Separate and combined effects of chronic administration of codeine and tramadol on food intake and body weight in male albino rats

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Abstract

Tramadol and Codeine are both opiates used as analgesics which act on the nervous and metabolic systems. However, their role in dietary disorder and body weight has not been established in the current trend among abusers. This study, therefore, examined the effects of chronic exposure to Codeine and Tramadol on food intake and body weight. Specifically, the study examined feeding behaviour and body weight of male albino rats. Male Albino rats numbering Twenty-Four, weighing between 150-200g and 7-9 weeks' old were used. They were collected from the University of Ibadan Veterinary animal farm. The rats were divided into 3 experimental groups of Codeine, Tramadol, combined Codeine and Tramadol and Control groups with 6 rats in each group and exposed to 8mg/kg of codeine, 20mg/kg of tramadol, combined 8mg/kg of codeine and 20mg/kg of tramadol, and normal saline for 28 days. Records of the amount of food ingested and the bodyweight of the rats were taken daily for the duration of the experiment. Randomized ANOVA at $p \leq 0.05$ showed a significant effect of Tramadol and Codeine on food intake ($F_{3,667} = 3.50$, $p < 0.05$, $\eta^2 = .02$. Male rats in the Tramadol and Codeine group ($\bar{x} = 94.29$), tramadol only ($\bar{x} = 93.22$) and Codeine only ($\bar{x} = 99.00$) groups significantly consumed less amount of food compared to the control group ($\bar{x} = 100.36$). Body weight was significantly influenced ($F_{3,667} = 3.55$, $p < 0.01$, $\eta^2 = .02$). Mean body weight was significantly lower for rats in codeine & tramadol ($\bar{x} = 133.21$), tramadol only ($\bar{x} = 132.31$) and codeine only ($\bar{x} = 133.79$) groups compared to the control group ($\bar{x} = 137.51$). It was concluded that chronic exposure to Tramadol and Codeine is associated with weight loss and reduced food intake, suggesting the risk of dietary health challenges and weight loss problems for abusers.

Keywords: *Food intake, Body Weight, Tramadol, Codeine, Male Albino Rats*

Introduction

Drug use and abuse has been a challenge to the society and the health systems. Studies have shown that those who engage in drug abuse particularly, young people do so for various reasons such as political, psychosocial, educational, physical, and moral gains. Recently, the trend of drug use and abuse indicate that tramadol and codeine are the leading drugs that are widely patronized especially in the West Africa. (Oraegbune et al., 2017; Fuseini et al., 2019).

Drug abuse has been identified to influence two negative outcomes on the bodyweight which is either weight gain or loss. Weight gain occurs when more energy received from

calories in food and beverages is gained than the energy expended by life activities, including normal physiological processes and physical exercise (Hodgkins et al. 2004; Funk et al. 2019). One may become overweight or obese if enough weight is gained due to increased body fat deposits, generally defined as having more body fat or adipose tissue than is considered good for health (Hodgkins et al., 2004; Funk et al., 2019).

A reduction of the total body mass, due to a mean loss of fluid, body fat or adipose tissue or lean mass, namely bone mineral deposits, muscle, tendon, and other connective tissue is referred to as Weight loss, in the context of medicine, health, or physical fitness (Stoppler, 2018). Generally, Weight loss is a decrease in body weight resulting from either voluntary activity such as diet or exercise or involuntary circumstances such as illness. It can either occur unintentionally due to malnourishment or an underlying disease or arise from a conscious effort to improve an actual or perceived overweight or obese state (Stoppler,2018) Weight loss may also be an outcome of drug use. There is considerable evidence from research reports to suggest that drug usage is linked to an increased risk of being underweight (Pasch et al., 2012).

Exposure to recreational, illicit, and prescription medication has effects on the social, physical, physiological and mental processes. Some drugs target the central nervous system (CNS) and just a single dose of such drugs and substances may result in temporary cognitive impairments. Some consequences of cognitive impairment may include lack of self-care, inability to remember to eat properly, leading to weight loss and lack of care for the immediate environment. According to Vieira, (2015), people who begin to abuse drugs may eventually suffer from permanent impairments in brain activity as well as physical changes that lead to dramatic weight loss and poor health.

There is a broad perception that drug use either suppresses or increases appetite resulting to decrease or increase in body weight. This poses a problem to the rehabilitation of people who use drugs because of the resultant potential relapse. Consequently, weight gain or loss contributes to the challenges of rehabilitation of drug users in the community treatment services, where experts are trying to tackle the weight problems of drug users with educational interventions to promote healthy food (Ersche et al., 2013). Based on this finding, the different types of drugs have a different impact on weight gain or loss. The drugs of special concern in the present study is the impact of Codeine and Tramadol on feeding behavior and weight gain or loss.

Tramadol, a synthetic analogue of codeine with central effects is an analgesic with an opioid like effect when taken orally (WHO, 2017). It is a choice prescription for treatment of mild to severe pain in both acute and chronic conditions (Fuseini et al., 2019; Grond & Sablotzki, 2004). Records of tramadol abuse, mostly by adolescents is alarming in some countries in Europe (Olsson et al., 2017). WHO (2017) report indicates that the level of tramadol abuse is unclear in Africa due to the lack of studies on the epidemiological statistics. However, there is evidence of a growing trend of abuse of tramadol in most African countries, particularly Nigeria, Togo, Ghana, Libya and Egypt among others. There is also evidence that Nigeria, Ghana, Togo, Sierra Leone, Cameroon and Côte d'Ivoire are major transit or destination countries for tramadol (Salm-Reifferscheidt, 2018). In Nigeria for instance, there is evidence that tramadol abuse has a prevalence rate of approximately 54.4%, with over 91% of these dependants obtaining the drug without prescriptions (Ibrahim et al., 2017).

The abuse potential of tramadol compared with other opioids like morphine is believed to be low (WHO, 2017), and it is not listed among the controlled substances regulated by the Food and Drug Authorities (Salm-Reifferscheidt, 2018; WHO, 2017). However, the risk for tramadol abuse is still very high, because, there are reports linking tramadol usage to overdose, as well as to serotonin syndrome, which can be fatal. (Hassamal et al., 2018). Tramadol has the potential

to activate the brain opioid receptors as well as interact with the serotonin and norepinephrine neurotransmitter systems using a similar mechanism like some antidepressant medications. (Hassamal et al., 2018). Tramadol also gives an experience of a pleasant rush of euphoria, the reason why most of the users abuse the drug sometimes. Reported side effects of tramadol especially when taken in high doses include, nausea and vomiting, constipation, sweating, dizziness, seizures and postural hypotension, abdominal pain, change of blood pressure, dry mouth, hallucination, sleepiness, sedation, respiratory depression among others (Jovanović-Čupić et al., 2006; Zhang & Liu, 2013; FDA, 2017; Hassamal et al., 2018). In spite of the enormous side effects, many people continue to abuse tramadol for physical, psychosocial and sexual reasons.

Codeine is a naturally occurring phenanthrene alkaloid and opioid agonist with analgesic, antidiarrheal and antitussive activities. Similarly, Codeine is used to treat mild to moderate pains and should not to be used for a prolonged time. Codeine binds to the opioid receptors at many sites within the central nervous system (CNS) thereby mimicking the actions of the endogenous opioid. Global reports indicate that codeine is the most consumed opioid based on tonnage (INCB, 2018). Codeine is widely abused because it is short acting, weak and a mild opiate (Tremlett et al., 2010). The drug is readily available because it is considered an Over the Counter (OTC) drug in formulations used for the treatment of mild to moderate pain or cough symptoms (Ferguson et al., 2019). A study by Cherian et al., (2018), using social media, suggests that codeine abuse may be becoming normalized, commercialized, and ritualized. Some names used for codeine among the users include lean (which is codeine cough syrup mixed with ice, soda, and occasionally hard candies) and depictions of codeine with other substances such as alcohol and cannabis in the preparation of lean (Cherian et al., 2018).

There is a global concern over the misuse and potential abuse of codeine and codeine-containing medications which have received attention in recent times in different countries of the world (Tobin et al. 2013; Stannard, 2013; Nielsen et al. 2015). Abuse of codeine may lead to addiction starting with occasional abuse of the drug and slowly develop into a physical dependence and then into addiction (Nielsen & Van Hout, 2017). The effects produced by codeine when taken in large amounts increases its addiction potential and once a physical dependence is formed, the individual will not be able to function normally without codeine in their system (Nielsen & Van Hout, 2017). The likelihood of overdose to the use of codeine is an additional risk factor to codeine addiction. The use of codeine with other central nervous system depressants like alcohol or other opioids increases its overdosing (Ferguson et al. 2019). Side effects produced by continuous use of codeine include altered perceptions, euphoria, stomach cramps, emotional responses to pain and sedation, nause, vomiting, diarrhea, loss of appetite and development of tolerance within relatively short timeframes on repeated use (Karamatic et al. 2011; Babalonis et al. 2013; Nielsen & Van Hout, 2017).

Tramadol and codeine are both opiates that are used to control pain which are prone to a lot of misuse and abuse despite the various side effects (Chikezie&Ebuenyi, 2019; Uwadiegwu et al. 2019). The use and abuse of opioids have been linked to several side effects suggestive of abnormalities in feeding behaviour such as loss of appetite, constipation, nausea, weight gain or weight loss and fatigue among others (Baldini et al. 2012; Zimatkin& Bon, 2014; FitzHenry et al. 2020). In a recent study, Balogun et al., 2020, reported that continuous exposure to tramadol and codeine was linked to low food consumption and weight loss in female Albino rats. However, studies establishing these relationships in male Albino rats are scarce. Therefore, this study examined the effects of separate and combined chronic administration of tramadol and codeine on food intake (feeding behaviour) and body weight of male Albino rats.

The specific objectives of the study were to:

• examine the effects of chronic Tramadol administration on feeding behaviour and body weight among male albino rats.

• examine the effects of chronic Codeine administration on feeding behaviour and body weight among male albino rats.

• examine the effects of combined chronic administration of both Tramadol and Codeine on feeding behaviour and body weight among male albino rats.

The following **research questions** were generated with a view to provide answers through the outcomes of this research;

• What are the effects of chronic administration of codeine and tramadol on food intake of male Albino rats?

• What are the effects of chronic administration of codeine and tramadol on body weight of male Albino rats?

The following **hypotheses** were tested to determine the relationship between chronic administration of tramadol and codeine on feeding behaviour and body weight in male albino rats;

Tramadol and Codeine will separately and jointly interact to affect the amount of food consumed by male albino rats exposed to chronic administration of the drugs.

Tramadol and codeine will separately and jointly interact to affect body weight of male Albino rats exposed to chronic administration of the drugs.

Methodology

This research is a part of a larger experiment that investigated the effects of separate and combined chronic ingestion of codeine and tramadol on feeding behaviour and body weight of Albino rats. In an earlier publication, the researchers (Balogun et al., 2020) presented the effect of these drugs on female Albino rats. This paper will therefore focus on the effects of combined chronic ingestion of codeine and tramadol on feeding behaviour and body weight of male Albino rats. The methodology presents the methods adopted for this study which includes research design, participants, setting, instruments used, procedure and method of statistical analysis.

Research design

Independent group randomized design was used in this study. The male Albino rats were randomly assigned into four groups; the Codeine, Tramadol, the both Codeine and Tramadol and the control groups. The independent variables are the chronic administration of Tramadol and Codeine, and the combination of both drugs to the male Albino rats. The dependent variables were feeding behaviour and weight gain displayed or exhibited by the male Albino rats.

Setting

The experiment took place at the Animal Science Laboratory, University of Ibadan, Oyo State, Nigeria.

Animal Population

The animals used were male Albino rats. A total of 24 male Albino rats weighing between 150 - 200g and 4 – 6 weeks old were used. They were divided into four (4) groups with six (6) male rats in each group. The groups were Tramadol group, Codeine group, combined Tramadol and Codeine group and control group. The rats were randomly assigned to different groups.

Drugs

Tramadol HCL (50 mg capsules) and Cough syrup (containing 220mg codeine) were used for this study. Tramadol and Codeine were administered orally with the use of an oral cannula. The rats were given 20mg/kg bodyweight of Tramadol following the recommended 5mg/kg – 20mg/kg dose for oral administration of tramadol in rats (National Research Council, 2011) while Codeine was administered at a dose of 8mg/kg body weight every 24 hours following the recommended therapeutic dose of 2mg/

kg/6hrs (Uwadiegwu Achukwu et al., 2019). The dosage administered in this study was, therefore, Tramadol, 20mg/kg and Codeine, 8 mg/kg.

Materials/Instruments

The following materials and instruments were used for this study;

1. 24 experimental rat cages.
2. Recording sheets
3. Distilled water/saline
4. Laboratory coat
5. Oral cannula for the administration of drugs
6. Hand Gloves.
7. Face/Nose Mask
8. Coloured labelling the cages and placing identification marks on the rats.
9. Measuring cylinders used in diluting and measuring the solution.
10. Weighing balance for the daily weighing of rats and food.
11. Disposable syringes
12. Mouse cubes for feeding the rat
13. Codeine syrup
14. Tramadol capsules (powder in capsule serially diluted with distilled water)

Procedure

The rats were kept in the laboratory under the normal day-night 24-hour cycle and allowed to acclimatize for 21 days before the commencement of the experiment while allowing them free access to food and water. They were then randomly assigned into 4 groups; the tramadol group, the codeine group, the Combined codeine and tramadol group and the Control group with 6 male rats in each group. All the male rats were housed in individual cages and each cage was clearly labelled with the drug category. The male rats were also marked for clear identification.

On each day of the experiment, all the rats were weighed and records of the weights against each rat were taken. This was to determine what volume of drugs to administer to each rat. The drugs were then administered to each experimental group of the rats according to their body weights. The control group was given normal saline. After the drug administration, the rats were allowed 30 minutes before the commencement of data collection to give enough time for the onset of drug action. Baseline record was taken for 8 days to establish the feeding pattern of the rats before the commencement of drug administration. Records taken on each day of the experiment were;

- Bodyweight of the male rats

- Weight of food remaining from the previous day

- Weight of food spilt from the previous day

The amount of food consumed after a 24-hour cycle was determined by subtracting the weight of food spilt from the weight of food remaining while weight gained or lost was determined by calculating the difference in weight for each rat daily. After the baseline records were taken for 8 days, daily treatment and record taking for each rat continued for 28 days' duration of the experiment.

The rats were handled according recommended procedures by the cruelty to animal Act for animals used for research purposes and discarded accordingly at the end of the experiment.

Drug Dosage:

Tramadol: The dose of tramadol for this study is 20mg/kg body weight. Tramadol used for this study was tramadol HCL containing 50mg in a capsule. This was serially diluted to 20mg dose used for this study. A stock solution of tramadol containing 50 mg tramadol was prepared and diluted to 20mg by dilution into one thousand parts per million. This was achieved by taking 40mls of a solution containing 50mg tramadol and adding 60mls of distilled water to make a 100mls solution of 20mg tramadol.

Codeine: The dose of codeine used for this study is 8mg/kg body weight. Codeine used for this study was codeine linctus cough syrup. Codeine linctus cough syrup contains 15mg codeine in every 5mls of the syrup. The rats were administered 2.5mls of the syrup containing 8mg of codeine.

Statistical analysis

One-way ANOVA was adopted for the result analysis for this study. Any P value less than 0.05 was considered as significant.

Results

This study investigated the effect of chronic administration of tramadol and codeine on food intake and body weight of male Albino rats and the results are presented in line with the proposed hypotheses.

Hypothesis 1, stated that Tramadol and Codeine will separately and jointly interact to affect the amount of food consumed by male albino rats exposed to chronic administration of tramadol and codeine presented. The result as presented in Table 1, indicate that there is a significant effect of exposure to chronic administration of tramadol and codeine on food consumption among male Albino rats, $F(3,667) = 3.50$, $p < 0.05$, $2= .02$. Result of mean differences among the treatment groups using LSD mean comparison test presented in Table 2, shows that rats exposed to chronic administration of the combination of Tramadol and Codeine ($x = 94.29$), Codeine only ($x = 99.00$) and Tramadol only ($x = 93.22$) significantly consumed less amount of food compared to male rats in the control group ($x = 100.36$). The mean differences in food consumption were significant ($p<.05$). Food consumption decreased with exposure to chronic administration of tramadol and codeine compared to the control group. There was a significant increase in food consumption for male rats in the control group while it declined significantly for male rats in the tramadol and codeine experimental group.

Hypothesis 2, stated that tramadol and codeine will separately and jointly interact to affect body weight among male Albino rats exposed to chronic administration of tramadol and codeine. The result is presented in Table 3. It indicates a significant effect of the exposure to chronic administration of tramadol and codeine on body weight among male Albino rats, $F(3,667) = 3.55$, $p < 0.001$, $2= .02$. Result of mean differences among the treatment groups using LSD mean comparison test as presented in Table 4. shows that rats exposed to chronic administration of a combination of Tramadol and Codeine ($x = 133.21$), Tramadol only ($x = 132.31$) and Codeine only ($x = 133.79$) significantly exhibited weight loss compared to rats in the control group ($x = 137.51$). The mean differences were significant ($p<.001$). There was significant weight loss with exposure to chronic administration of tramadol and codeine compared to the control group. The decline in weight was seen to be directly proportional to the increase in numbers of days of exposure to the drugs. The result in Fig. 1, demonstrated that weight increased for the control group while weight declined significantly for exposed rats as the chronic exposure increase for more than 14 days.

Discussion

Significant links are suggesting a relationship between food intake and drug use (Salamone & Correa, 2013). Behavioural and neurophysiological data in support of this proposition abound. Naturally, humans experience psychological rewards that cause a person to repeat certain behaviours, such as eating, having sex or engaging in physical activity controlled at the level. Using brain imaging research, Volkow et al. (2011) discovered parallels between dysfunction in response to foods and drugs, as well as striatal dopamine function in the obese and drug dependence, as well as the signals linked with both. Brain systems such as the habenula, a structure near the pineal gland, and involuntary motions are other areas of brain dysfunction in obese and drug-addicted persons. This natural reward system is known to be influenced by the habenula and medications (Volkow et al., 2011). Cross-sensitization from sugar to medicines

in animals, as well as other behavioral similarities, corroborate these theories.

Several research has suggested that drug usage may protect body weight when in active use. Chronic moderate alcohol use has been linked to a normal or low Body Mass Index (BMI) (Barry & Petry, 2009; Yeomans, 2010). Similarly, despite its reputation for increasing appetite, Warren et al. (2005) found an inverse linear relationship between cannabis use and BMI in a sample of women. The lowest BMIs were identified in people with the highest overall drug use in a study of people in treatment for Substance Use Disorder (SUD) (Cofrancesco et al. 2007). Other studies that looked at weight and the chance of SUD diagnosis came up with similar conclusions (Pasch et al. 2012). There is considerable evidence to suggest that drug usage is linked to an increased risk of being underweight (Pasch et al., 2012). According to certain research, there may be variations in BMI between men and women. SUD diagnosis was linked to a reduced BMI in males, but not in women, according to a research (Pickering et al. 2011). Similarly, (Balogun et al., 2020) showed weight loss in female albino rats exposed to chronic medication therapy in a study involving exclusively female albino rats.

There is strong evidence of shared brain substrates for food and drug reinforcement in the literature on food consumption and drug addiction. However, whether drug usage influences food consumption or vice versa, as well as body weight, is an essential subject that has to be answered. Is there any other proof of a link between eating habits, body weight, and drug use?

The study therefore, examined the effect of tramadol, codeine, and combination of codeine and tramadol on food intake and body weight among male Albino rats. We hypothesized that tramadol and codeine will separately and jointly interact to affect the amount of food consumed by male albino rats given chronic treatment of the drugs. Chronic treatment of tramadol and codeine significantly influenced food consumption among male Albino rats in support of the proposed hypothesis. From Table 1 the result shows that food consumption was significantly influenced among male Albino rats, $F(3,667) = 3.50$, $p < 0.05$, $2 = .02$. Male rats which ingested the combination of codeine and tramadol, codeine only and tramadol only significantly consumed less food compared to male rats in the control group. This observation is in line with similar findings by Marrazzi et al. (1996), who concluded from their research result that chronic intake of morphine opioid drugs was associated with a decline in food intake among albino rats. In a recent and similar study, (Balogun et al., 2020), observed that female Albino rats exposed to the chronic treatment of tramadol, codeine and combined tramadol and codeine consumed less food compared to controls. The findings may be an indication that gender differences may not exist on the effect of exposure to tramadol and codeine and food intake.

The observed effects have credible empirical explanations. Despite the fact that tramadol and codeine are mild opiates that aren't as potent as other opioids like heroin, their use can nevertheless lead to the same issues as other opioids, including death from overdose. Serotonin syndrome has been connected to the usage of tramadol and codeine (Milano et al. 2017). Serotonin syndrome occurs when serotonin receptors are overstimulated, resulting in a high fever, rapid pulse, shivering, sweating, trembling, muscular spasms, agitation, and confusion (Milano et al., 2017). One of the reported negative effects of prolonged tramadol and codeine exposure is weariness, which could be attributed to the effects of serotonin syndrome (Walder et al. 2001). Fatigue slows metabolic rate and, as a result of a lack of hunger, produces a change in eating habits. This explains the probable reasons for the observed low food intake and decrease in body weight among the codeine only group, combined codeine and tramadol group and tramadol only group compared to control group.

The researchers also hypothesized that tramadol and codeine would interact independently and jointly to influence the

body weight of male Albino rats subjected to chronic drug administration. The male Albino rats' body weight was significantly affected by chronic tramadol and codeine administration. Weight loss was seen in the male Albino rats that were administered the medications. From The Table 3 the result shows that administration of tramadol and codeine significantly influenced body weight among the male Albino Rats. Male rats given chronic treatment combined tramadol and codeine, tramadol only and codeine only groups significantly exhibited weight loss compared to male rats in the control group. The result showed that there was significant weight loss with exposure to tramadol and codeine compared to the control group.

However, Findings from a study showed that daily oral administration of naltrexone, a similar opioid agonist with a relatively longer half-life, was associated with zero to minimal weight loss in humans with a conclusion that opioid agonists generally stimulate food intake, and may or may not be associated with increased BMI in human (Mysels & Sullivan, 2010). In a similar study, (Balogun et al., 2020), observed a decrease in weight among female Albino rats exposed to chronic administration of tramadol and codeine indicating that there may not be gender differences in the effect of opioid drugs on weight gain or loss. In another study, Barry & Petry, (2009), observed that there were no associations between opiate, marijuana, and cocaine dependence and BMI in men or women. Various mental processes leading to behavioural deficits are influenced by recreational, illicit and prescription drugs. According to (Gould, 2010), just a single dose of certain drugs may result in temporary cognitive impairments causing the inability of the person to remember to eat properly and the possible onset of weight loss. Weight loss as shown from the findings of this research are outcomes of abuse, addiction and dependence to drugs. According to Vieira, (2015), individuals who begin abusing drugs may have irreversible changes in their brain function as well as physical changes such as severe weight loss and poor health.

Some side effects of opiate analgesic drugs include: drowsiness, nausea, vomiting and constipation, leading to decreased appetite, slowed digestion and weight loss over time. (Ersche et al., 2013; McCabe et al., 2015; Vieira, 2015). One probable reason for reported weight loss among opiate dependence and addicted individuals may be that they are usually seen to be engaged in drug-seeking behaviours much more than eating properly (Fishbain et al., 2008). Opiate use can also have major effects on the body, and damage a user's eating habits and appetite. Symptoms of the reported side effects of opiates particularly nausea and vomiting can lead to lack of nutrients and an imbalance of electrolytes in the body resulting into a lack of appetite and difficulty to maintain a healthy diet.

One of the most debated aspects of opiate use is how the drug affects weight, appetite, and food intake (Owens, 2020). Opiates, like all addictive medications, alter the reward circuit in the brain. Drugs frequently impair this natural reward mechanism (Volkow et al., 2011). When drugs are taken to feel high, increase mood and energy, or reduce pain, the brain views these benefits as rewarding, according to Owens (2020). As a result of repeated drug use, the brain begins to associate the substance with pleasure, and an individual loses interest in other activities that previously provided natural sensations of satisfaction. Addicts' brain reward circuits have been altered to the point where the brain desires more of the drug to feel fulfilled. They get fixated on maintaining their drug use because the brain equates the opiate drug with pleasure and loses interest in previously rewarding things like eating or exercising. When people become addicted to opiates, they frequently lose weight and lose their appetite, and the more severe the addiction becomes, the more severe the weight problems grow, eventually harming one's general health and attractiveness. (2020, Owens).

Conclusion

There is strong evidence from this study establishing a clear association with chronic opiate use and weight loss and low food intake. The findings show that chronic intake of tramadol and codeine significantly influenced weight loss or weight reduction among the male Albino rats. Similarly, male Albino rats given chronic treatment of combined (tramadol and codeine), tramadol only and codeine only significantly exhibited lower weight compared to control male rats. On the same note, male rats exposed to the combination of tramadol and codeine, codeine only and tramadol only significantly consumed less food compared to control male rats. Findings of this study therefore, indicate high implications for nutritional problems and weight loss among opioids addicts and this represents health risk in itself.

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Conflict of Interest

The Authors unanimously declare that there is no conflict of interest in this study.

Tables and Figures

Table 1: Summary of Factorial ANOVA table showing the influence of exposure to Chronic administration of Tramadol and Codeine on food intake.

Source	SS	Df	Mean Square	F	Sig.	p2	
Block	14.272	1	14.272	.024	.876	.000	
Treatment	6149.350	3	2049.783	3.499	.015	.015	
Error	390772.664	667	585.866				
Corrected Total	396936.286	671					

Table 2: Summary Bonferonni mean comparison analysis showing the mean difference between male rats exposed to chronic administration Tramadol and Codeine and male rats in the control group on food intake.

Treatment	Mean	S.E.M	1	2	3	4
Codeine	99.00	1.867	-	5.78*	1.35	4.72*
Tramadol	93.22	1.867		-	7.14*	1.06
Combined	94.29	1.867			--	6.07*
Control	100.36	1.867				-

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: LSD.

Table 3: Summary of Factorial ANOVA table showing the influence of exposure to Chronic administration of Tramadol and Codeine on weight gain.

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.	Partial 2
Block	88.932	1	88.932	.360	.549	.001
Treatment	2637.195	3	879.065	3.555	.014	.016
Error	164944.943	667	247.294			
Corrected Total	167671.070	671				

Table 4: Summary LSD mean comparison analysis showing the mean difference in weight between rats exposed to chronic administration Tramadol and Codeine and those exposed to Normal saline.

	Mean	S.E.M	1	2	3	4
Codeine	133.79	1.213	-	1.48	.58	-3.73*
Tramadol	132.31	1.213		-	.89	5.20*
Combined	133.21	1.213			--	4.30*
Control	137.51	1.213				-

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: LSD.

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