of SUD	No	57 (57)	43 (57)	100 (57)	0.905
	Yes	44 (44)	32 (43)	76 (43)	

There was no difference between the two groups regarding age, age of onset or duration of addiction. The difference was observed in number of treatment trials without abstinence, abstinence more than one month, previous admission for addiction problems, suicidal attempt and history of over dose. Patients with MDD had higher numbers and significant statistical differences in these items A higher percentage of patients with MDD comorbidity had a history of suicidal attempts, 36% versus 12% in the group with no co-morbidity. A higher percentage of patients with MDD comorbidity had a history of overdose, 43% versus 28% in the group with no co-morbidity. (**Table 3**).

Table (3): Comparison of patients with MDD versus of opioid addicts with no comorbidity in clinical data

		N	Mean	SD	P-value
Age	No comorbidity	101	27.9	8.8	0.622
	MDD	74	28.6	8.4	
Age of onset	No comorbidity	101	22.9	7.9	0.475
	MDD	74	22.1	6	
Duration	No comorbidity	101	4.1	2.3	0.2
	MDD	74	4.7	3.7	
Number of treatment trials without abstinence	No comorbidity	101	1.6	1.5	<0.001
	MDD	74	2.6	1.9	
Abstinence more than one month	No comorbidity	101	0.6	0.7	<0.001
	MDD	74	1.1	0.8	
Previous admission for addiction problems	No comorbidity	101	0.3	0.6	<0.001
	MDD	74	0.9	0.9	
Suicidal attempts	No comorbidity, N(%)	12 (12)			0.001
	MDD , N(%)	27 (36)			
History of overdose	No comorbidity, N(%)	28 (28)			0.033
	MDD, N(%)	32 (43)			

Comparison of ASI between MDD and no co-morbidity groups was done using Mann Whitney U test as shown in table 4. The only ASI component that showed a significant difference between the two groups is the psychiatric component which is more severe in the MDD group (**Table 4**).

Table (4): Comparison of ASI between patients with MDD and no co-morbidity groups

	No comorbidity			MDD			P-value
ASI	Median	Q1	Q3	Median	Q1	Q3	
Employment	3.00	2.00	3.00	3.00	2.00	4.00	0.880
Medical	3.00	2.00	3.00	3.00	2.00	4.00	0.769
Drug	3.00	2.00	4.00	3.00	2.00	4.00	0.397
Family	3.00	2.00	3.00	3.00	2.00	4.00	0.468
Social	3.00	2.00	3.00	3.00	2.00	4.00	0.274
Psychiatric	3.00	2.00	4.00	4.00	3.00	4.00	<0.001
Legal	1.00	1.00	2.00	1.00	1.00	3.00	0.053

DISCUSSION

Clinical and epidemiological studies have revealed a high rate of comorbid psychiatric disorders in opioid-dependent patients including those with prescription opioid dependence *(Gros et al., 2013* and *Pereiro et al., 2013)*. The age of our sample was almost similar to the results of other Egyptian studies on substance use, in which the mean age of participants was 30.2 *(El-Sheikh et al., 2017)*, 29.1 *(Shahin et al., 2018)*, and 26-35 years old *(Hamdi et al., 2016)*. 47.6% of the patients were living in rural areas, while 52.4% were living in urban areas. Female patients were only 14% of the study group. This was in agreement with the results of an Egyptian study carried out by *El-Sawy et al., (2010)* who studied possible gender differences in the ways of first exposure to drugs, the risks of abuse, and the pattern of drug dependence. They found that males start drug abuse earlier in age than females with a longer duration of addiction. The same result was concluded also by the Egyptian National Addiction Survey which showed that substance abuse was more common in males than in females *(Hamdi et al., 2011)*. Both studies related this under-representation to the possibility of lower rates of substance abuse among women in the general population and/or higher barriers to accessing treatment stemming from the social stigma towards substance users, especially women. Patients had different levels of education as non-educated were 18.3%, those with primary education were 30.7%, secondary education 29.8%, while those with a university degree were 23.7%. This was consistent with *Hamdi et al. (2016)* that associated substance usage with lower education, as 34.2% of those who had a primary school education, 25.1% of illiterate persons, 23.2% who completed preparatory school education and 22.8% who can barely read and write were substance users. Our result was inconsistence with *Teixidó-Companó et al. (2017)* who showed that higher educational level was associated with substance used, 66.1% of males had secondary education, 20% of males had a university education, and 13.9% of males had primary or lower education. This difference may be attributed to the difference in education status in both countries. The employment status was as follows: unemployed 14.4%, worker 25.8%, student 21.0%, employee 18.8%, business owner 15.3% and housewives 4.8%. 45.4% of the participants said that they had an irregular occupation in the last 3 years and 44.1% said that they are receiving financial support from their families .This result was consistent with that of *Hamdi et al. (2011)* that found substance abuse was more common among those who are manual workers. It was also consistent with the result reached by *Abd el Wahab et al., (2018)* who found that 53% of opioid dependents had irregular work history in the past three years, and 45 % received financial help/support from their families. This may be explained by the public attitude towards drug addicts that they are rejected and are not being hired/ employed by work owners *(Silverman et al., 2016)*. A problem that is related to the associated stigma, the doubt of treatment affectivity and policy support, and the functional impairment and performance decline of the addicts in general. Almost half of the participants were single 48.5%, the married patients are 38.0%, the divorced

are 10.9% while the widows are 2.8%. This result is consistent with international results as in a survey on hard drug users in *Nepal (2010)*, where close results were observed showing that the percentage of never-married (64%), the married (30%) and 4.1% were divorced. The highest percentages of participants (56.8%) are from the middle social class, 21.8% are from high class and 21.4% are from the low class. The result isn't consistent with other studies *(El-Sheikh et al., 2017)* that stated that 66.7% of substance-dependent men were divorced. There was a positive family history for psychiatric disorders in 37.1% of patients and a positive family history of substance abuse in 41.5% of them. Those findings are consistent with *Asaad et al. (2014)* who found that (46%) of subjects of their sample had a positive family history of substance abuse. The highest percentage of patients in the study group were addicted on tramadol (55.0%), followed by heroin (26.2%) and the least was Nalbuphine addicted by 18.8% of the sample. These results are supported by the results of The Fund Prevention and Treatment of Addiction and Abuse in Egypt in the first six months in 2013 that showed that Tramadol was at the top of narcotic substances in Egypt.

The most common psychiatric comorbidity in our was the major depressive disorder, found in 75 patients representing 32.8% of the total sample, followed by anxiety disorder in 7% of patients It is also consistent with *Gross et al. (2013)* who found that 47.1% of opioid dependents were diagnosed with a comorbid mood disorder and also consisted with *Sordo et al. (2012)* who suggest that the lifetime risk of a comorbid diagnosis with depression can

range from 38% to 56% amongst those with an opioid addiction. Understanding the bidirectional relationship between opioid addiction and depression and the factors contributing to the comorbidity can provide a critical insight into preventing, diagnosing, and identifying risk factors associated with the development of the disorders. However, factors underlying the overrepresentation of mood disorders among opioid addicts remain unclear *(Veilleux et al., 2010)*. Depressed individuals use opioid to alleviate negative mood *(Koob, 2013)*, and it is the subsequent improvement in mood state that increases the reinforcement value of drug use.

Comparison of ASI between MDD and no co-morbidity groups was done using Mann Whitney U test. The only ASI component that showed significant difference between the two groups is the psychiatric component which is more severe in the MDD group These findings were consistent with the findings reported by other researchers who suggested that SUD would exacerbate depressive disorder, make the subject more withdrawn, more depressed, might lead to increased number of episodes of depression, and at the same time SUD might lead to chronicity of major depressive disorder (MDD) and with *Erfan et al. (2010)*, 93.3% of comorbid depression and substance use disorder were within the "very severe" and "severe" categories of psychiatric status impairment.

Comparison of the sociodemographic factors between patients with major depressive disorder and patients with no co-morbidity showed that the only

significant difference was observed in the educational level higher percentage of patients with MDD (35%) are not educated as compared to the percentage of those who are not educated in the patients with no co-morbidity (9%). It was consistent with *Mohamed et al. (2013)* that found in the study dual diagnosis and psychosocial correlates in substance abuse that patients with comorbid substance use disorder and psychiatric disorder had increase percent in illiterates than compared with participants without comorbidity.

The difference was observed in number of treatment trials without abstinence, abstinence more than one month, previous admission for addiction problems, suicidal attempt and history of overdose. Patients with MDD had higher numbers and significant statistical differences in these items. This result is consistent with a lot of studies. Depression increases the risk of relapse after withdrawal *(Goesling et al., 2015*; *Sullivan, 2016*; and *Feingold et al., 2018)*, and, simultaneously, the severity and duration of depressive symptoms in MDD are greater if people who suffer from MDD also suffer addiction *(Scherrer et al., 2016)*, and also consisted with *Erfan et al. (2010)* that found 86% of his study group with comorbid depression and substance use disorder had suicidal attempt compared to 43.3% of the control group patients.

CONCLUSION

The most common psychiatric comorbidity was major depressive disorder representing 32,8% of total sample. The highest percentages of patients using opioid were addicted on tramadol, followed by heroin, and the least was Nalbuphine addicted. There was a significant relation between the severity of addiction and psychiatric comorbidity.

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دراسة التصاحب المرضي بين إدمان المواد الأفيونية ومرض الاكتئاب الجسيم في مستشفى الحسين الجامعي

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خلفيـــــة البحـــــث: الاعـــتلال المشـــترك لتعـــاطي المخـــدرات والاضـــطرابات النفســية هـــي قضــية رئيســية فـــي الطــب النفســي، لأن الاعـــتلال المشـــترك يـــؤدي إلـــي زيـــادة حـــدة الاعـــراض، وزيـــادة فتـــرة المـــرض، واســتخدام أعلـــى للخـــدمات. لـــذلك، فـــإن تحديـــد الصـــفات الرئيســية للاعـــتلال المشـــترك يمثـــل خطوات مهمة نحو تحسين رعاية الصحة النفسية.

الهـــدف مـــن البحـــث: تقيـــيم العلاقـــة بـــين إدمـــان المـــواد الأفيونيـــة والاعـــتلال المشـــترك لاضـــطراب الاكتئـــاب الجســيم، واستكشـــاف خصـــائص المرضـــى الـــذين يســتخدمون أنواعًـــا مختلفـــة مـــن المـــواد الأفيونيـــة، وتقيـــيم شـــدة الإدمـــان والاكتئاب.

المرضـــى وطـــرق البحـــث: تكونـــت العينـــة مـــن 229 مريضًـــا تـــم تشخيصـــهم باضـــطراب تعـــاطي المـــواد الأفيونيـــة وفقًـــا لـــلدليل التشخيصـــي الإحصـــائي الرابـــع المعـــدل للاضـــطرابات النفســية ، وتتـــراوح أعمـــارهم بـــين 15-50 عامًـــا. وخضـــعوا لمـــا يلـــي مقابلـــة ســريرية منظمـــة لتشـــخيص الاضطرابات النفسية، مقيـــاس مؤشـــر شـــدة الإدمـــان، فحـــص مخـــدرات عـــن طريـــق البـــول، ومقياس هاملتون للاكتئاب.

نتـــائج البحـــث: كـــان الاعـــتلال النفســي الأكثـــر شـــيوعا لـــدي مـــدمني المـــواد الأفيونيـــه هـــو اضـــطراب الاكتئـــاب الجســيم الـــذي يمثـــل 32.8٪ مـــن إجمـــالي العينـــة. كـــان لـــدى المرضـــى الـــذين يعـــانون مـــن الاكتئـــاب الجســيم دلالات

إحصــائية هامــه مــن حيــث زيــادة محــاولات الانتحــار، وتعرضــهم للتســمم بجرعــات زائــده مــن الأفيونــات، ومحــاولات اكثــر للعــلاج، وزيــاده بعــدد مــرات الحجــز بمستشــفيات عــلاج الإدمــان مقارنــة بالمرضــى الــذين لا يعانون من اعتلال مشترك.

الاستنتاج: أظهــرت نتيجــة الدراســة وجــود علاقــة قويــه بــين إدمــان المــواد الأفيونية واضطراب الاكتئاب الجسيم، بين شدة الإدمان وشدة الاكتئاب.

الكلمات الدالة: إدمان المواد الأفيونية، التصاحب المرضي، الاكتئاب.