RESEARCH ARTICLE

Effects of Separate and Combined Chronic Ingestion of Codeine and Tramadol on Feeding Behaviour of Female Albino Rats.

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Abstract

Tramadol and codeine are both opioids used for pain control and management but are prone to misuse and abuse despite the various side effects. This study, therefore, examined the effects of chronic exposure to Codeine and Tramadol on feeding behaviour. Twenty-Four (24) Female Albino Rats weighing between 150-200g and 4-6 weeks old, were used. They were divided into 4 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 block ANOVA showed a significant effect of Codeine and Tramadol on feeding behavior (F (3,641) = 25.53, p < 0.001, \( \eta^2 = .11 \)), and body weight (F (3,641) = 76.67, p < 0.001, \( \eta^2 = .26 \)), among the female rats. Female rats in the combined codeine and tramadol group ingested less food (\( \bar{x} = 33.45 \)), compared to codeine group alone (\( \bar{x} = 40.71 \)), tramadol group alone (\( \bar{x} = 39.96 \)) and control group (\( \bar{x} = 49.38 \)). Female rats in the combined codeine and tramadol group gained less weight (\( \bar{x} = 132.67 \)), compared to codeine group alone (\( \bar{x} = 137.67 \)), tramadol group alone (\( \bar{x} = 133.33 \)) and control group (\( \bar{x} = 164.25 \)). The mean differences were significant (p<.001). It was concluded that chronic exposure to tramadol and codeine has effects on feeding behaviour and subsequent body weight.

Keywords: Feeding Behavior, Codeine, Tramadol, Female Albino Rats

1 | INTRODUCTION

Feeding is one of the characteristics of living organisms. Living organisms take in food to carry out life activities. Feeding behaviour can be defined as “normal behaviour related to eating habits, selecting foods that you eat; food preparations and quantities of ingestion”(Horáč, 2016). Feeding behaviour is important in the life of humans and other animals because it has implications for long term
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health outcomes as unhealthy eating habits such as consuming nutrient-deficient food, skipping meals, and a lack of timely diet are understood to cause various health problems and nutritional deficiencies (El Ansari et al., 2015 Papadaki et al., 2007). On the other hand, taking a balanced diet and the consumption of quality food can contribute to sustaining the physical well-being and mental stability of individuals (Hilger et al., 2017 Abraham et al., 2018).

Feeding behaviour is a complex type of behaviour and humans make hundreds of food decisions daily which are influenced by a variety of personal, social, cultural, environmental, and economic factors. (LaCaille, 2013). What people eat and how much they eat has a considerable influence on their health (El Ansari et al., 2015). Specific factors peculiar to individuals influencing eating behaviour and food choice include physiological processes like hunger, satiety, innate preference for sweet foods, brain mechanisms, and psychological processes like learned food preferences, knowledge, motivations, attitudes, values, personality traits, cognitive processes and self-regulation (LaCaille, 2013). The social environment has also been implicated to have a substantial effect on feeding behaviour. Behaviours related to feeding are known to be shaped indirectly through observing others and internalization of food rules, as well as directly. The physical environment, including the availability of foods, the context in which foods are provided, and the external cues, such as proximity to food, salience of food, packaging, plate/serving size, and variety of food assortments, have all been shown to affect the type and amount of food eaten (LaCaille, 2013).

Feeding behaviour is also influenced significantly by substance abuse. According to the American Psychiatric Association, substance abuse is the excessive use of substances, including alcohol and drugs, that cause an individual to suffer from clinical impairments as well as the dramatic loss of academic, professional, and social skills (GUZE, 1995). Diets of individuals involved in substance abuse are usually altered leading to irregular eating patterns and poor nutrition resulting in significant health problems which may include fluctuations in weight (Vieira, 2015). One major means by which substance abuse affect feeding behaviour is by obstructing metabolism. Metabolism is the process by which the body breaks down food and convert them to nutrients and energy to nourish the body against damage and provide energy for growth. Most often, the consequence of substance abuse is poor diet and nutrition, which can lead to brain damage, organ damage, and different types of diseases (Zimatin & Bon, 2014 Haseba & Ohno, 2010).

Abused prescription drugs affect humans and other animals as well. Scientists are increasingly warning that prescription drugs can affect wildlife and ecosystems when they find their way into the environment. In a recent Environmental Toxicology and Chemistry study, anxiety and depression drug, Escitalopram, at concentrations similar to those measured in the environment was reported to inhibit fish foraging and eating behaviour (Nielsen et al., 2019). Similarly, recreational, illicit, and prescription medication all influence various mental processes. Certain drugs may cause temporary cognitive impairments after taking just a single dose which may result in the person’s inability to remember to eat properly, the onset of weight loss and dangerous development of low blood sugar (Gould, 2010). Individuals 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 (Vieira, 2015). Some of these drugs can be broadly categorized into three types commonly taken by adolescents and adults which include: depressants, stimulants and hallucinogens. Depressants are substances that can slow normal processes in the body and reduce physical activity by altering how the brain sends and receives signals. Alcohol, marijuana (cannabis) and opiates such as morphine, codeine, tramadol, heroin, methadone, hydrocodone and oxycodone are all categorized as depressants (Vieira, 2015).

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Opiates are naturally occurring substances derived from the opium poppy and are part of a larger drug category called opioids (UNODC, 2016). Opioids include both naturally occurring substances and synthetic forms of the drugs. Opiates including the opioid substances work in the brain to change the way the body perceives pain and produce feelings of euphoria in the user. Opiates are highly habit-forming leading to addiction if drugs are used without a physician’s prescription (Tsai Id et al., 2019). Both natural and synthetic opiates cause dependence, and many people abuse these drugs for their ability to induce euphoria (Baldini et al., 2012). One of the major effects of opiates on the body is damage to the user’s eating habits and appetite (Ersche et al., 2013). Common side effects of opiate abuse include constipation, nausea, and vomiting (FitzHenry et al., 2020). These symptoms can lead to a lack of nutrients and an imbalance of electrolytes. The side effects of nausea and vomiting often decrease the user’s appetite, making it difficult to maintain a healthy diet (Baldini et al., 2012). Another side effect of opiate abuse is fatigue (Zimatkin & Bon, 2014). This can lower the user’s metabolic rate, causes a change in eating habits due to lack of appetite. Codeine and tramadol are all medications classified as opiates and opioids.

Tramadol is a unique type of opioid pain medication used to treat moderate to moderately severe pain. Tramadol is an opioid agonist drug with an estimated potency of 10% to that of morphine (Zhang & Liu, 2013). It also acts as a norepinephrine and serotonin reuptake inhibitor in addition to its opioid effects. Tramadol is available in brand names such as Ultram, Ultracet, ConZip (WHO, 2017). Historically, tramadol was first used to treat post-operative pain in Germany during the 1970s (WHO, 2017). In 1994, it was approved for medical use in the U.K. and, in 1995, it was approved by the FDA for use in the United States (Rajabizadeh et al., 2009). Abuse, dependency and addiction to tramadol were originally considered to be at very low risk, but recent reports on the use of tramadol suggest that abuse of the drug is on the increase mostly among the adolescents. A report in 2016 showed that 19 million people aged 12 years or older reported having used tramadol in the past one year while 1.5 million reported misuses of the drug in the past one year (Hassamal et al., 2018 Lipari & Horn, 2017 FDA, 2017). Granting that potential for abuse with the use of tramadol is low compared to some other prescription opioids, the abuse still carries a lot of risks. An increasing number of reports have linked tramadol usage to overdose, as well as to serotonin syndrome, which can be fatal. (Hassamal et al., 2018)

Tramadol like many other prescription painkillers activates the brain opioid receptors and also interacts with the serotonin and norepinephrine neurotransmitter systems using a similar mechanism like some antidepressant medications. (Hassamal et al., 2018) In addition to pain relief, tramadol gives an experience of a pleasant rush of euphoria for which the users abuse the drug sometimes. Side effects of the use of tramadol, even when prescribed include (FDA, 2017 Hassamal et al., 2018) abdominal pain, changes in blood pressure, constipation, dizziness, dry mouth, hallucinations, headache, nausea, sleepiness, sedation, respiratory depression, sweating, tremors, vomiting, seizures etc.

Codeine is a phenanthrene derivative extracted from opium or produced synthetically by the methylation of morphine. Codeine or 3-methylmorphine is the most commonly consumed opiate worldwide and is used for its analgesic, antitussive and anti-diarrheal properties. It is the most consumed opioid globally based on tonnage (INCB, 2018). Misuse and potential abuse of codeine and codeine-containing medications have received attention in recent times in different countries of the world (Nielsen et al., 2015 Stannard, 2013 Tobin et al., 2013). In Nigeria, there is an overwhelming concern over the addiction of thousands of youths to cough syrup formulations containing codeine products (BBC, 2018 Akande-Sholabi et al., 2019). The BBC documentary titled “Sweet Sweet Codeine” reported the trend in May 2018 (BBC, 2018). Subsequently, the National Agency for Food and Drug Administration (NAF-DAC) in Nigeria banned the importation and sale of codeine as an active pharmaceutical ingredient (API) (Akande-Sholabi et al., 2019). Codeine is a short-acting, weak and mild opiate (Tremlett et al., 2010). It is considered an Over the Counter (OTC) drug and is available in formulations for the treatment of symptomatic relief of mild to moderate pain or
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cough (Ferguson et al., 2019). Side effects to continuous use of codeine include euphoria, altered perceptions, emotional responses to pain and sedation, and development of tolerance within relatively short timeframes on repeated use (Babalonis et al., 2013 Karamatic et al., 2011 Nielsen & Van Hout, 2017).

Tramadol (Ultram) and codeine are both opioids or opiates that are used to control pain. They are both extended-release tablets used for moderate to moderately severe chronic pain in adults who require continuous treatment for an extended period. Also, codeine is useful for suppressing cough. However, these drugs have been prone to a lot of misuse and abuse for its various side effects and in the suppression of pain among the general populace (Chikezie & Ebuenyi, 2019 Uwadiegwu Achukwu et al., 2019). Although there are limitations in the utility of these drugs for the management of acute pain for surgery and other forms of pain (Moore, 1999 Becker & Phero, 2005), anecdotal evidence suggests its use for suppression of pain among the general populace. Several studies have linked the use of opioids to side effects suggesting abnormalities in feeding behaviour such as loss of appetite, constipation, nausea, weight gain and loss, fatigue etc. (FitzHenry et al., 2020; Baldini et al., 2012 Baldini et al., 2012 Zimatkin & Bon, 2014), but study reports are, however, scarce on the specific link of any of these effects to tramadol and codeine as opioids. Therefore, this study was designed mainly to experimentally examine the effects of separate and combined chronic administration of tramadol and codeine on feeding behaviour of female albino rats. This study will specifically;

1. Tramadol and Codeine will singly and jointly interact to affect the feeding behaviour of female albino rats exposed to chronic administration of the drugs.
2. Tramadol and codeine will singly and jointly interact to affect the weight gain or weight loss of female Albino rats exposed to chronic administration of the drugs.
3. Female Albino rats exposed to chronic combined treatment of codeine and tramadol will consume less food than female albino rats exposed to a single treatment of codeine or tramadol.
4. Female Albino rats exposed to chronic combined treatment of codeine and tramadol will lose more weight than female rats exposed to single treatment of codeine and tramadol.

2 | METHODOLOGY

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

The design used in this study is an independent group randomized. Participants in the study were selected and placed in four different groups. The first group was administered Codeine, the second was administered Tramadol, the third group was administered both drugs, Tramadol and Codeine and the fourth group was administered normal saline as the control group. The independent variables are the chronic administration of Tramadol and Codeine, and the combination of both drugs to the female Albino rats. The dependent variable was feeding behaviour displayed or exhibited by the female Albino rats.

Setting

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

Animal Population

The animals used were female Albino rats. A total of 24 female Albino rats weighing between 150 - 200g and 4 – 6 weeks old were used. They were divided
into four (4) groups with six (6) female 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**

The drugs used for this study were Tramadol HCL (50 mg capsules) and Cough syrup (containing 220mg codeine). 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**

Before the commencement of experiments, the rats were brought into the laboratory and left to acclimate in the laboratory for 21 days. During this period, the rats were allowed free access to food and water without any form of deprivation under the normal day-night 24-hour cycle. The rats 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 female rats in each group. All the female rats were housed in individual cages and each cage was clearly labelled with the drug category. The female 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 dose 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;
- weight of female 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.

At the end of the experiment, all the rats were discarded following the procedures recommended for disposal of animals used for research purposes by the cruelty to animal act.

**Statistical analysis**

All results were analyzed using one-way ANOVA. Any P value less than 0.05 was considered
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3 | RESULTS

The results of this study on the effect of chronic administration of tramadol and codeine on the feeding behaviour of female Albino rats are presented. The data collected were subjected to Randomized Block Analysis of Variance (ANOVA), descriptive statistics of mean and standard deviation as well as a graphical representation.

**TABLE 1: Summary Factorial ANOVA table showing the influence exposure to chronic intake of Codeine and Tramadol on food intake.**

![Interaction graph showing the average food consumption based on time of exposure and treatment to Codeine and Tramadol among female Wister rats.](image)

The analysis showed the mean differences in feeding behaviour in female rats exposed to chronic intake of codeine and tramadol; rats exposed to a combination of Codeine and Tramadol X=33.45, Tramadol only X=39.96 and Codeine only X=40.71 significantly consumed lesser amount of food compared to female rats in the control group X=49.38. The mean differences in food consumption were significant \( p < 0.001 \). The result demonstrated that food intake decreased by 10.7% with exposure to chronic intake of Codeine and Tramadol compared to the control group.

The result demonstrated that food consumption increased for the control group while it declines significantly for exposed rats by 16% as the chronic exposure increase more than 18 days.

**TABLE 2: Summary Bonferroni mean comparison analysis showing the mean difference between rats exposed to chronic intake of Codeine and Tramadol and rats in the control group.**

![Interaction graph showing the average food consumption based on time of exposure and treatment to Codeine and Tramadol among female Wister rats.](image)

The result from Table 1 shows that exposure to chronic intake of Codeine and Tramadol significantly influenced food consumption among female Wister rats, \( F (3,641) = 25.53, p < 0.001, \eta^2 = .11 \). Further analysis was carried out to determine the mean differences among the treatment groups using Bonferroni mean comparison Test and the result is presented in Table 2.

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

![Interaction graph showing the average food consumption based on time of exposure and treatment to Codeine and Tramadol among female Wister rats.](image)

The result from Table 3 shows that exposure to Chronic intake of Codeine and Tramadol significantly influenced lower weight gain or weight reduction among Wister rats \( F (3,641) = 76.67, p < 0.001, \eta^2 = .26 \). Further analysis was carried out to determine the mean differences among the treatment groups using Bonferroni mean comparison Test and the result is presented in Table 4.

**FIGURE 1: Interaction graph showing the average food consumption based on time of exposure and treatment to Codeine and Tramadol among female Wister rats.**
TABLE 4: Summary Bonferroni mean comparison analysis showing the mean difference between rats exposed to Chronic intake of Codeine and Tramadol and those exposed to Normal saline on weight gain

| Source          | Sum of Squares | df | Mean Square | F   | Sig | Partial Eta Squared |
|-----------------|----------------|----|-------------|-----|-----|---------------------|
| Block           | 26033.875      | 27 | 964.218     | 1.953 | .003 | .076                |
| Treatment       | 113578.20      | 3  | 37859.403   | 76.675 | .000 | .264                |
| Treatment       | 8              |    |             |      |     |                     |
| Error           | 316593.62      | 641| 489.765     |      |     |                     |
| Corrected Total | 456115.70      | 671|             |      |     |                     |

The analysis showed the mean differences in weight gain among female rats exposed to chronic intake of codeine and tramadol; combined Codeine and Tramadol $\bar{X}$=133.33, Tramadol only $\bar{X}$=132.67 and Codeine only $\bar{X}$=137.67 significantly exhibited lower weight gain compared to female rats in the control group $\bar{X}$=164.25. The mean differences were significant ($p<.001$). The result demonstrated that weight gain decreased by 26% with exposure to chronic intake of Codeine and Tramadol compared to the control group. The result demonstrated that weight gain increased for the control group while it declined significantly for exposed rats by 16% as the chronic exposure increase more than seven days.

FIGURE 2: Interaction graph showing the interaction between time of exposure and treatment to Chronic intake of Codeine and Tramadol among Wister rats.

The line graph shows that longer period of chronic exposure induced weight loss in the Chronic intake of Codeine and Tramadol treated rats from the 18th _28th days of the exposure.

4 | DISCUSSION

We carried out a laboratory investigation on the effect of acute intake of codeine and tramadol in single and combined doses on the feeding behaviour of female Wister Albino rats. Behaviours related to feeding habits are normal activities of humans and animals for nutrients, energy and healthy living (Abraham et al., 2018). Feeding behaviours are defined as “the attitudes and psychosocial factors related to the selection and decision of which foods to eat” (Gallagher et al., 2000). Exposure to drugs for various reasons has been implicated as one major factor affecting the feeding behaviour of humans and animals alike (Vieira, 2015). Opiates and opioid substances have been linked to abnormalities in feeding behaviour. (FitzHenry et al., 2020). Codeine and Tramadol belong to such substances but literature to our knowledge are scarce on their effects on feeding behaviours at single and combined doses.

It is a social and public health concern that these drugs are used either as prescribed or by self-medication for several reasons (Ferguson et al., 2019), leading to addiction in most cases. For instance, the use of tramadol and codeine in combination is common in post-operative surgical procedures. Patients for most surgeries usually associate procedures with pain, and, since their experience is perceived as painful, this can lead them to avoid or
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delay treatment. (Carr & Goudas, 1999) To meet patients’ expectations of comfort, to enable them to continue to seek good healthcare, there is a need for drug development and technical association with pain to meet the need of patients.

In support of one the hypotheses postulated for this study, exposure to chronic intake of Codeine and Tramadol significantly influenced food intake among female Wister Albino rats, F (3,641) = 25.53, p < 0.001, $\eta^2 = .11$. Similarly, there was a significant effect of the exposure to chronic intake of Codeine and Tramadol on weight gain or weight loss of the female Wister Albino rats, F (3,641) = 76.67, p < 0.001, $\eta^2 = .26$.

Single-dose treatment of tramadol at 20 mg/kg body weight administered to the tramadol group reduced the amount of food consumed by the rats compared to the control group. The female rats in the control group ($\bar{x} = 49.38$), consumed more food within the period of treatment compared to the female rats in the tramadol group ($\bar{x} = 39.96$) Also, female rats exposed to tramadol were low in weight gain compared to female rats in the control group. Female rats in the control group ($\bar{x} = 164.25$), gained more weight than female rats in the tramadol group ($\bar{x} = 132.67$).

Similarly, female rats exposed to 8mg/kg body-weight single dose of codeine significantly showed low food intake and low body weight compared to the control group. Female rats in the control group ($\bar{x} = 49.38$), consumed more food within the treatment period compared to female rats in the codeine group ($\bar{x} = 40.71$). Bodyweight of females rats in the codeine single-dose group ($\bar{x} = 137.67$) was observed to be lower than the bodyweight of female rats in the control group ($\bar{x} = 164.25$).

Codeine and Tramadol are classified as opiates which are highly habit-forming and can lead to addiction and possible abuse if used in ways other than physician’s prescription predisposing the users to serious side effects. (Paolini, 2020) Such side effects as observed from the results of this research include weight gain or loss and loss of appetite. This is in line with the findings of similar studies. In a study, (Nielsen et al., 2019), reported inhibition of fish foraging and eating behaviour after exposure to prescription drugs at doses similar to environmental concentrations. 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 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.

Studies have shown that analgesic drugs in the opiate class cause varying degrees of side effects which include: drowsiness, nausea, vomiting and constipation. Such side effects can lead to a decrease in appetite, slowed digestion and weight loss over time. (Ersche et al., 2013 Vieira, 2015 McCabe et al., 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.

We observed that the combined group of codeine and tramadol significantly showed less food intake and lower body weight compared to Single doses of codeine, tramadol and control. Female rats in the combined codeine and tramadol treatment group ingested less food ($\bar{x} = 33.45$), compared to codeine group alone ($\bar{x} = 40.71$), tramadol group alone ($\bar{x} = 39.96$) and control group ($\bar{x} = 49.38$). Fe-male rats in the combined codeine and tramadol group gained less weight ($\bar{x} = 132.67$) compared to codeine group alone ($\bar{x} = 137.67$) compared to tra-madol group alone ($\bar{x} = 133.33$) and control group ($\bar{x} = 164.25$).

Reported use of tramadol and codeine among adolescents and as combined doses has been a source of concern, particularly in the West African Sub-region. (WHO, 2012). Using tramadol together with
other narcotic pain or cough medications can lead to serious side effects including seizures, respiratory distress, coma, and even death. (WHO, 2012). Physical examination of the female rats in the codeine only group, tramadol only group, and the combined codeine and tramadol group showed that they were sluggish and restless during the treatment period. We recorded one death on the 21st day of treatment in the combined Codeine and tramadol treatment group. The physically observed conditions are in line with some of the listed side effects of combined use of codeine and tramadol.

Although tramadol and codeine are reported to be mild opioids and are not as strong as some other opioid drugs like heroin, their use may still cause some of the same problems like other opioid drugs including death with overdose. Tramadol and codeine use has been linked with serotonin syndrome (Milano et al., 2017). Serotonin syndrome is a potentially life-threatening condition where the serotonin receptors are overstimulated leading to high fever, rapid pulse, shivering, sweating, trembling, muscle twitches, agitation and confusion (Milano et al., 2017). Reported fatigue as one of the side effects of continuous exposure to tramadol and codeine may be due to outcomes of the effects of serotonin syndrome (Walder et al., 2001). Fatigue lowers metabolic rate and causes a change in eating habits due to lack of appetite. (Walder et al., 2001). This explains the probable reasons for the observed low food intake and decrease in body weight among the codeine only group, tramadol only group, and combined codeine and tramadol group compared to the control group.

5 | CONCLUSION

Codeine and tramadol are opioids and widely used prescription drugs for the treatment of mild and severe pain. However, they are the most abused medicines by adolescents and young adults. Several reasons given for abusing opioid drugs include; enhancing sexual drive/ prolong ejaculation, extra energy for manual workers, euphoria, staying alert for long hours especially for commercial vehicle drivers and their mates and students, and dazed/drift to deep restful sleep. The use of these drugs continues to increase despite the side effects.

In this study, we showed that the chronic administration of codeine and tramadol in single and combined doses as drugs used for different purposes and particularly abused can affect the feeding behaviour of female Albino rats leading to low food intake and weight loss. These effects can be observed in the single administration of codeine and tramadol as well as in combined administration of codeine and tramadol. Codeine and tramadol are linked to several side effects including serotonin syndrome which may account for the observed outcomes of this research.

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