Abant Tıp Dergisi

Abant Medical Journal

Abant Med J 2022;11(2):231-242, doi:10.47493/abantmedj.1120849

The Effects of Bupropion and Varenicline on Morphine Withdrawal Syndrome in Rats

Sıçanlarda Bupropion ve Vareniklinin Morfin Yoksunluğu Sendromu Üzerine Etkileri

Oruç YUNUSOĞLU [1*], Çagla KÖSE [2], Andleeb SHAHZADİ [3], Sibel ÖZYAZGAN [3], Bülent DEMİR [2], Burak ÖNAL [4], Ahmet Gökhan AKKAN [5]

[1] Department of Pharmacology, Medical Faculty of Bolu Abant Izzet Baysal University, Bolu, Türkiye

[2] Department of Medical Pharmacology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Türkiye

[3] Department of Medical Pharmacology, Medical Faculty, Istanbul Cerrahpasa University, Istanbul, Türkiye

[4] Department of Medical Pharmacology, Medical Faculty, Biruni University, Istanbul, Türkiye

[5] Department of Medical Pharmacology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye

Geliş Tarihi (*Received*): 30.05.2022 **Kabul Tarihi (*Accepted*):** 22.06.2022 **Yayın Tarihi (*Published*):** 31.08.2022

Abstract

Objective: Opioid dependence is a chronic complicated disorder characterized by relapse and remission. Chronic administration of morphine causes symptoms of physical and psychological dependence. The purpose of the present study was to investigate the effect of anti-addictive drugs such as bupropion and varenicline on morphine dependence and naloxone precipitated withdrawal syndrome in a rat model.

Materials and Methods: To assess the physical dependence of morphine, adult male Wistar rats were administered intraperitoneally (i.p.) increasing doses of morphine twice daily for 5 days, 4 hours after a single dose of morphine on day 6, and 15 minutes before subcutaneous (s.c.) naloxone (2 mg/kg, s.c.) administration to elicit withdrawal symptoms. Physical dependence was evaluated by injecting bupropion (5, 10, and 20 mg/kg, i.p.) and varenicline (0.5. 1, and 2 mg/kg, s.c.) for 15 minutes.

Results: The morphine-dependent rats more significantly demonstrated withdrawal symptoms than naive control rats. The results elucidated that administration of bupropion and varenicline during induction of morphine dependence attenuated the most of the severity of withdrawal symptoms. Co-administration of bupropion with morphine reduced withdrawal symptoms such as jumping, wet dog shaking, weight loss and total withdrawal symptoms. Co-administration of varenicline with morphine was found to be effective on withdrawal symptoms such as bupropion, but had no effect on weight loss.

Conclusion: These outcomes provide preliminary data which show that bupropion and varenicline can be used as a candidate drugs to attenuate morphine withdrawal symptoms.

Keywords: Morphine, Bupropion, Varenicline, Naloxone, Opioid Withdrawal Syndrome

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Öz

Amaç: Opioid bağımlılığı, nüks ve remisyon ile karakterize kronik ve karmaşık bir hastalıktır. Kronik morfin uygulaması, fiziksel ve psikolojik bağımlılık semptomlarına neden olur. Bu çalışmanın amacı, bupropion ve vareniklin gibi anti-bağımlılık ilaçlarının morfin bağımlılığı ve nalokson ile hızlanırılmış yoksunluk sendromu üzerindeki etkisini sıçan modelinde araştırmaktı.

Gereç ve Yöntemler: Morfine bağlı fiziksel bağımlılığı değerlendirmek için, yetişkin erkek Wistar sıçanlarına 5 gün boyunca günde iki kez artan dozlarda morfin intraperitoneal (i.p.) uygulandı. 6. günde tek doz morfin uygulamasından 4 saat sonra yoksunluk semptomlarını ortaya çıkarmak için subkutan (s.c.) nalokson (2 mg/kg, s.c.) uygulaması yapıldı. Fiziksel bağımlılık, 15 dakika süreyle intraperitoneal (i.p.) bupropion (5, 10 ve 20 mg/kg, i.p.) ve vareniklin (0,5, 1 ve 2 mg/kg, s.c) verilerek değerlendirildi.

Bulgular: Morfin gurubunda kontrol grubuna göre önemli ölçüde yoksunluk semptomları görüldü. Sonuçlar, morfin bağımlılığının indüklenmesi sırasında bupropion ve vareniklin uygulamasının, yoksunluk semptomlarının şiddetinin çoğunu azalttığını gösterdi. Bupropionun birlikte uygulanması, sıçrama, ıslak köpek silkelenmesi, kilo kaybı ve toplam yoksunluk semptomlarını azaltmıştır. Vareniklinin birlikte uygulanmasının bupropion gibi yoksunluk semptomları üzerinde etkili olduğu, ancak kilo kaybı üzerinde etkisi olmadığı saptandı.

Sonuç: Bu sonuçlar, bupropion ve vareniklinin morfininin yoksunluk semptomlarını hafifletmek için aday ilaçlar olarak kullanılabileceğine dair ön veriler sağlamaktadır.

Anahtar Kelimeler: Morfin, Bupropion, Vareniklin, Nalokson, Opioid Yoksunluk Sendromu

Atıf/Cite as: Yunusoğlu O. , Köse Ç. , Shahzadi A. , Özyazgan S. , Demir B. , Önal B. , Akkan A. G. The Effects of Bupropion and Varenicline on Morphine Withdrawal Syndrome in Rats. Abant Med J. 2022; 11(2): 231-242. doi:10.47493/abantmedj.1120849

[*]**Sorumlu Yazar (Corresponding Author):** Oruç Yunusoğlu, **e-mail**: orucfarm@gmail.com

Introduction

Substance/drug addiction is a mental disease characterized by a relapse back to continue taking the drug despite the damaging consequences (1-3). Numerous neural networks in the central nervous system including the reward pathway, stress/anti-reward pathway, and the main immune system, are implicated in the development of substance/drug dependence and relapse after withdrawal from substance/drug of abuse (1, 4-7). Substance/drug use disorder occurs as a result of long-term use of substances/drugs that contain psychological, physical, or both addictions that have the potential to create reward (pleasure) (6). Physical addiction is also associated with the formation of neuroadaptive changes in the brain at the molecular level as well as at the cellular level (1, 4, 8). These changes are responsible for the emergence of substance/drug-specific withdrawal symptoms after the cessation of the substance/drug intake (5). The severity and type of substance/drug withdrawal symptoms depend on various factors such as the type of substance/drug used for the reward (pleasure) effect, the doses of the substance/drug, the duration of substance/drug use, the age of the patient, the age at which substance/drug use was initiated, or genetic predispositions (4, 6). Psychological addiction is defined as compulsive substance/drug use to increase the feeling of reward (pleasure) (5). Specific psychological addiction syndrome in humans includes persistent and recurrent persistent obsessions, characterized by persistent pleasurable substance/drug-seeking behavior, even after years of abstinence, as well as compulsive substance/drug use despite the recognizable negative effects (2, 4, 8). Various scientific studies show that despite many social, psychological and medical projects aimed at reducing the number of substance/drug addiction cases, the number of people with opioid use disorder is increasing day by day around the world. Today, opioid addiction is considered a global public health problem (2, 4, 6). Different scientific researches show that although there are social, psychological and medical projects to reduce the cases of substance/drug addiction, the number of people who use opioids for non-purposes is increasing worldwide (1, 5). According to data from the World Health Organization prevalence study, deaths from unintended opioid use increased from 69,000 in 2014 to 118,000 in 2015 (5, 8). Maternal abuse of opioids and related withdrawal syndrome in newborns has recently reached the level of crisis.

In previous studies, it was emphasized that there is a significant connection between the nicotinergic system and the endogenous opioid system (9-11). Various scientific studies have proven that nicotinic receptors are closely related to the rewarding effect of morphine (12). Stimulation of nicotinic receptors significantly increases the levels of endogenous opioids. In similar studies, nicotine administration reduced the morphine-induced withdrawal symptoms and increased the morphine-induced analgesic effect (13, 14). Sympathetic hyperactivation occurs in morphine withdrawal (15, 16), and the resulting sympathetic hyperactivation has been shown to be associated with increased firing of noradrenergic neurons in the locus coeruleus (17, 18).

Bupropion is a synaptic dopamine and noradrenaline reuptake inhibitor (19, 20), developed primarily as an antidepressant drug (21), which also has an antagonistic effect on nAChR (19, 20). In clinical studies, bupropion has shown to reduce smoking addiction, and non-nicotine is approved by the FDA for use in the treatment of smoking addiction (19, 20, 22). In various preclinical studies, different doses of bupropion reduced the firing of noradrenergic neurons in the locus coeruleus (23, 24). Again, similar experimental studies showed that hydroxybupropion metabolite of buprapion reduced the firing of noradrenergic neurons in locus coeruleus (23, 24). It was reported that bupropion decreases whole-body norepinephrine turnover by increasing the level of 6-hydroxymelatonin (25, 26). Chronic administration of bupropion in a preclinical study reduced the rebound from morphine withdrawal symptoms in mice. There are studies showing that bupropion reduces addiction to cocaine, methamphetamine and methadone (27-31).

Varenicline is a partial agonist of nicotinic acetylcholine (nACh) receptors and is a heterocyclic compound approved by the FDA for the treatment of nicotine addiction (27-31). It passes quickly and easily to the central nervous system. Acting as a partial α4β2-nAChR agonist and a full α7-nAChR agonist, it interacts with important reward centers, the mesolimbic and mesocortical pathways (32, 33). It can cause

approximately 40-60% less dopamine release compared to nicotine (34). Since it is a partial agonist, its abuse potential is low (35), because of which it may be useful in the treatment of addictive substances such as amphetamine (36). Varenicline is considered to be a well-tolerated drug, and various experimental studies have shown that varenicline reduces alcohol consumption (37, 38). Varenicline has been reported to reduce alcohol seeking behavior and alcohol consumption in preclinical studies at various doses (39). Similarly, in another study, it has been reported to alleviate alcohol withdrawal and relapse (38, 40-42). In numerous studies, it has been shown that varenicline reduces alcohol dependence in rats, mice and humans. Also, in a recent study, varenicline reduced cannabis addiction (43).

Based on the literature findings provided above, the effect of anti-addictive drugs bupropion and varenicline on morphine withdrawal syndrome was investigated in the current study.

Materials and Methods

Experimental Animals and Laboratory

Adult Wistar albino male rats weighing 260-320 g were used in our study. The rats were housed with 4-5 in a cage. The study was carried out in an environment with a laboratory temperature of 21-23 °C and natural lighting. No water or feed restrictions were made throughout the study. Our research was approved by the Istanbul University Experimental Medicine Research Institute Experimental Animals Ethics Committee (29/12/2011) to comply with the ethical committee principles.

Drugs

Drugs were administered intraperitoneally (i.p.) by dissolving bupropion hydrochloride (5, 10, and 20 mg/kg, i.p.) morphine hydrochloride (10 mg/kg, i.p.) in physiological saline (0.9% NaCl). Varenicline tartrate was dissolved in physiological saline (0.5, 1, and 2 mg/kg) and administered subcutaneously (s.c.). The control group was given saline (0.9% NaCl) i.p. way applied. Bupropion hydrochloride and varenicline tartrate were obtained from Sigma. The drug doses used in the study were selected by taking into account similar studies that had been done before (20, 44, 45). Morphine hydrochloride was obtained from the cabinets registered in the warehouses of our Department. Solutions were prepared fresh daily and administered at room temperature.

Effects of Varenicline and Bupropion on Morphine Withdrawal Symptoms

Increasing doses of morphine (1st day 10, 2nd day 20, 3rd day 30, 4th day 40, 5th day 50 mg/kg) were applied to the experimental animals twice a day (8:00 am to 8:00 pm) for 5 days (45, 46). To elicit withdrawal symptoms, on day 6, rats were administered subcutaneous naloxone (2 mg/kg) and their withdrawal symptoms were evaluated for 15 minutes. To evaluate the effect of varenicline and bupropion on physical dependence, bupropion (0.5, 1, and 2 mg/kg) and varenicline (5, 10, and 20 mg/kg) were administered 15 minutes before the naloxone injection. The control group was given saline (i.p).

Evaluation of Withdrawal Symptoms

On the 6th day of morphine injection, rats in all groups were first weighed and 2 mg/kg naloxone was administered subcutaneously (45). To observe the withdrawal symptoms, the rats were placed in the monitoring cages alone and their withdrawal symptoms were evaluated for 15 minutes. Withdrawal symptoms included splashing, wet dog shaking, defecation, and ejaculation. Teeth grinding was graded from 1 to 10, and diarrhea and ptosis were graded from 1 to 3 by researcher who is naive to the experiment. Abnormal posture, tremor, salivation, vocalization during handling, and voiding were evaluated (45). After the evaluation, the rats were weighed again and weight loss was evaluated. Experiments were carried out between 12:00-15:00 hours.

Statistical Evaluation

The data obtained using the Graphpad statistical program was statistically evaluated by, one-way analysis of variance (ANOVA) and Bonferroni multiple comparison test were applied in group comparisons as post-hoc. P<0.05 was accepted as the significance value.

Results

Effects of Bupropion On Physical Dependence of Morphine

In the comparison of the morphine group and the control group, the withdrawal symptoms and wet dog shake symptoms were significantly higher in the morphine group (p<0.001). There was no statistical significance in the morphine+buproion (5, 10, and 20 mg/kg) groups compared to the control group (p<0.001). When the morphine+bupropion (10 and 20 mg/kg) groups were compared with the morphine group, wet dog shake was found to be significantly lower in the morphine+bupropion (10 and 20 mg/kg) groups (respectively: p<0.05; p<0.01) (Figure 1A). In the comparison of the morphine group and the control group, the wet dog symptom, which is one of the withdrawal symptoms, was significantly higher in the morphine group (p<0.001). Compared to the control group, statistical significance did not change in the wet dog sign morphine+buproion (5, 10 and 20 mg/kg) groups (p<0.001). When the morphine+bupropion (10 and 20 mg/kg) groups were compared with the morphine group, the wet dog sign, which is one of the withdrawal symptoms, was found to be significantly lower in the morphine+bupropion (10 and 20 mg/kg) groups (respectively: p<0.01; p<0.001) (Figure 1B). In the comparison of the morphine group and the control group, weight loss, which is one of the withdrawal symptoms, was significantly higher in the morphine group (p<0.001). In comparison with the control group, statistical significance did not change in the wet dog sign morphine+buproion (5, 10 and 20 mg/kg) groups (p<0.001) (Figure 1C). When the morphine+bupropion (5, 10 and 20 mg/kg) groups were compared with the morphine group, weight loss from withdrawal symptoms was found to be significantly lower in the morphine+bupropion (20 mg/kg) groups (p<0.01 1C). When the control group and morphine group were compared, the total withdrawal score was found to be significantly higher in the morphine group (p<0.01) (Figure 1D). Compared to the morphine group, the total withdrawal score was found to be significantly lower in the morphine+20 mg/kg bupropion group (p<0.05) (Figure 1D).

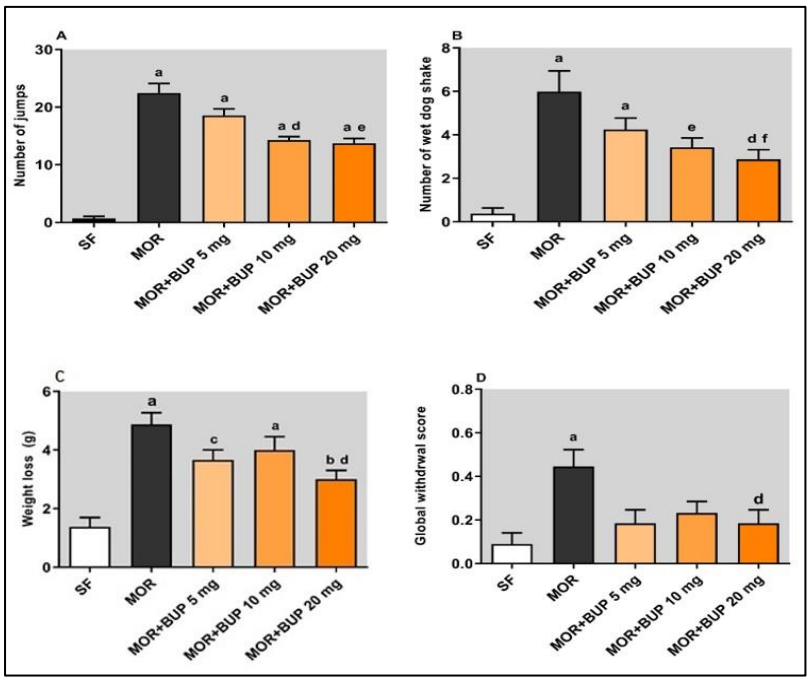

Figure 1. Effects of bupropion administration on morphine withdrawal symptoms.

For 5 days, twice a day (8:00 am – 8:00 pm) in increasing doses (1st day 10, 2nd day 20, 3rd day 30, 4th day 40, 5th day 50 mg/kg) morphine administrations were performed and 4 hours after morphine administration on the 6th day, subcutaneous naloxone (2 mg/kg) was administered and withdrawal symptoms were evaluated for 15 minutes. According to the control group: ap<0.001, bp<0.01, cp<0.05; According to the morphine group: dp<0.05, ep<0.01, fp<0.001 Values are given as Mean±Standard Error/(number of animals in each group n=7-8). Serum physiologic-SAL, Morphine-MOR. Bupropion-BUP.

The other qualitative withdrawal symptoms (teeth chattering, salivation, ptosis, urination, diarrhea, abnormal posture, defecation, tremor, making noise and ejaculation) are shown in Table 1.

Table 1

Qualitative withdrawal symptoms of control, morphine and morphine+varenicline (0.5, 1, and 2 mg/kg) groups

	Control/SAL	Morphine	MOR+VAR (0.5 mg)	MOR+VAR (1 mg)	Mor (VAR 2 mg)
Teeth chattering	0.4286±0.2974	6.429±0.9221	5.000±0.5774[a]	4.857±0.7997[b]	4.429±0.6494[b]
Salivation	0.2857±0.1844	0.8571±0.1429	0.5000±0.2236	0.7143±0.1844	0.1429±0.1429
Ptosis	0.1429±0.1429	1.857±0.4592	1.333± 0.4944	1.286± 0.4206	0.5714±0.2020
Urination	0.4286±0.2020	0.8571±0.1429	0.5000±0.2236	0.7143±0.1844	0.4286±0.2020
Diarrhea	0.2857±0.1844	2.286±0.2857[a]	1.667±0.4216	1.571±0.3689	0.4286±0.2020[b]
Abnormal posture	0.2857±0.1844	0.7143±0.1844	0.8333±0.1667	0.2857 ±0.1844	0.5714±0.2020
Defecation	1.750±0.3660	9.000±1.035	7.500±0.7792	8.875±0.6391	7.750±1.161
Tremor	0.1429±0.1429	0.7143±0.1844	0.6667±0.2108	0.2857±0.1844	0.1429±0.1429
Making noise	0.1429±0.1429	0.4286±0.2020	0.6667±0.2108	0.3333±0.2108	0.2857±0.1844
Ejaculation	0.0±0.0	0.4286±0.2020	0.5000±0.2236	0.5714±0.2020	0.1429±0.1429

For 5 days, twice a day (8:00 am – 8:00 pm) in increasing doses (1st day 10, 2nd day 20, 3rd day 30, 4th day 40, 5th day 50 mg/kg) morphine administrations were performed and 4 hours after morphine administration on the 6th day, subcutaneous naloxone (2 mg/kg) was administered and withdrawal symptoms were evaluated for 15 minutes. According to the control group: ap<0.001; bp<0.01. According to the morphine group: dp<0.05. Values are given as Mean±Standard Error/(number of animals in each group n=7-8). Serum physiologic-SAL, Morphine-MOR. Varenicline-VAR.

Effects of Varenicline On Physical Dependence of Morphine

In the comparison of the control group and the morphine group, it was found that there was a significant increase in withdrawal symptoms in the morphine group (p<0.001) (Figure 2A). In comparison with the morphine group, the jump from withdrawal symptoms was found to be significantly lower in the morphine+0.5 mg/kg varenicline and morphine+2 mg/kg varenicline groups (respectively; p<0.05; p<0.01) (Figure 2A). In the comparison of the control group and the morphine group, the wet dog symptom, which is one of the withdrawal symptoms, was significantly higher in the morphine group (p<0.001) (Figure 2B).

In comparison with the morphine group, the wet dog shake symptom was found to be significantly lower than the withdrawal symptoms in the morphine+2 mg/kg varenicline groups ($p<0.05$) (Figure 2B). In the comparison of the control and morphine groups, weight loss, which is one of the withdrawal symptoms, was found to be significantly higher in the morphine group ($p<0.001$) (Figure 2C). In comparison with the morphine group, weight loss was found to be insignificant in all of the morphine+varenicline groups ($p>0.05$) (Figure 2C). In the comparison of the control group and the morphine group, the total withdrawal score, which is one of the withdrawal symptoms, was found to be significantly higher ($p<0.05$) (Figure 2D). In comparison with the morphine group, the total withdrawal score was found to be significantly lower in the morphine+0.5 mg/kg varenicline and morphine+1 mg/kg varenicline group ($p<0.05$) (Figure 2D).

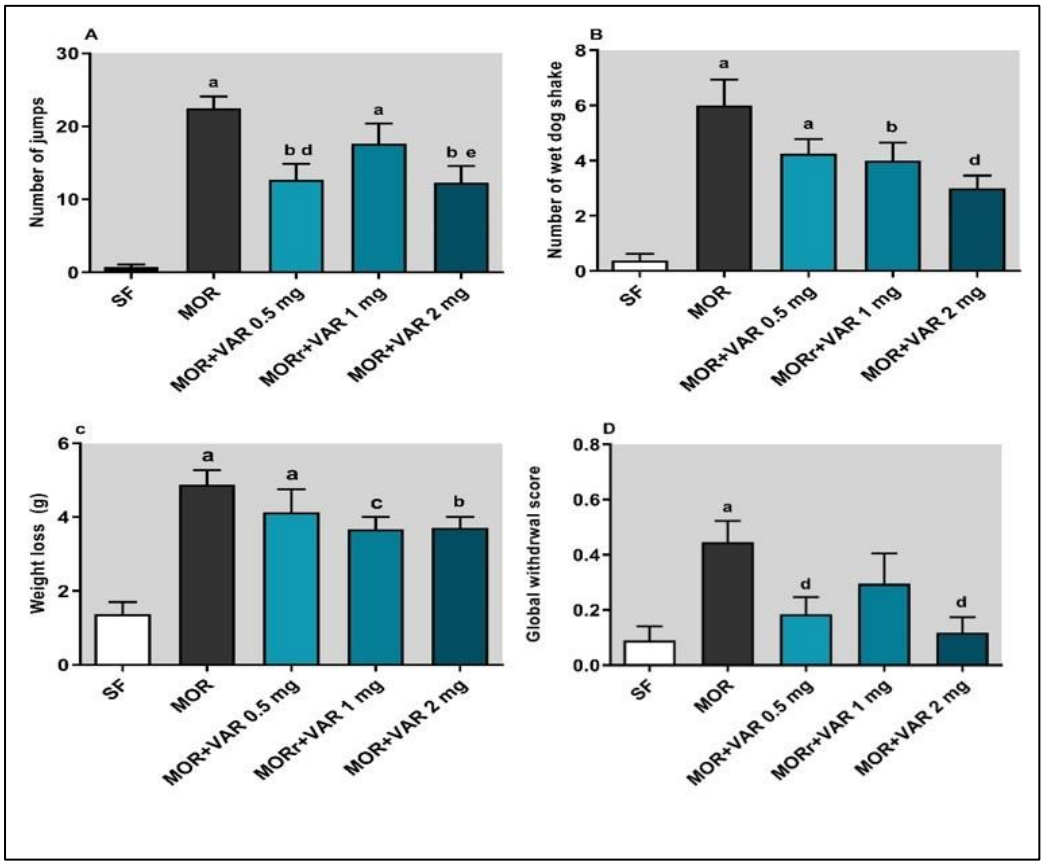

Figure 2. Effects of varenicline administration on morphine withdrawal symptoms

For 5 days, twice a day (8:00 am – 8:00 pm) in increasing doses (1st day 10, 2nd day 20, 3rd day 30, 4th day 40, 5th day 50 mg/kg) morphine administrations were performed and 4 hours after morphine administration on the 6th day, subcutaneous naloxone (2 mg/kg) was administered and withdrawal symptoms were evaluated for 15 minutes. According to the control group: ap<0.001, bp<0.01, cp<0.05; According to the morphine group: dp<0.05, ep<0.01, Values are given as Mean±Standard Error/(number of animals in each group n=7-8). Serum physiologic-SAL, Morphine-MOR. Varenicline-VAR.

Table 2

Withdrawal symptoms (teeth chattering, salivation, ptosis, urination, diarrhea, abnormal posture, defecation, tremor, making noise and ejaculation) of control and treatment groups.

	Control/SAL	Morphine	MOR+BUP (5 mg/kg)	MOR+BUP (10 mg/kg)	MOR+BUP (20 mg/kg)
Teeth chattering	0.4286±0.2974	6.429±0.9221[a]	4.333±0.5578	2.667±0.3333[b]	3.500±0.5627[b]
Salivation	0.2857±0.1844	0.8571±0.1429	0.6667±0.2108	0.5714±0.2020	0.2857±0.1844
Ptosis	0.1429±0.1429	1.857±0.4592	1.333±0.4944	1.571±0.4809	1.286±0.5216
Urination	0.4286±0.2020	0.8571±0.1429	0.6667±0.2108	0.5714±0.2020	0.5714±0.2020
Diyare	0.2857±0.1844	2.286±0.2857	1.667±0.4216	1.571±0.3689	0.8571±0.4592
Diarrhea	1.750±0.3660	9.000±1.035[a]	5.875±0.4407[c]	7.625±0.8224	5.375±0.5650[b]
Abnormal posture	0.2857±0.1844	0.7143±0.1844	0.6667±0.2108	0.7143±0.1844	0.4286±0.2020
Tremor	0.1429±0.1429	0.7143±0.1844	0.6667±0.2108	0.2857±0.1844	0.2857±0.1844
Making noise	0.1429±0.1429	0.4286±0.2020	0.5000±0.2236	0.1667±0.1667	0.1429±0.1429
Ejaculation	0.0±0.0	0.4286±0.2020	0.3333±0.2108	0.1429±0.1429	0.0±0.0

For 5 days, twice a day (8:00 am – 8:00 pm) in increasing doses (1st day 10, 2nd day 20, 3rd day 30, 4th day 40, 5th day 50 mg/kg) morphine administrations were performed and 4 hours after morphine administration on the 6th day, subcutaneous naloxone (2 mg/kg) was administered and withdrawal symptoms were evaluated for 15 minutes. According to the control group: ap<0.001; According to the morphine group: bp<0.05, cp<0.01. Values are given as Mean±Standard Error/ (number of animals in each group n=7-8). Serum physiologic-SAL, Morphine-MOR. Bupropion-BUP.

Discussion

Opioids are natural, semi-synthetic, or synthetic narcotics which are mostly utilized to treat chronic and acute pain. These drugs are frequently abused recreationally due to their tranquilizing, ecstatic, euphoric, and sedative qualities. Opioid abuse and misuse associated overdose is defined as opioid use constitues severe public health problem. It is well demonstrated that withdrawal from substances/drugs of abuse is a contributing factor for the development of diseases caused by substance abuse. We found that bupropion was ineffective at 5 mg/kg dose on jumping and wet dog shaking however, decreased the jups and wet dog shaking at 10 and 20 mg/kg doses. Nevertheless, 5 and 10 mg/kg doses were found to be ineffective on weight loss and total withdrawal score, which are the main withdrawal symptoms, while it reduced weight loss and total withdrawal score at 20 mg/kg dose. The doses used in a previous addiction study in rats were selected to determine the dose of bupropion (20).

The dopaminergic system has a very important role in opioid addiction and withdrawal symptoms (47, 48). However, other systems have been shown to play a role in opioid addiction (49-51). Many studies have shown that mesolimbic dopamine activity is reduced during opioid withdrawal (48, 52, 53). In a study conducted in rats, different doses of bupropion showed that tolerance to the analgesic effect of morphine and reduced withdrawal symptoms (54). Administration of the dopamine receptor antagonist NAc elicited withdrawal symptoms similar to those in opioid withdrawal (48). Systemically administered dopamine agonist apomorphine significantly reduced opioid withdrawal (48). At the same time, chronic opioid administration decreases dopaminergic sensitivity (51, 55). It has been shown that naloxone-induced

withdrawal symptoms increase when a D2 antagonist is given, but this effect disappears when a D2 receptor agonist is given (56-58). It has been shown in various studies that dopamine levels in the brain's reward centers decrease both with naloxone-induced withdrawal and spontaneous opioid withdrawal. Our findings are in line with other findings reported in the literature. However, it is contrary to the study conducted by Martin et al. (59). The reason for this may be the administration routes which were intracranial in the aforementioned study and intraperitoneal in our study.

While, varenicline was ineffective at a dose of 1 mg/kg upon rebound from withdrawal symptoms, it reduced spasm at 0.5 and 2 mg/kg doses. Again, on wet dog shaking, which is one of the classic main withdrawal symptoms, it was insignificantly effective at 0.5 and 1 mg/kg doses, while on wet dog shaking it was found to be insignificant at 2 mg/kg dose, and it was found to be ineffective on weight loss at all doses. In addition, while it was ineffective on the total withdrawal score from withdrawal symptoms at a dose of 1 mg/kg, it decreased the total withdrawal score at 0.5 and 2 mg doses. Since, there is no previous study on the use of varenicline in opioid addiction in experimental animals, the doses used in a previous CPP study in rats were selected to determine the varenicline dose (44).

It has been demonstrated that the opioidergic system is closely related to the nicotinergic system (15, 60). Activation of nicotinic receptors increases the level of endogenous opioids (15). Nicotine reduced morphine-related withdrawal symptoms in a previous study (15). In another study, nicotine has been reported to increase analgesic effect due to morphine (16). Cross-tolerance is developed against the hypothermia effects, addiction development, analgesic effects and effects on CPP of morphine and nicotine (44, 61, 62). However, it has been shown that cross-tolerance and cross sensitization develop between morphine and nicotine (63). In a different study, nicotine has beeen reported to reduce opioid withdrawal (10, 64). In rats, kappa receptor agonists reduced the withdrawal symptoms associated with precipitated nicotine with the nicotinic receptor blocker mecamylamine. At the same time, in the study in which chronic nicotine was given, the change of endogenous enkephalin synthesis elicited by giving naloxone changed the nicotine withdrawal symptoms (65, 66). Chronic nicotine administration up-regulates μ opioid receptors and alteres striatal met-enkephalin levels in male and female mice (67). In morphine addiction, the level of endogenous opioids is decreased (13, 66). Activation of nicotinic receptors causes an increase in the level of endogenous opioids (66, 68, 69). Possibly, varenicline decreases morphine withdrawal symptoms by increasing endogenous opioids and dopamine levels via nicotinic receptors.

Development of on morphine physical dependence in mice and rats can be attained by adding morphine to food, adding a morphine pellet or mini-osmotic pump in drinking water or administering subcutaneously, subcutaneous application of slow-release morphine emulsions, continuous infusion of morphine, or repetitive subcutaneous and peritoneal injections of morphine. The protocols for developing dependece vary, especially in applications performed with injection. Morphine injections are performed in various ways, including administration for a short time or at a fixed dose or at a gradually increasing dose for a long time, at a low or very high dose once a day or more. Deprivation; sensitive and reliable indicators of the degree of morphine dependence in rats and mice were evaluated with jumping, wet dog shaking, weight loss and diarrhea, which are considered classic dominant and vegetative/autonomic symptoms. As a conclusion, bupropion and varenicline reduced naloxone accelerated morphine-induced withdrawal symptoms. In the future, it is planned to fully elucidate the underlying mechanisms by conducting more comprehensive mechanistic studies.

Ethics Committee Approval: The Istanbul University Experimental Medicine Research Institute Experimental Animals Ethics Committee (29/12/2011) to comply with the ethical committee principles.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: BAP Istanbul University funded the project (grant no: 21845).

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