ORIGINAL ARTICLE

DOI: 10.4274/hamidiyemedj.galenos.2022.29290

Hamidiye Med J 2022;3(3):191-196

Effect of Different Psychoactive Substances on Hematological Parameters of Dependents in Türkiye

Türkiye'de Farklı Psikoaktif Maddelerin Bağımlılarda Hematolojik Parametreler Üzerine Etkisi

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ABSTRACT

Background: In this study we aimed to define the effects of psychoactive substances on hematological parameters.

Materials and Methods: Three hundred-nineteen dependents, 82 control subjects were involved in this study. Diagnostic and statistical manual of mental disorders-IV criteria is used to determine patient group. We obtained the complete blood count and toxicology parameters in all cases and controls. Study participants with additional chronic diseases are not included.

Results: Changes in hematological parameters according to the urine toxicology results were evaluated for statistical significance. There were statistically significant differences in red blood cell (RBC), mean corpuscular value (MCV), hemoglobin (HGB), hematocrit (HCT), medians between dependent group and control group ($p<0.05$). We found a statistically significant difference in RBC, MCV, HGB and HCT levels between the opium dependent group and control group ($p<0.05$). The difference was also significant between HGB, neutrophil (NEU)%, MCH, RDW levels of cannabinoid dependent group compared to control group ($p<0.05$). We found a statistically significant difference in monocyte%, lymphocyte%, NEU%, eosinophil% levels between benzodiazepine group and control group ($p<0.05$). Whereas in ethyl glucuronide group significant difference observed only in neutrophile count ($p<0.05$).

Conclusion: Monitoring hematological parameters in psychoactive substance dependents can be used to confirm need for special treatment programs.

Keywords: Hematological parameters, psychoactive substance, urine toxicology

ÖZ

Amaç: Bu çalışmada farklı psikoaktif maddelerin hematolojik parametreler üzerine etkisini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada, 319 bağımlı ve 82 kontrol yer almıştır. Hasta grubu ruhsal bozuklukların tanısal ve istatistiksel el kitabı-5 kriterlerine göre belirlenmiştir. Tüm hastalar ve kontroller hematolojik parametreler açısından ve idrar toksikoloji parametreleri açısından test edilmiştir. Diyabet, kanser, metabolik bozukluk ve benzeri tanısı olan olgular ve kontroller çalışma dışı bırakılmıştır.

Bulgular: İdrar toksikoloji sonuçları ve hematolojik parametreler arasındaki ilişki istatistiksel olarak değerlendirilmiştir. Kırmızı kan hücresi (RBC), ortalama korpüsküler değer (MCV), hemoglobin (HGB), hematokrit (HCT) değerleri açısından, bağımlı grubu ve kontrol grubu medyanları arasında istatistiksel olarak anlamlı fark bulunmuştur ($p<0,05$). Bu çalışmada, opiat bağımlı grup ve kontrol grubu arasında RBC, MCV, HGB, HCT düzeyleri açısından istatisksel anlamlı fark bulunmuştur ($p<0,05$). Cannabinoid bağımlılarının yer aldığı grupta, HGB, nötrofil (NEU)%, MCH, RDW düzeylerinde istatistiksel olarak kontrol grubuna göre farklılık görülmüştür ($p<0,05$). Benzodiazepin kullanıcıları ile kontrol grubu karşılaştırıldığında, monosit%, lenfosit%, NEU%, eozinofilik% düzeylerinde istatistiksel olarak anlamlı fark görülmüştür ($p<0,05$). Etil glucuronid grubunda ise, sadece NEU sayısında kontrol grubu ile karşılaştırıldığında istatistiksel anlamda fark izlenmiştir ($p<0,05$).

Sonuç: Psikoaktif madde bağımlılarında, yoğun takip ve tedavi programlarına olan ihtiyacın belirlenmesinde, hematolojik parametreler yol gösterici olabilir.

Anahtar Kelimeler: Hematolojik parametreler, psikoaktif madde, idrar toksikoloji

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Received: 26.07.2022 **Accepted:** 27.10.2022

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Introduction

The effects of psychoactive substances on different neuroendocrine and physiologic functions have been reported (1). Many psychoactive drugs have a high addiction potential by usually affecting the central nervous system (CNS). In clinical practice psychoactive drugs also used for therapeutic purposes like anesthesia and analgesia to relieve pain (2).

The psychoactive substance abuse appears to be a world-wide problem. Since large majority of addicts have used different types of psychoactive drugs concurrently defining the effects of only one type of substance is difficult (3).

The immunomodulatory effects of psychoactive substances have been demonstrated in animal and human studies (4,5,6). Changes in the immunologic functions of dependents, return to normal if withdrawal period was longer than 2 years (7). Previous reports on animals showed that not all opioids have similar immunosuppressive effects. Morphine can alter natural and adaptive immune functions but buprenorphine produces strong analgesia without compromising immune function (8).

It has been demonstrated that psychoactive substance dependence like opium can be associated with increases in erythrocyte sedimentation rate, white cell count, monocytes (MON) and platelets (9). Richards et al. (10) suggested that amphetamines may be related with idiopathic leukocytosis. This may be attributable to the unique pharmacologic, neuroendocrine and immunomodulatory properties of these substances.

Previous studies have documented the effect of different psychoactive drugs on many chronic diseases like; coronary artery disease, diabetes mellitus, thyroid disorders (11,12,13). Cocaine may likely to increase the risk of acute myocardial infarction by altering blood viscosity due to cocaine induced erythrocytosis and increase in Von Willebrant factor (14,15). Cocaine use is associated with elevated hemoglobin (HGB) and hematocrit (HCT) levels. Cocaine abuse induces constriction of blood vessels in the spleen and cause altered hematologic parameters. Contribution of bone marrow to cocaine induced erythrocytosis may be negligible due to the lack of reticulocytosis (16).

Urine analysis is the usually preferred method for monitoring psychoactive substance abuse. The concentrations of psychoactive substances are higher in urine compared to blood. The frequency of testing and definition of reference intervals important to determine psychoactive substance abuse (17).

There is not enough data in previous literature about effects of psychoactive drugs on hematologic parameters (18).

In this study we aimed to evaluate and compare, the effects of different psychoactive drugs on hematological parameters.

Material and Methods

This study was conducted at the Erenköy Mental Health and Neurology Training and Research Hospital. The hospital has an AMATEM Clinic for treatment of substance use disorders. In our study we evaluated retrospectively the data of 319 patients and 82 controls admitted to hospital. Diagnostic and statistical manual of mental disorders-IV criteria is used to determine the patient group. Hospital admissions for routine control with negative urine toxicology results and without any accompanying chronic disease selected as control group.

Before starting treatment first urine and blood samples are taken from every patient who admitted to the AMATEM Clinic. Study participants with additional chronic diseases like diabetes, cancer, metabolic disorders etc. are excluded from the study. In urine samples; heroin, cannabinoids, cocaine, benzodiazepines, opiates, buprenorphine, amphetamines, ecstasy and ethyl glucuronide levels determined by HITACHI Automatic Analyzer (hitachi high-technologies corporation, roche diagnostics) using an enzyme immunoassay method (Microgenics CEDIA, Fremont, CA, USA for urine toxicology). Hematological values [red blood cell (RBC), white blood cell (WBC), HGB, HCT, Mean corpuscular values (MCV, MCH, MCHC), red blood cell distribution width (RDW), platelets (PLT), mean platelet volume (MPV), platecrit (PCT), platelet distribution width (PDW), monocyte% (MON%), lymphocyte% (LYM%), neutrophil% (NEU%), basophile% (BAS%) eosinophil% (EOS%), monocyte (MON), lymohocyte (LYM), neutrophil (NEU), basophile (BAS) and eosinophil (EOS) count] were tested by Cell-Dyn 3700 Hematology analyzers (Abott Diagnostics).

The study was approved by the Local Ethical Committee of Erenköy Mental Health and Neurology Training and Research Hospital (no: 12/1, date: 03.02.2014).

Statistical Analysis

We used SPSS IBM 20.0 software for statistical analysis. We accepted a p-value less than 0.05 ($p<0.05$) as statistically significant.

Results

Totally 319 patients (312 men and 7 women) and 82 controls (77 men and 5 women) were included in the study. The median age of participants of study group were 26 (23-34) and 27.5 (22-37) years (Table 1).

We evaluated the changes in hematologic parameters of the substance dependent group and control groups (Table 2). There were statistically significant differences between RBC, MCV, HGB, HCT medians in the patient and control groups (p<0.05).

Table 1. Demographic data of subjects involved in this study

Subjects	Dependent group	Control group
	n (%)	n (%)
Gender		
Male	312 (97.8)	77 (93.9)
Female	7 (2.2)	5 (6.1)
Age		
<20	33 (10.3)	16 (19.5)
≥20 - <30	177 (55.5)	30 (36.6)
≥30 - <40	61 (19.1)	23 (28.0)
≥40	48 (15.0)	13 (15.9)
Age (median quartiles)	26 (23-34)	27.5 (22-37)

A total of 92 of the patients tested positive for only opium (cut-off 300 ng/mL). We compared the hematological parameters of opium dependent group and control groups (Table 3). When the data evaluated RBC, MCV, HGB and HCT levels of the opium dependent group was found significantly lower than control group (p<0.05).

We found 9 of the patients test results positive for only cannabinoids (cut-off 50 ng/mL). The difference was significant for HGB, NEU%, MCH, RDW parameters of the cannabinoid dependent group compared to control group (p>0.05).

The consumption of only benzodiazepine was detected in 13 of all addicts (cut-off >300 ng/mL). Compared to control group, benzodiazepine dependents showed significant differences in MON%, LYM%, NEU%, EOS% levels (p<0.05).

Positive test results for only ethyl glucuronide observed in 7 patients (cut-off >500 ng/mL). We found significant difference in only NEU count of ethyl glucuronide group compared to control group (p<0.05).

Table 2. Comparison of hematological parameters in dependent and control groups

Tests	Dependent group median (quartiles)*	Control group median (quartiles)*	p
PLT (K/µ)	217 (256-298)	243 (216-278)	0.312
RBC (M/µL)	4.8 (4.51-5.10)	4.95 (4.70-5.20)	0.010
WBC (K/µ)	8.10 (6.8-9.4)	8.10 (6.41-9.17)	0.609
MCV (fL)	90.4 (88.3-92.8)	91.7 (89.28-94.10)	0.014
HGB (g/dL)	14.4 (13.5-15.1)	15.0 (14.20-15.53)	<0.001
HCT (%)	43.2 (40.7-45.8)	45.10 (42.90-47.65)	<0.001
MON%	6.7 (5.12-8.16)	6.56 (5.36-8.30)	0.996
LYM%	33.5 (26.6-39.9)	31.95 (27.35-37.23)	0.213
NEU%	55.2 (48.8-63.9)	58.20 (52.0-62.98)	0.164
BAS %	0.8 (0.5-1.05)	0.80 (0.45-1.20)	0.589
EOS%	2.3 (1.4-3.45)	1.88 (1.15-2.81)	0.088
MON (K/µ)	0.5 (0.4-0.7)	0.50 (0.34-0.70)	0.745
LYM (K/µ)	2.61 (2.0-3.2)	2.60 (2.06-2.90)	0.249
NEU (K/µ)	4.5 (3.3-5.62)	4.56 (3.49-5.32)	0.647
BAS (K/µ)	0.03 (0.10-0.10)	0.074 (0.038-0.100)	0.615
EOS (K/µ)	0.2 (0.1-0.3)	0.136 (0.100-0.201)	0.110
MCH (pg)	30.0 (28.9-31.0)	30.15 (29.3-31.3)	0.144
MCHC (g/dL)	33.2 (32.7-33.6)	33.0 (32.5-33.7)	0.215
RDW (%)	14.9 (14.2-15.7)	14.90 (14.47-15.50)	0.667
PDW (%)	17.3 (16.8-18.0)	17.50 (16.68-18.0)	0.659
MPV (%)	7.6 (6.9-8.4)	7.54 (6.99-8.46)	0.711
PCT (%)	0.200 (0.188-0.217)	0.20 (0.18-0.21)	0.168

* 25 and 75 percentiles,
p-value less than 0.05 (p<0.05) were accepted as statistically significant, PLT: Platelets, RBC: Red blood cell, WBC: White blood cell, MCV: Mean corpuscular values, HGB: Hemoglobin, HCT: Hematocrit, MON: Monocyte, LYM: Lymphocyte, NEU: Neutrophil, BAS: Basophile, EOS: Eosinophil, RDW: Red blood cell distribution width, PDW: Platelet distribution width, PCT: Platecrit

Table 3. Comparison of hematology parameters in all groups according to medians

	Control group (n=82) median (quartiles)	Opiate group (n=92) median (quartiles)	Cannabinoid group (n=9) median (quartiles)	Benzodiazepine group (n=13) median (quartiles)	Glucuronide group (n=8) median (quartiles)
PLT (K/µ)	243 (216-278)	259 (223-310)	228 (191-258)	249 (196-286)	268 (201-286)
RBC (M/µL)	4.95 (4.70-5.20)	4.8 (4.50-5.08)*	5.00 (4.85-5.25)	5.00 (4.65-5.30)	4.65 (4.05-5.10)
WBC (K/µ)	8.10 (6.41-9.17)	8.15 (7.07-9.48)	8.30 (6.20-8.65)	8.40 (7.30-9.15)	6.45 (6.23-7.63)
MCV (fL)	91.7 (89.28-94.10)	90.0 (86.52-91.78)**	95.10 (91.55-96.45)	93.20 (90.75-94.90)	94.40 (90.85-96.75)
HGB (g/dL)	15.0 (14.20-15.53)	14.4 (13.53-14.90)***	15.90 (14.75-16.70)*	15.00 (14.35-16.45)	14.90 (13.05-15.48)
BAS %	0.80 (0.45-1.20)	0.80 (0.51-1.00)	1.10 (0.75-1.20)	0.90 (0.75-1.10)	1.05 (0.83-1.58)
MON %	6.56 (5.36-8.30)	6.75 (5.60-7.98)	8.40 (5.95-9.90)	7.30 (6.95-9.75)*	7.90 (6.80-8.95)
LYM %	31.95 (27.35-37.23)	34.00 (27.55-38.78)	39.60 (27.10-45.90)	35.20 (33.60-39.55)*	38.95 (28.48-42.13)
NEU %	58.20 (52.0-62.98)	54.95 (50.03-63.03)	45.80 (40.20-60.40)*	51.90 (49.00-54.55)**	46.50 (44.30-61.18)
MON (K/µ)	0.50 (0.34-0.70)	0.56 (0.415-0.70)	0.60 (0.50-0.85)	0.70 (0.55-0.80)**	0.50 (0.50-0.68)
LYM (K/µ)	2.60 (2.06-2.90)	2.77 (2.01-3.30)	3.00 (2.10-3.45)	2.90 (2.65-3.45)*	2.30 (2.13-2.58)
PDW (%)	17.50 (16.68-18.0)	17.30 (16.80-17.98)	18.00 (16.95-18.55)	17.70 (16.95-18.30)	17.30 (16.28-18.0)
MPV (%)	7.54 (6.99-8.46)	7.30 (6.80-8.28)	7.50 (6.80-8.10)	7.60 (6.60-8.50)	7.55 (6.13-8.75)
PCT (%)	0.20 (0.18-0.21)	0.20 (0.20-0.20)	0.20 (0.15-0.20)	0.20 (0.12-0.20)	0.20 (0.13-0.20)
MCHC (g/dL)	33.0 (32.5-33.7)	33.40 (32.90-33.90)**	33.20 (33.05-33.95)	33.30 (32.55-33.55)	33.15 (33.0-33.88)
MCH (pg)	30.15 (29.3-31.3)	30.05 (28.65-30.98)	31.70 (30.40-32.75)*	30.70 (29.95-31.25)	31.75 (29.50-32.10)
EOS %	1.88 (1.15-2.81)	2.35 (1.50-3.38)	2.90 (1.10-4.45)	3.40 (1.88-3.95)*	2.35 (1.60-4.68)
BAS (K/µ)	0.074 (0.038-0.100)	0.100 (0.047-0.100)	0.10 (0.10-0.10)	0.10 (0.10-0.10)*	0.10 (0.10-0.10)
EOS (K/µ)	0.136 (0.100-0.201)	0.200 (0.100-0.300)	0.200 (0.050-0.350)	0.300 (0.200-0.350)*	0.15 (0.10-0.28)
NEU (K/µ)	4.56 (3.49-5.32)	4.55 (3.33-5.68)	3.60 (2.55-5.05)	4.40 (3.50-5.05)	2.90 (2.50-4.65)*
RDW (%)	14.90 (14.47-15.50)	14.70 (14.00-15.58)	14.40 (13.55-14.95)*	14.80 (13.95-15.05)	14.60 (14.05-16.45)
HCT (%)	45.10 (42.90-47.65)	43.0 (40.60-44.68)***	46.40 (44.60-50.25)	45.90 (42.85-50.05)	44.55 (39.23-45.80)

Significantly different from control group *p<0.05, **p<0.01, ***p<0.001, PLT: Platelets, RBC: Red blood cell, WBC: White blood cell, MCV: Mean corpuscular values, HGB: Hemoglobin, HCT: Hematocrit, MON: Monocyte, LYM: Lymphocyte, NEU: Neutrophil, BAS: Basophile, EOS: Eosinophil, RDW: Red blood cell distribution width, PDW: Platelet distribution width, PCT: Platecrit

Since other patients test results were positive for more than one drug they were not included in statistical analysis.

Discussion

Clinical studies have demonstrated that psychoactive substance addiction could affect immune function. Previous studies have shown that some psychoactive substances can influence the function of natural killer cells, T-cells, neutrophil, macrophages and affect the secretion of immunoregulatory cytokines (4,5,6) Stress also causes impairments in immune system functions (19). Psychoactive substance dependence is a long-lived stress condition. Both substance abuse and stress induced by these psychoactive drugs together cause the reinforcement of immunosuppressive effects (20). Decreased LYM numbers and changes in cytokine levels in psychoactive substance dependents would influence susceptibility to infection, inflammation or cancer (21). Studies have documented that both natural and endogenous cannabinoid compounds regulate resistance to bacterial, viral and protozoan infections (22). Increased rate of infections in addicts could be related with immunosuppression. Findings of previous studies showed that number of LYM decreased significantly in some opium and heroin addicts (23).

Deficits in immune function in psychoactive substance addicts might be due to direct effect of psychoactive drugs on receptors of immune cells or by a central mechanism through receptors in the CNS. The effects of some psychoactive substances on CNS could be related with hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. HPA axis activation cause release of glucocorticoids and increase peripheral release of dopamine, epinephrine and norepinephrine from the adrenal medulla. Norepinephrine and glucocorticoids act as immunosuppressors by decreasing the number of LYMs (24,25,26).

Psychoactive substance users usually spend their money for drugs and have increased risk of poor nutrition (27). Some hematology parameters are affected by nutritional factors (28). Psychoactive substances are known to cause hematological abnormalities. Finding of previous studies showed that addiction caused changes in RBC counts, HCT and HGB values in human (29). The current study demonstrated that RBC, MCV, HCT, HGB levels significantly decreased in opium dependent group ($p<0.05$). Since psychoactive substance users usually came from lower socio-economic groups, nutritional problems may contribute to appearance of anemia in dependents. It is important to increase awareness about different physiologic complications associated with psychoactive substance use.

Opioids exert their effects through specific receptors and four different opioid receptor was previously defined (30). A new opioid receptor named as zeta with different functions have been identified. This receptor usually named as opioid growth factor receptor (OGFr) (31). Results of previous studies demonstrated that OGFr inhibits cell proliferation in normal cells and act as negative growth factor. Since OGFr receptors are also located in kidney tissue (32), there might be a negative regulatory action through erythropoetin production to decrease cellular proliferation on bone marrow and this may explain decreased HGB levels opioid dependents.

Previous studies reported that opioid addiction can cause pancytopenia; decreased number of erythrocytes, leucocytes and platelets by bone marrow suppression. Together with decreased RBC, WBC, LYMs, PLT, HCT, HGB levels, significantly increased EOS count reported in opioid addiction (29). In this study we didn't found statistically significant difference between WBC, PLT and EOS counts in opium dependent and control groups ($p>0.05$). We found significant increase in EOS and basophile count only in benzodiazepine dependent group ($p<0.05$). This may be due to individual differences in susceptibility.

Cannabinoids are the most typical component of marijuana plant. Oseni et al. (21) indicated that hematological values did not show a significant change in marijuana smokers compared to control group. In our study we found a significant increase in HGB and MCH levels in cannabinoid dependent group ($p<0.05$). On the other hand, neutrophil% significantly decreased compared to control group ($p<0.05$). Atwood and Mackie (33) demonstrated that two types of cannabinoid receptors are found; type one receptors mainly located in the brain and type two receptors are located in the immune system and hematopoietic cells. Cannabinoids can reduce cell mediated immune response and inflammation (33). Murikinati et al. (34) showed that stimulation of type two cannabinoid receptors decreased ischemic damage and caused a decreased number of the neutrophils in the ischemic brain.

Buprenorphine can also be abused by psychoactive substance users since these drugs are cheap and easily available. In a study carried out in buprenorphine treated mice it was shown that LYM and MON counts decreased together with severe leucopenia, NEU count increased and blood HCT levels decreased. Periodic monitoring of hematological parameters recommended in human buprenorphine abusers (35). In our study buprenorphine abusers were using concurrently more than one type of psychoactive substance so we couldn't determine the effects of buprenorphine on hematological parameters. On the other hand, in benzodiazepine group (13 of all addicts tested positive for only benzodiazepine) we found significant increase in MON, LYM, EOS, basophile count, MON%, LYM%, EOS% and a significant decrease in NEU% ($p<0.05$). Therefore, periodic monitoring of blood parameters in abusers of the drug may be important.

Heroin is a semi synthetic opioid commonly used. ElHamady HS Nabil et al. (29) demonstrated that RBC, WBC, LYM, PLT count, HCT, HGB value decreased and EOS number significantly increased in heroin dependent group compared to controls. In our study, we found a significant decrease in RBC, MCV, HGB, HCT values but other parameters not significantly changed in opium addicts compared to controls ($p>0.05$). In previous studies, both increase and decrease in LYM numbers were demonstrated (23). In our study, we excluded accompanying disorders which may contribute to changes in LYM numbers or other parameters.

Conclusion

In this study, we evaluate the potential effects of many psychoactive substances like heroin, cannabinoids, cocaine, benzodiazepine, opiate, buprenorphine, amphetamine, ecstasy, ethyl glucuronide on hematological parameters. In conclusion, we suggest that monitoring hematological parameters in psychoactive substance dependents can be used to confirm need for special treatment programs. Early detection of physiologic health problems related with substance abuse may decrease the burden over health care resources.

Acknowledgements

Profound thanks to all laboratory technicians and clinicians of the AMATEM Clinic of Erenköy Mental Health and Neurology Training and Research Hospital.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of Erenköy Mental Health and Neurology Training and Research Hospital (no: 12/1, date: 03.02.2014).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.B., Concept: D.B.Ş., Design: D.B.Ş., Data Collection or Processing: R.B., Analysis or Interpretation: D.B.Ş., Literature Search: D.B.Ş., Writing: D.B.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009;25:170-175. [Crossref]
2. Kreek MJ, Bart G, Lilly C, Laforge KS, Nielsen DA. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. Pharmacol Rev. 2005;57:1-26. [Crossref]
3. Musshoff F, Madea B. Driving under the influence of amphetamine-like drugs. J Forensic Sci. 2012;57:413-419. [Crossref]
4. Saurer TB, Carrigan KA, Ijames SG, Lysle DT. Suppression of natural killer cell activity by morphine is mediated by the nucleus accumbens shell. J Neuroimmunol. 2006;73:3-11. [Crossref]
5. Saurer TB, Ijames SG, Carrigan KA, Lysle DT. Neuroimmune mechanisms of opioid- mediated conditioned immunomodulation. Brain Behav Immun. 2008;22:89-97. [Crossref]
6. Baldwin GC, Roth MD, Tashkin DP. Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. J Neuroimmunol. 1998;15,83:133-138. [Crossref]
7. Govitrapong P, Suttitum T, Kotchabhakdi N, Uneklabh T. Alterations of immune functions in heroin addicts and heroin withdrawal subjects. J Pharmacol Exp Ther. 1998;286:883-889. [Crossref]
8. Sacerdote P. Opioids and the immune system. Palliat Med. 2006;20(Suppl 1):9-15. [Crossref]
9. Reece AS. Relative and age-dependent stimulation of soluble and cellular immunity in opiate dependence. J Addict Med. 2012;6:10-17. [Crossref]
10. Richards JR, Farias VF, Clingan CS. Association of leukocytosis with amphetamine and cocaine use. The ScientificWorldJournal. 2014;2014:207651. [Crossref]
11. Najafi M, Sheikhvatan M, Ataie-Jafari A. Effects of opium use among coronary artery disease patients in Iran. J Subst Use Misuse. 2010;45:2579-2581. [Crossref]
12. Azod L, Rashidi M, Afkhami-Ardekani M, Kiani G, Khoshkam F. Effect of opium addiction on diabetes. Am J Drug Alcohol Abuse. 2008;34:383-388. [Crossref]
13. Gozasht MH, Mohammadzadeh E, Divsalar K, Shokoohi M. The effect of opium addiction on thyroid function tests. J Diabetes Metab Disord. 2014;13:5. [Crossref]
14. Hollander JE, Hoffman RS, Burstein JL, Shih RD, Thode HC. Cocaine-associated myocardial infarction: mortality and complications. Arch Intern Med. 1995;155:1081-1086. [Crossref]
15. Arthur J, Siegel MD, Michelle B, Sholar BA, Jack H, Mendelson MD, et al. Cocaine-induced erithrocytosis and increase in von willebrant factor. Arch Intern Med. 1999;159:1925-1929. [Crossref]
16. Weber JE, Larkin GL, Boe CT, Fras A, Kalaria AS, Maio RF, et al. Effect of cocaine use on bone marrow- mediated erythropoiesis. Acad Emerg Med. 2003;10:705-708. [Crossref]
17. Taracha E, Habrat B, Chmielewska K, Baran-Furga H. Excretion profile of opiates in dependent patients in relation to route of administration and type of drug measured in urine with immunoassay. J Anal Toxicol. 2005;29:15-21. [Crossref]
18. Mami S, Eghbali M, Cheraghi J, Mami F, Salati AP, Bayaz Dasht JJ. Effect of Opium Addiction on Some Hematological Parameters in Rabbit. World Journal of Zoology. 2011;6:246-248. [Crossref]
19. Novio S, Nunez-Iglesia MJ, Freire-Garabal M. Psychoactive drugs against effects of stress in infectious and non-infectious viral diseases. Science against microbial pathogens: Communicating current research and technological advances. Formatex, Spain, 2011. [Crossref]
20. Fox HC, D'Sa C, Kimmerling A, Siedlarz KM, Tuit KL, Stowe R, et al. Immune system inflammation in cocaine dependent individuals: implications for medications development. Hum Psychopharmacol. 2012;27:156-166. [Crossref]
21. Oseni BS, Togun VA, Taimo OF. Effect of marijuana smoking on some hematological parameters of smokers. World Journal of Medical Sciences. 2006;1:82-85. [Crossref]
22. Massi P, Vaccani A, Parolaro D. Cannabinoids, immune system and cytokine network. Curr Pharm Des. 2006;12:3135-3146. [Crossref]
23. Haghpanah T, Afarinesh M, Divsalar K. A review on hematological factors in opioid- dependent people (opium and heroin) after the withdrawal period. Addict Health. 2010;2:9-16. [Crossref]
24. Vallejo R, Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. Am J Ther. 2004;11:354-365. [Crossref]
25. Budd K. The immune system and opioimmunotoxicity. Review in Analgesia. 2004;8:1-10. [Crossref]
26. Fecho K, Maslonek KA, Dykstra LA, Lysle DT. Assesment of the involvement of central nervous system and peripheral opioid receptors in the immunomodulatory effects of acute morphine treatment in rats. J Pharmacol Exp Ther. 1996;276:626-636. [Crossref]
27. Asgary S, Sarrafzadegan N, Naderi GA, Rozbehani R. Effect of opium addiction on new and traditional cardiovascular risk factors:do duration of addiction and route of administration matter? Lipids Health Dis. 2008;7:42. [Crossref]
28. Díaz-Flores Estévez JF, Díaz-Flores Estévez F, Hernández Calzadilla C, Rodríguez Rodríguez EM, Díaz Romero C, Serra-Majem L. Application of linear discriminant analysis to the biochemical and haematological differentiation of opiate addicts from healthy subjects: a case-control study. Eur J Clin Nutr. 2004;58:449-455. [Crossref]
29. ElHamady HS Nabil, Nasher T, Eddin R, AlMadi A. Some Biochemical and hematological parameters on some cases of dependence amaong Yemenies. EJHM. 2006;23:226-230. [Crossref]
30. Corbett AD, Henderson G, Mc Knight AT, Paterson SJ. 75 years of opioid research:the exciting but vain quest for the Holy Grail. Br J Pharmacol. 2006;147(Suppl 1):S153-162. [Crossref]
31. Zagan IS, Verderame MF, Mc Laughlin PJ. The biology of the opioid growth factor receptor (OGFr). Brain Res Brain Res Rev. 2002;38:351-376. [Crossref]
32. Cheng F, Mc Laughlin PJ, Verderame MF, Zagon IS. The OGF-OGFr axis utilizes the p16 INK4a and p21WAF1/CIP1 pathways to restrict normal cell proliferation. Molecular biology of the cell. Mol Biol Cell. 2008;20:319-327. [Crossref]
33. Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. Br J Pharmacol. 2010;160:467-479. [Crossref]
34. Murikinati S, Jütter E, Keinert T, Ridder DA, Muhammad S, Waibler Z, et al. Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment. FASEB J. 2010;24:788-798. [Crossref]
35. Banerjee D, Sarkar NK. Hematological changes in buprenorphine-treated mice. Folia Biol (Krakow). 1997;45:157-162. [Crossref]