Effects of Separate and Combined Chronic Ingestion of Tramadol and Codeine on Aggressive Behaviour among Female Albino Rats

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Abstract: The relationship between drug use and aggressive behaviour and its consequences on social and financial burden on society is a source of recent concern. This study, therefore, examined the effects of acute exposure to Codeine and Tramadol on aggressive behaviour. Twenty-Eight (28) participants (Female Albino Rats) weighing between 120-150g and 4-6 weeks old, collected from the University of Ibadan Veterinary animal farm were used for this study. They were divided into 5 experimental groups of Codeine, Tramadol, combined Codeine and Tramadol, Control and intruder groups with 6 rats in each group except the intruder group with 4 rats. They were exposed to, 8mg/kg of codeine for the codeine group, 20mg/kg of tramadol for the tramadol group, combined 8mg/kg of codeine and 20mg/kg of tramadol for the combined group, normal saline for the control group and no treatment for the intruder group for 28 days. The rats were observed daily after treatment for, biting, dominant posture and scratching as attributes of aggressive behaviour. Randomized block ANOVA showed a significant effect of Codeine and Tramadol on aggressive behaviour among female albino rats, F (3,2010) = 53.53, p < 0.001, η²= .07. Female albino rats in the tramadol treatment group significantly exhibited more aggression (x̅= 14.08) than control group (x̅=11.53) codeine group (x̅=11.41) and combined group (x̅=7.36). The mean differences were significant (p<.001). It was concluded that chronic exposure to tramadol has implications for aggressive tendencies and combined exposure to tramadol and codeine may be injurious to health.

Keywords: Aggressive Behaviour; Codeine; Tramadol; Female Albino Rats

Introduction

The concern over social violence and aggression among young and old in many countries around the world cannot be overemphasized. More worrisome is the manifestations of
aggressive traits and violence among young adults and adolescents in colleges and higher institutions. Consequently, the frequent news of gun violence, police brutality, political violence, domestic abuse, resistance to police authorities, homicides and murder, and a host of behaviours associated with aggression or its tendencies are common in many societies.

Violence and aggressive behaviour are common terms used interchangeably. However, Eichelman (1992), in an attempt to draw a line between aggression and violent behaviour noted that there is ongoing confusion between the terms aggressive and violent behaviour. For this paper, the term violence specifically will be used to delineate behaviours motivated by the goal of the infliction of physical harm to others. Aggression, according to many authors is not a unitary behaviour but a constellation of adaptive behaviours that are amenable to topological classification and neurobiological manipulations (Brain and Al-Maliki, 1978, Valzelli, 1981). According to Moyer (1968) ethological framework, aggression is classified into the following classes, which highlight its adaptive character:

1. Predatory aggression which is produced by hunger and the presence of an object of prey,
2. Competitive aggression which involves fighting for dominance, social rank, and reproductive advantage,
3. Defensive or fear-induced aggression which occurs in response to an inescapable threat,
4. Irritative aggression which occurs in response to internal or external aversive stimuli in the absence of a significant fear component,
5. Territorial aggression is triggered by threats of intrusion into regions of established living activities,
6. Maternal aggression is characteristic of female animals defending their offspring against real or perceived threats,
7. Instrumental aggression is a learned behaviour reinforced by environmental contingencies.

Thus, aggression may be thought of as a complex behaviour that is highly specific to situational demands. It may be difficult to be reduced to one predictable construct. Also, the pharmacologic effects of a psychoactive substance are likely to connect directly and indirectly to the expression of these behaviours in a complex fashion. In nature, aggression can occur without violence like the aggressive displays of some animals, whereas violence, defined as behaviour motivated by the desire to physically harm another, almost always occurs within the context of aggression and is consequently synonymous with the concept of violent aggression.

Although the above definitions provide a framework in which to conceptualize aggression, the specific method by which it can be measured was not discussed. There are various approaches in the literature on how the measurement of aggression can be achieved and they vary widely. Some of the methods used by some studies include self-report scales of aggression, such as the Buss–Perry Aggression...
Questionnaire (Buss & Perry, 1992), the State-Trait Anger Inventory (Spielberger, Jacobs, Russell, & Crane (1983) and the Novaco Anger and Provocation Inventory (Novaco, 2003) and others use behavioural measures, like the Competitive Reaction Time Task (Epstein & Taylor, 1967) and the Point Subtraction Aggression Paradigm (Cherek, 1981, 1992). Others still use a combination of self-report and behavioural aggression measures, of which there are over 200 (Ronan, Dreer, Maurelli, Ronan, & Gerhart, 2013). In animal studies, aggression is often operationalized using the resident intruder test (Miczek, 1979) or direct attack-related behaviours.

It is commonly known that using drugs can increase paranoid and irrational thoughts, mood swings, and irritability, amongst many other side effects (Chermack, Grogan-Kaylor, Perron, Murray, De Chavez, & Walton, 2010). Over time, drugs have been linked to anger and aggression. Drugs have either been used to alleviate uncomfortable emotional states or have been implicated in the precipitation of anger and aggression. Not only do many of the mood-altering substances impair perception but also there is proof that drugs, through their ability to alter neurotransmitter levels alter mood state (Chermack, et al., 2010). Generalizations about the linkage of drugs of abuse and violence are complicated by the direct and indirect levels of interaction (Goldstein, 1985). These include drugs activating aggression-specific brain mechanisms; drugs acting as a reason for indulgent in violent and aggressive behaviour; and violent behaviour representing how a drug habit is maintained and preserved.

Research has implicated several psychological characteristics to have a direct link to the risk of substance abuse. These behavioural characteristics include aggression hyperactivity, impulsivity (McCord and McCord,1960; Hechunan, Weiss, & Perlman, 1984), antisocial behaviour (Robins, 1966; Whitesell, Bachand, Peel, and Brown, (2013)), a disinhibitory motivational state (Gorenstien and Newman, 1980), and deviant temperament (Tarter, Kabene, Escallier, 1990), all of which may involve poor regulation of aggressive impulses.

Aggressive behaviour and drug use among humans have frequently been linked together (Pihl & Sutton, 2009). Research studies have shown that individuals who engage in both drug use and display of aggressive behaviour are more likely to be irresponsible, put themselves and others at risk, and are entangled in the legal system which all amount to a significant social problem (Hammersley, 2011). There is an ongoing and increasing serious concern on the relationship between drug use and aggressive behaviour (Hoaken, Hamill, Ross, Hancock, Lau, & Tapscott 2012). The relationship between drug use and aggression as well as other antisocial behaviours have generated a wealth of research majorly because of the social and financial costs on the society. Evidence supporting the link between drug use and aggression, antisocial behaviour, and crime has been mounting since the 1930s (East, 1939). Evidence are in the comprehensive reviews of this relationship which have been periodically published since then
Overall, the literature suggests that the relationship between drugs and aggression is highly complex and is governed by a combination of both transient and permanent physiological, environmental, and individual differences factors. Although multiple factors are associated with the relationship between drug use and aggression, substantial research has been devoted to isolating specific factors such as physiological (Julien, 2003; Lee, Schroeder, Karschner, Goodwin, Hirvonen, Gorelick, & Huestis, 2014; Hoaken and Pihl, 2000; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998; Neal & Fromme, 2007; Smith, Homish, Leonard, & Collins, 2013), the individual difference (Giancola, Godlaski, and Parrott, 2005; Parrott, 2007; Krueger, Markon, Patrick, Benning, & Kramer, 2007; Moeller, Dougherty, Barratt, Oderinde, Mathias, Harper, & Swann, 2002), and environmental (Hoaken et al., 2012; Moeller et al., 2002), to better understand causal pathways between drug use and aggressive behaviour.

Sex differences in physical aggression are found early in childhood and are maintained through childhood into adulthood, mostly. A persistently aggressive group would typically contain a higher proportion of boys and a consistently non-aggressive group would normally contain a higher proportion of girls (Archer, 2012). This leads to implications that the early development of sex differences in aggression implies that they are not the result of socialization influences. The implication is that, although humans learn behaviours from society, differences in aggression could have innate properties. In their paper, Sex differences in Aggression: A Rejoinder and Reprise, Eleanor and Carol, (1980), discussed that evidence on the differential socialization of boys and girls support the view that boys do not receive more reinforcement for aggression than girls.

Animal models of experimental and human studies have provided insight into the acute effects of drugs and psychoactive substances on aggressive behaviour. Some of the psychoactive, psychopharmacological or psychotropic drugs include alcohol, hallucinogens, and psychedelics, (cannabis, psilocybin, lysergic acid diethylamide), stimulants (cocaine, amphetamines, methamphetamine), opioids (morphine, codeine, heroin, tramadol), anabolic-androgenic steroids, designer drugs (bath salts, plant food), and depressants (ketamine, \(\gamma\)-hydroxybutyric acid or GHB). These substances may be used medically, recreationally, to purposefully improve performance or alter one’s consciousness or for research. Some of the numerous drugs and substances abused that usually have an effect on aggressive behaviour are opioids (tramadol and codeine).

**Tramadol**

Tramadol is an analgesic with opioid-like effects when taken orally and a unique pharmacokinetic and pharmacodynamics profile relative to other opioids (Schnabel, Reichl, Meyer-FriBem, Zahn, Pogatzki-Zahn, 2015; Vlok, Melhuish, Chong, Ryan, &White, 2017). It is primarily prescribed to treat mild to severe pain.
in both acute and chronic cases. When taken orally at high doses, tramadol may produce a euphoric sensation similar to oxycodone, when abused. Reported side effects of tramadol include itching, nausea, and constipation. Serious side effects include seizures, serotonin syndrome, decreased alertness, and dependence (Beakley, Kaye, & Kaye, 2015). It is available in the market as an immediate and extended-release formulation and used for the treatment of mild to severe pain at doses up to 200 (immediate) or 300 (extended-release) milligrams per day. The World Health Organization (WHO) classification of Tramadol as a step 2 medication on its analgesic ladder makes it the only opioid classified as a step 2 medication, therefore, making it the only opioid-like medication available for the management of moderate and severe pain in countries whose policies limit patient and provider access to step 3 “strong” medications (Santos Garcia, Lech, Campos Kraychete, Rico, Hernandez-Castro, Colimon, 2017; Vijayan, Afshan, Bashir, Cardosa, Chadha & Chaudakshetrin, 2018). The first synthesis of Tramadol was in 1962 and it became commercially available as an analgesic medication since 1977 (Grond, and Sablotzki, 2004). Tramadol as a synthetic compound inhibits serotonin and norepinephrine reuptake before being converted through hepatic metabolism to active and inactive metabolites (Miotto, Cho, Khalil, Blanco, Sasaki, & Rawson, 2017). It is marketed as a hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal (spray), rectal (suppositories), subcutaneous, and intramuscular administration. It is also available in combination with acetaminophen (paracetamol), immediate-release and extended-release formulations. Continuous exposure to Tramadol like other opioids can lead to opioid physical dependence which can lead to withdrawal syndrome if exposure is subsequently discontinued (Lofwall, Walsh, Bigelow, & Strain, 2007). Unlike many other opioids, tramadol exerts effects on multiple neurotransmitter systems, including the opioid and also serotonin and norepinephrine systems. The effects of tramadol are only partially blocked by the opioid antagonist naloxone (Apaydin, 2000; Desmeules, 1996). Cross-tolerance with other opioids is minimal with tramadol, suggesting that its full profile of effects is a combination of its activities on opioid, serotonin and norepinephrine systems (Lofwall, Babalonis, Nuzzo, Siegel, Campbell, & Walsh, 2013; Dunn, Tompkins, Bigelow, & Strain, 2017; Lanier, Lofwall, Mintzer, Bigelow, & Strain, 2010).

Tramadol is abused worldwide and its abuse is dependent on the regulatory status in a particular country or region. Countries in which a wide variety of opioid products are available generally report low rates of tramadol abuse relative to other opioids while countries that impose greater restrictions on opioid products and rely more heavily on tramadol for primary pain management often report tramadol abuse (Radbruch, Glaeske, Grond, Munchberg, Scherbaum, & Storz, 2013; Zosel, Bartelson, Bailey, Lowenstein, & Dart, 2013). According to Salm-Reifferscheidt (2018), the
abuse potential of tramadol in Egypt and other African countries was of particular concern, and there had been an observed increase in the importation of illicit and adulterated tramadol into these countries (Klein, 2019). Tramadol abuse among adolescents and young adults in those countries have been reported to be as high as 8.8% - 12.3%, respectively (Bassiony, Salah El-Deen, Yousef, Raya, Abdel-Ghani, El-Gohari, 2015; Bassiony, Abdelghani, Salah El-Deen, Hassan, El-Gohari, & Youssef, 2018). For instance, studies in Nigeria indicate the use of Tramadol cuts across all parts of the country. In Kano, Northern Nigeria, a cross-sectional study amongst commercial bus drivers reported that 85.2% of respondents’ misuse Tramadol (Yunusa, Bello, Idris, Haddad, & Adamu, 2017). Another cross-sectional study among ‘Almajiris’ (street children), in Borno Northern Nigeria, reported a 7% prevalence of Tramadol misuse (Abdulmalik, Omigbodun, Beida, & Adedokun, 2009). In Owerri, South-East Nigeria, a survey of the use of psychoactive substances amongst university students indicated that 53.4% admitted they use of Tramadol (Duru, Oluoha, Okafor, Diwe, & Iwu, 2017). According to 39th WHO, ECDD Report, 2017, There is a widespread misconception regarding the use of tramadol among the general population with some viewing it as a mood enhancer, means to increase sexual stamina or as an energy booster during work. Individuals who abuse tramadol report that such mood-elevating properties cause them to take higher doses of the drug or to take it more often than had been prescribed leading to abuse of tramadol, causing psychological or physical dependence and increasing the potential for overdose risks.

**Codeine**

Codeine is an alkaloid of phenanthrene and naturally occurring. It is an opioid agonist with analgesic, antidiarrheal and antitussive activities. Codeine extremely mimics the effects of Morphine as morphine is a major metabolite of codeine (Benini, Barbi, Gangemi, Manfredini, Messeri, & Papacci, 2010). Codeine binds with stereospecific receptors at many sites within the Central Nervous System (CNS) to alter processes affecting both the perception of pain and the emotional response to pain. Precise sites and mechanisms of action have not been fully determined. It has been proposed that there are multiple subtypes of opioid receptors, each mediating various therapeutic and/or side effects of opioid drugs. Codeine has a very low affinity for opioid receptors and the analgesic effect of codeine may be due to its conversion to morphine (Gilman, Goodman, Rall, & Murad, 1985).

Codeine is commercially available as water-soluble hydrochloride, sulfate or phosphate and is administered orally in the form of linctuses for the relief of coughs, and as tablets for the relief of pain. Codeine phosphate is also given parenterally for the relief of pain. Codeine, usually as the phosphate, is often administered by mouth together with acetylsalicylic acid or paracetamol. The equivalence of the analgesic effects is 120 mg of codeine corresponds to 10 mg of morphine and 30 mg of codeine to 325 to 600 mg of aspirin (Gilman, Rall, Nies, & Taylor, 1990).
Codeine and codeine-containing products are among the drugs of abuse majorly by youths and young adolescents which has become a foremost emerging health challenge in various nations around the world. This might be attributed to the fact that the drugs are accessible in the range of over-the-counter (OTC) medications which are constantly bought without the need for a doctor’s prescription (Robinson, Robinson, McCarthy, & Cameron, 2010). According to a documentary titled “Sweet Sweet Codeine” released by British Broadcasting Corporation (BBC) in May 2018, thousands of youths in Nigeria, for instance, are addicted to codeine-containing products, especially the cough syrup formulation. This, however, led to the subsequent ban on the importation and sale of codeine as an active pharmaceutical ingredient (API) by the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria (Washington Post, 2018). The ban on the importation and sale of codeine as an API has led to a drastic scarcity of codeine-containing products within the country, although, there is presently no legal backing on obtaining these products as a prescription-only medicine.

**Drug-Drug Interaction between Tramadol and Codeine**

Tramadol and codeine are both opiates. Codeine is made from the poppy plant, just like morphine, heroin, and opium. Tramadol is chemically similar to codeine, but it's synthesized from precursor molecules in a laboratory. Opiates work because the central nervous system has three main opioid receptors in the nerve cells that, when coupled with natural opioids help the body to govern pain sensation, reward, aspects of gastrointestinal function, aspects of respiratory function, and aspects of urogenital function. These receptors are named after Greek letters: Mu receptors, Delta receptors, and Kappa receptors. They sit on the membrane of nerve cells and activate when an opioid, whether naturally occurring in the body or introduced in the form of a drug, fits into the molecule like a key in a lock. Opiate drugs mimic the natural opioids produced by the body. Their molecules fit into the same receptors and activate them. Codeine, tramadol, morphine, and all other poppy derivatives target and activate mostly the Mu receptors, meaning they are "Mu receptor agonists" (Epstein, Preston, & Jasinski. 2006).

These receptors and the naturally occurring (endogenous) opioids they pair with are responsible for the body’s own efforts to deaden the pain. Because of this, flooding the Mu receptors with pharmaceutical opioids like codeine, tramadol, and others can increase the painkilling (analgesic) properties of that part of the central nervous system. Unfortunately, because the endogenous opioid system also governs reward pathways, pharmaceutical opioids are highly addictive. Endorphins are the main endogenous opioids the nervous system secretes in response to sex, a delicious meal, and other forms of pleasure. Because opiate drugs activate the same Mu receptors endorphins do, euphoria and a profound sense of well-being are potential side effects of all the opiate drugs on the market. Patients can become addicted physically and mentally as both their bodies and minds begin to crave that state of bliss.

URL http://journals.covenantuniversity.edu.ng/index.php/cijp
Research on tramadol and codeine relationship with aggressive behaviour is scanty even more scant than the research on other opioids and aggressive behaviour. This is an indication that researches on the link between opioids and aggression-eliciting properties are scarce and perhaps poorly understood. Although past research has shown acute codeine administration (at a dose of 50 mg/70 kg) to increase aggressive behaviour in a sample of young, healthy male participants after being provoked by a fake opponent (Spiga, Cherek, Roache, & Cowan,1990), further research is, therefore, needed to determine how other variables, such as sex or age, may moderate this relationship. Overall, there is no evidence to support a direct pharmacological relationship between opioid use and aggression, although third variable factors may contribute to the relationship between heroin use and increased aggression in some cases.

Purpose of Study
This research is, therefore, aimed at mainly, to experimentally examine the effects of separate and combined chronic administration of the opioids, Codeine and Tramadol on the aggressive behaviour of female albino rats, and specifically to;

- examine the effects of chronic Codeine administration on aggressive behaviour among female albino rats.
- examine the effects of chronic Tramadol administration on aggressive behaviour among female albino rats.
- examine the effects of the combined acute administration of both Codeine and Tramadol on aggressive behaviour among female albino rats.
- determine which drug elicits higher or lower aggression levels in female albino rats in comparison to the other drug.

Hypotheses
In determining the relationship between the chronic administration of drugs (codeine and tramadol) and aggressive behaviour in female albino rats, the following hypotheses were formulated and tested.

1. Chronic exposure to Tramadol and Codeine will significantly affect the aggressive behaviour of female albino rats exposed to the drugs.
2. Female albino rats exposed to tramadol will display more aggressive behaviour than female albino rats exposed to codeine.
3. Tramadol and Codeine will singly and jointly interact to affect the aggressive behaviour of female albino rats exposed to chronic administration of the drugs.

Methodology
Research design
The design used in this study is an independent group randomized design. 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, Codeine and Tramadol and the fourth group was the control group. The independent variables are the chronic administration of Codeine, Tramadol, and the combination of both to the female albino rats. The dependent variable is aggressive 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 28 female Albino rats weighing between 120 -150g and 4 – 6 weeks old were used. They were divided into five (5) groups with six (6) female rats in each group except the fifth group which had only four rats. The groups were Codeine group, Tramadol group, combined Codeine and Tramadol group, control group, and the intruder group with four (4) rats used as intruder rats in the aggression experiment. The rats were randomly assigned to the different groups.

Drugs
The drugs used for this study were Tramadol HCL (50 mg capsules) and Cough syrup (containing 220mg codeine). Codeine and Tramadol 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 (Rat Medication Guide, 2010), while Codeine was administered at a dose of 8mg/kg body weight every 24 hours following the recommended therapeutic dose of 2mg/kg/6hrs (Achukwu, Omorodion, Erabor, Alohi, Eze & Okoyeocha, 2019). The dosage administered in this study was, Codeine- 8 mg/kg and Tramadol- 20mg/kg.

Materials/Instruments
The following materials and instruments were used for this study;
1. 6 experimental rat cages.
2. Recording sheets
3. Distilled water/saline
4. Laboratory coat
5. Oral cannula for administration of drugs
7. Face/Nose Mask
8. Colored markers for easy identification of female albino rats from, the control and experimental rat.
9. Measuring cylinders used in diluting and measuring the solution.
10. Weighing balance for the daily weighing of rats.
11. Stopwatch for time keeping and recording
12. Disposable syringes
13. Mouse cubes for feeding the rat
14. Codeine syrup
15. Tramadol capsules (powder in capsule serially diluted with distilled water)

Procedure
Two weeks before the commencement of experiments, the rats were brought into the laboratory and left to acclimatize in the laboratory. During this period, the rats were provided with food and water without any form of deprivation. The rats were then randomly assigned into 5 groups, the Codeine group, the tramadol group, the Combined group, the Control group, and the intruder group.

The study took 28 days, in which the rats in the experimental group were exposed to the drugs (oral ingestion of the drugs). Each cage was clearly labelled with the drug category. Rats were also marked for identification and rats in each cage were labelled 1 to 6. The resident-intruder paradigm was used. It is a method of studying or observing aggressive behaviour which
introduces an intruder rat to the resident rat.

At the start of the experiment each day, all the rats were weighed and records of the weights against each rat were kept in a chart. This is to determine what dose of drugs to administer to each rat daily. 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. During the first 30 minutes of post-drug administration, food and water were withdrawn from all the cages.

After the 30 minutes of post-drug administration, one rat from the experimental group was placed in a free experimental cage and an intruder rat was introduced. The behaviour of the resident rat was observed and data was collected. Each experimental session lasted for 5 minutes during which observations for aggressive behaviour for each rat were made. The attributes of aggression observed were dominant posture, scratching, and biting. These behaviours were recorded with a recording sheet marking the number of times the experimental rat exhibited any of the behaviours. After 5 minutes, both the experimental rat and the intruder rat were removed from the experimental cage and returned to their respective cages. The process was repeated for all the remaining rats in all of the experimental groups of Codeine, Tramadol, Combined Codeine and Tramadol, and then the control group. This same procedure of observation was repeated for three trials for each rat daily for the 28-day duration of the experiment.

On each day of the experiment, the following including regular feeding was carried out:
- Weighing of each rat
- Oral administration of drugs
- Observation of the dominant postures, scratching, and biting.

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

Results

The results of the study on the effect of chronic administration of tramadol and codeine on the aggressive 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 Randomized block ANOVA Table showing the effect of administration of Tramadol and Codeine on aggressive behaviour of female albino rats.

<table>
<thead>
<tr>
<th>Source</th>
<th>Type III Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
<th>Partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block</td>
<td>7737.128</td>
<td>2</td>
<td>3868.564</td>
<td>53.354</td>
<td>.000</td>
<td>.050</td>
</tr>
<tr>
<td>Treatment</td>
<td>11643.557</td>
<td>3</td>
<td>3881.186</td>
<td>53.528</td>
<td>.000</td>
<td>.074</td>
</tr>
<tr>
<td>Error</td>
<td>145739.453</td>
<td>2010</td>
<td>72.507</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>165120.138</td>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The result from Table 1 shows that Tramadol and Codeine significantly affected the aggressive behaviour among the female albino rats. \( F(3,2010) = 53.53, p < 0.001, \eta^2 = .07. \)

The result demonstrated that aggressive behaviour increased by 7% with the intake of the psychoactive substances.

Table 2: Summary Bonferonni mean comparison analysis showing the mean difference between aggressive behaviour of female albino rats ingested with different drugs.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.E.M</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CODEINE</td>
<td>11.413</td>
<td>.379</td>
<td>-</td>
<td>4.046*</td>
<td>-.113</td>
<td>-2.669*</td>
</tr>
<tr>
<td>COMBINED</td>
<td>7.367</td>
<td>.379</td>
<td>-</td>
<td>-4.16*</td>
<td>-6.71*</td>
<td></td>
</tr>
<tr>
<td>CONTROL</td>
<td>11.526</td>
<td>.379</td>
<td>-</td>
<td>-2.56*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAMADOL</td>
<td>14.081</td>
<td>.379</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

b. Adjustment for multiple comparisons: Bonferroni.

From the analysis, mean differences showed that female albino rats in the tramadol treatment group (\( \bar{x} = 14.08 \)) and control group (\( \bar{x} = 11.53 \)) significantly exhibited more aggressive behaviour compared to rats in the codeine (\( \bar{x} = 11.41 \)) and combined group (\( \bar{x} = 7.36 \)). The mean differences were significant \( (p < .001) \).
Female albino rats in the Tramadol treatment group and control group were shown to exhibit more aggressive behaviour compared to rats in the codeine and combined group. Based on this, the hypothesis that states that there would be a significant difference in the aggressive behaviour of female albino rats ingested with different drugs is accepted.

The line graph shows how the effects of a long period of exposure to chronic intake of psychoactive drugs (Codeine & Tramadol) on rats was evident from the 14th – 28th days of the exposure. Rats ingested with drugs displayed lower aggression levels when compared with the control group. Rats ingested with tramadol exhibited more aggressive behaviour when compared to that of the codeine and combined group.
Discussion

The findings of this study show the significant effect of the link between Codeine and Tramadol on the aggressive behaviour of female albino rats. The hypothesis which stated that chronic exposure to Tramadol and Codeine will significantly affect the aggressive behaviour of female albino rats exposed to the drugs was thus validated.

The administration of tramadol and codeine on the rats significantly increased the aggressive behaviour of the rats by about 7%. The group with the highest aggression mean was the tramadol group with 14.08, the control group with 11.53, the codeine group with 11.41, and the combined group with 7.37.

The results of this study show that the tramadol group displayed the highest level of aggression compared to all the other groups. The tramadol group was observed during the experiment to be very jumpy, easily agitated and very swift to attempt to inflict harm on the intruder rats when compared to the rats in other groups. There are indications that Tramadol is unique and may be different from other opiates laying some doubts about the erroneous belief that tramadol may not be as harmless as we are popularly led to believe. Researches show that tramadol is a complex synthetic opiate, which has actions on multiple neurotransmitters and receptors over and above other opioids. It is a serotonin releasing agent, a noradrenaline reuptake inhibitor (Serotonin-norepinephrine reuptake inhibitor-SNRI), and an NMDA receptor (BMJ, 2013). They affect two important brain chemicals, serotonin, and norepinephrine an indication that the physical withdrawal symptoms may not be as severe as other opiates. Tramadol acts in a way to inhibit the reuptake of serotonin and norepinephrine, thus increasing the amount of both neurotransmitters in the system (Spies, Swart, van der Zanden, de Rooij, van Munster, 2017). These neurotransmitters are responsible for mood and their increase may lead to the increased activity observed in the tramadol group. The symptoms that accompany the use of tramadol are very severe and distressing for the individual that uses it. These symptoms include aggression and insomnia, severe anxiety, increased heart rate, depression, hyperactivity, serotonin syndrome, respiratory depression, and liver failure (Duke, Bigelow, Lanier, & Strain, 2011). It also possesses a marked ability to induce seizures leading to the death of the victim. Report of symptoms identical to those of serotonin syndrome (symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhoea), were present in this study. Serotonin syndrome is a serious condition caused by excess serotonergic activity and characterized by altered mental status and heightened neuromuscular and autonomic activity (Junji, & Mark, 2009). This may explain why the rats in the tramadol group were relatively more active than the rats in the other drug groups.

Tramadol is a drug that is most commonly abused for its calming effects. Results from this study show that the aggression in the codeine group was very low and is only slightly higher than the least aggressive group, the combined group. During the experiment, the rats in this group appeared to be relatively less active
than other groups except for the combined group. They were observed to exhibit drowsiness, shakiness, and weakness leading to inactivity and were not eating as much as rats in the other groups except the combined group. Codeine is known to have a higher analgesic activity than tramadol and produces more euphoric effects on the body system (Benini et al., 2010). Codeine is an analgesics agent that selectively relieves pain by acting in the Central Nervous System without changing consciousness. Its higher analgesic activity suggests that it is stronger than tramadol and hence further depresses the system in more ways than tramadol could. This makes the reactions to this opioid more adverse and included drowsiness, sedation, and shortness of breath as observed in the experimental rats in the codeine group. Concerning aggression, the codeine group displayed way less aggression than the tramadol group. The causal factors may be linked to the identified higher analgesic property that codeine has over tramadol.

The results show that female rats in the combined group of Tramadol and Codeine exhibited the lowest level of aggression with a mean difference of 4.0 when compared to the codeine group and 6.7 when compared with the tramadol group. Rats treated with the combination of codeine and tramadol had the effects of both opioids working in them simultaneously, leading to a stronger force of analgesic activity on them. They were the least aggressive as they had combined strength of two depressants at work on their body system. Both tramadol and codeine cause respiratory depression. Respiratory depression or hypoventilation is a breathing disorder characterized by slow and ineffective breathing. The combination of opioids and central nervous system depressants had an additive effect on the oversedation and respiratory depression of the female albino rats in this group. Respiratory depression is a potentially lethal complication that occurs when opioids are used in combination with other opioids or depressants. The rats in the codeine and tramadol (combined) treatment group experienced higher sedation, were quick to assume a subdued position when faced with an intruder rat, greatly reduced weight gain, lessened self-grooming practices, slowed down physical activity and eventually death of four out of six rats in the group. Other physical defects observed in the rats of the combined group throughout the experiment were extreme weight loss, observable discomfort in hind limb(s), bloodshot eyes, bleeding nose, inactivity for several hours even when faced with an intruder rat, loss of appetite, shakiness, dizziness, and drowsiness. The average weight of the rats in the combined group dropped by 34% at the end of the experiment.

**Conclusion**

The opioids, Codeine, and tramadol are drugs that reduce the perception of pain felt by an individual, = resulting in a relaxed, euphoric feeling. This feeling should, therefore, reduce the chance that one will display aggression when the drug is administered, which was observed to be very true for codeine and also in combination with tramadol. However, prolonged use of tramadol usually leads to an excess of serotonergic activity, known as serotonin syndrome. This results in increased alertness, jerky movements,
paranoia, which could all be contributing factors to aggressive behaviours. It has been concluded, therefore, from this study that the chronic intake of Codeine reduces aggressive behaviour. Although the symptoms associated with tramadol and codeine are quite non-identical (the former including feelings of agitation or restlessness; and the latter including drowsiness), this study has shown that they have similar neurological effects on aggressive behaviour. Prolonged intake of one or both of the drugs can cause nearly irreversible damage to the nervous system. A lot of times, death is the effect of the combined intake of the drugs as observed among the rats used for this study. Tramadol, on the one hand, creates a state of restlessness and agitation in users which could translate to aggressive behaviours in certain situations. Codeine, on the other hand, creates a state of drowsy and relatively inactive disposition on the users. Awareness of the serotonergic effects of tramadol is important in avoiding potential side effects and unwelcome interactions with other medications. Combining codeine and tramadol is dangerous because their combined effects on the Central Nervous system can increase dramatically and can lead to accidental overdoses. While this might not seem to have any relationship with aggression, we can only assume or infer that a person who is sick, nearly to the point of death would not be strong enough to be aggressive.

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