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# Sildenafil Citrate and Tramadol Administered Separately and in Combination Affects Basal Metabolic Rate, Triiodothyronine ($T_3$) and Cortisol Levels in Albino Wistar Rats

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## ABSTRACT

Studies have reported abuse of medications used in treating erectile dysfunction and premature ejaculation, with several adults taking far above recommended doses. A variety of negative effects (including exhaustion) have been associated with the use of these drugs. This study therefore assessed the effects of separate administration of sildenafil citrate, tramadol and their combination on Basal Metabolic Rate (BMR) in relation to body weight, $T_3$ and cortisol levels in rats. Twenty male albino Wistar rats weighing 150-180 g were randomly assigned into 4 groups (n = 5) thus: control (0.2 mL normal saline), sildenafil-treated (10 mg $kg^{-1}$), tramadol-treated (20 mg $kg^{-1}$) and sildenafil+tramadol-treated (10 and 20 mg $kg^{-1}$, respectively) groups. The different drugs were administered orally, every 2 days, for 3 weeks, after one week acclimatization period. The body weight and BMR were measured weekly and serum concentrations of $T_3$ and cortisol were measured at the end of 21 days of treatment. Tramadol significantly ($p<0.05$) reduced mean food intake, compared with control. Sildenafil and sildenafil+tramadol-treated groups had significantly ($p<0.001$, $p<0.05$) lower body weight change, compared with control. Sildenafl-treated group had a lower change in BMR, significantly ($p<0.05$) different from control and sildenafil+tramadol-treated groups. Serum $T_3$ concentration was significantly ($p<0.001$) increased in tramadol and sildenafil+tramadol-treated groups, compared with control and sildenafil treated groups. Serum cortisol concentration was significantly ($p<0.001$) reduced in all treated groups, compared with control. Sildenafil citrate decreased body weight, BMR, serum $T_3$ and cortisol concentrations, while tramadol increased BMR and serum $T_3$ concentration, but decreased serum cortisol concentration and body weight. A combination of these drugs seems to act in a pattern similar to tramadol. This probably explains the feeling of exhaustion reported by users of these drugs.

**Key words:** Basal metabolic rate, cortisol, sildenafil citrate, tramadol, triiodothyronine

## INTRODUCTION

Basal Metabolic Rate (BMR) is the rate at which energy is used by an organism at complete rest measured in humans by the heat given off per unit time and expressed as the calories released per kilogram of body weight. It is the energy required by a person at complete rest to carry out the body's chemical reactions and accounts for 50-70% of the daily energy expended in most sedentary individuals (Guyton and Hall, 2000). Basal metabolic rate is affected by factors such as weight (Leibel *et al*., 1995), climate, age (Alexander, 1979), temperature (Britt *et al*., 1991), thyroid hormones (Guyton and Hall, 2000) and cortisol.

Sildenafil citrate (Viagra) is a phosphodiesterase type 5 (PDE5) inhibitor that was discovered by Pfizer scientists and is used to treat Erectile Dysfunction (ED) in men (Terrett *et al*., 1996). Sildenafil is also used to treat pulmonary arterial hypertension. Sildenafil citrate acts by inhibiting cyclic guanosine monophosphate (cGMP) specific PDE5, an enzyme that promotes degradation of cGMP (Salam *et al*., 2015). Phosphodiesterase-5 is primarily distributed within the arterial wall, smooth muscles of the lungs and penis, thus, making sildenafil citrate to act selectively in these areas without inducing vasodilatation in other areas of the body. Documented cardiovascular effect of sildenafil is widespread. It poses minimal cardiovasculars risk to healthy people taking it (Shinlapawittayatorn *et al*., 2005). At recommended doses (25-100 mg one hour before sexual intercourse and not more than once daily), sildenafil has little (not clinically significant) effect on blood pressure and heart rate in men with ED and is likely to be clinically insignificant in men taking concomitant anti-hypertensive medication (Kloner and Zusman, 1999; Zusman *et al*., 2000). Sildenafil citrate is known for its vasodilatory and venodilatory effects on the peripheral vasculature of humans (Cheitlin *et al*., 1999), unlikely inotropic effect on cardiac muscle of humans and dogs (Corbin *et al*., 2003), pre-conditioning-like cardioprotective effect in the rabbit, rat and mouse heart (Salloum *et al*., 2003) and powerful cardioprotective effects through opening of mitochondrial ATP-sensitive potassium channels in rabbits (Ockaili *et al*., 2002). In addition to the cardiovascular system, documented research with sildenafil also cuts across the respiratory (Goldberg *et al*., 2011), nervous (Fazan *et al*., 2008; Kyratsas *et al*., 2013), gastrointestinal (Eherer *et al*., 2002) and renal (Eherer *et al*., 2002; Lauver *et al*., 2014) systems as well as the liver (Ji *et al*., 2005; Eweka and Eweka, 2011; Nna *et al*., 2015a).

Tramadol is a strong opioid drug used to treat severe pain in adults and children over 12 years of age. Tramadol acts on the nervous system to reduce pain sensation. The mode of action of tramadol is not fully understood but some researchers (Desmeules *et al*., 1996; Grond and Sablotzki, 2004) suggested that tramadol acts by binding of parent and $M_1$ metabolite to μ opioid receptors in animals and also, by weak inhibition of re-uptake of nor-epinephrine and serotonin, which justifies it use for treatment of Premature Ejaculation (PE) (Safarinejad and Hosseini, 2006; Salem *et al*., 2008). Tramadol reduces sweating threshold (De Witte *et al.,* 1998) and postoperative shivering (Scott and Perry, 2000) but has no significant cardiac effect (Tarkkila *et al.,* 1997). The respiratory effect of tramadol has been widely documented. Generally, opioid analgesics decrease tidal volume and respiratory rate (Lee *et al*., 1993). Tramadol has been reported to cause decreased respiratory rate (Vickers *et al.,* 1992) and life threatening respiratory depression (Shipton, 2000; Scott and Perry, 2000). Reported adverse effects of tramadol include nausea, vomiting, constipation, dizziness, autonomic nervous effect headache, sedation, asthenia (weakness) and fatigue (Nna *et al*., 2014a).

Previous studies had reported that ED and PE medications are widely abused (Nna *et al*., 2014b) and associated the abuse of these drugs with various degrees of discernable side effects (Nna *et al*., 2014a). Some studies have demonstrated that chronic administration of these medications may be toxic to male reproductive tissues (Bliesener *et al*., 2005; Cacciola *et al*., 2008; Al-Fartosi, 2009) and the liver (Eweka and Eweka, 2011; Nna *et al*., 2015a), among other toxic effects. Despite the vast research done with sildenafil citrate and tramadol respectively, there is paucity of scientific literature on their combined effects (as used in Nigeria today) on BMR in relation to $T_3$ and cortisol concentrations. Thus, the purpose of the present study is to assess the respective and combined effects of both drugs on BMR in relation to $T_3$ and cortisol concentrations.

## MATERIALS AND METHODS

**Experimental animals:** Twenty male albino Wistar rats weighing 150-180 g were obtained from the Department of Physiology, College of Medical Sciences, University of Calabar, Nigeria. The rats were allowed to acclimatize in their respective metabolic cages in the research laboratory for one week. All animals had access to rat feed and water *ad libitum*. They were kept under standard environmental conditions and ethical conditions guiding animal handling was adhered strictly.

**Experimental design and drug administration:** The experimental animals were divided into 4 groups (n = 5) thus; control, sildenafil-treated, tramadol-treated and sildenafil+tramadol-treated group. Sildenafil citrate (Maxheal Laboratories Pvt Ltd, India) was administered at a dose of 10 mg $kg^{-1}$, tramadol (Glow Pharma Pvt Ltd, India) was administered at a dose of 20 mg $kg^{-1}$, while sildenafil+tramadol-treated group received sildenafil (10 mg $kg^{-1}$) and tramadol (20 mg $kg^{-1}$), as previously used by Nna *et al*., (2015a, b). The control group received 0.2 mL normal saline. Administration was done per oral route for 21 days, at two days interval.

**Measurement of food and water intake:** Food intake was measured using previously described method as used by (Nna *et al*., 2013a, b). Briefly, 30 g of rat feed was measured using the electronic weighing balance and poured into the food trough of each animal and left till the following day. At about the same time the following day (24 h of feeding period), the quantity of feed remaining in the trough was weighed and recorded. The difference between the original quantity (30 g) and the remainder after 24 h of feeding was recorded as the food intake. This was done daily.

Also, using the method previously used (Nna *et al*., 2013a, b), 50 mL of water was measured using a syringe and poured into the water bottle of each animal and left till the following day. At about the same time the following day (24 h period), the volume of water remaining was measured and recorded. The difference between the original volume (50 mL) and the leftover was calculated and recorded as water intake.

**Measurement of body weight:** The body weight of the animals was measured using an electronic weighing balance. This was done on weekly basis before the measurement of the oxygen consumption. Each animal once removed from its cage was placed on the electronic weighing balance then reading and recording of the body weight was done when the animal must have rested on it. The average body weight for each animal and the changes in the body weight was calculated at the end of the experiment. The body weight of each animal on the day of the experiment was used to calculate the BMR.

**Determination of Basal Metabolic Rate (BMR):** The close system technique was used to determine the basal metabolic rate. The method used by Osim *et al.* (1994) and Owu *et al.* (2006), was modified and used for this study. The method depends on the principle that all energy used by the body in carrying out external and internal work is ultimately degraded into heat. A burette filled with water to the 0 mL mark, held in place by a clamp stand was connected to a conical flask through a tube fixed to a cork to make the flask airtight. The conical flask was connected to the lid of a desiccator by another tube. A fixed manometer containing water to a certain level was also connected through its right arm to the lid of the desiccator through another tube. The base of the desiccator contained soda lime to absorb $CO_2$ and was separated from the rest of it by wire gauze. The desiccator was made air tight using petroleum jelly. Prior to BMR determination, the animals were fasted for 12 h. The body weight of each animal was measured and the animal immediately

put inside the desiccator. The animal was allowed to acclimatize in the desiccator for 3-5 min before the lid was finally closed. This was done to ensure that the animal is in a resting state and comfortable position to eliminate the effects of exercise and excitation. The chamber was then covered with its lid and made air tight using petroleum jelly. The animal was then allowed to breath for 5 min during which the water in the right arm of the manometer was seen rising steadily due to a decrease in pressure within the system. At the 5th minute, water was added from the burette into the conical flask to bring the water level in the right arm of the manometer back to the original level (where it equilibrates with the water level in the left arm). The quantity of water added from the burette into the conical flask was recorded and is equal to the quantity of air removed (inspired) by the animal within the desiccator at that particular time. The lid was then slightly opened to let air into the desiccator. The difference between the final and initial volumes of water in burette gave the volume of oxygen consumed by each animal. This measurement was repeated three more times at five minutes interval each. The average volume was then calculated and used to calculate the oxygen consumption rate for 1 h and the latter was used to calculate the BMR.

The BMR was calculated in terms of oxygen consumption per hour per gram body weight of the rat (Hoar and Hicksman, 1975), because no suitable formula exists for calculating surface area of animal species other than man. The ratio of the volume of oxygen consumed per hour by each animal to the weight of the animal gave the BMR.

**Collection of blood samples and measurement of serum cortisol and $T_3$ concentrations:** The rats were anesthetized with chloroform and sacrificed. Blood was collected through cardiac puncture into plain capped sample bottles and allowed to stand for 2 h after which they were centrifuged at 1,000 rpm for 5 min using a bucket centrifuge machine (B-Bran Scientific and Instrument Company, England). Serum was obtained and used for hormonal assay. Serum concentrations of cortisol and $T_3$ were assessed using appropriate ELISA kits for cortisol and $T_3$ determination.

**Statistical analysis:** Results were expressed as Mean±SEM. Statistical analysis was done using computer software SPSS version 17.0 and Excel Analyzer. One way analysis of variance (ANOVA) followed by post hoc multiple comparisons test were used to compare mean values among groups. $p<0.05$ was the criterion for statistical significance.

## RESULTS

**Mean daily food and water intake:** The mean daily food intake for tramadol-treated group (16.59±1.09 g) was significantly ($p<0.05$) lower, compared with the control (20.67±1.57 g). Although, mean daily food intake for sildenafil+tramadol-treated group (17.29±1.62 g) was decreased compared with control and sildenafil-treated group (20.40±0.95 g), the difference was not significant (Fig. 1).

There was no significant difference in the mean daily water intake (mL) for control (30.03±1.27), sildenafil-treated (32.44±1.38), tramadol-treated (28.93±1.73) and sildenafil+tramadol-treated (28.68±1.16). The sildenafil-treated group presented an increase compared to other groups, but was insignificant (Fig. 2).

**Weekly body weights and body weight change:** The body weight of the animals in all the groups increased throughout the duration of study. The body weight of animals treated with

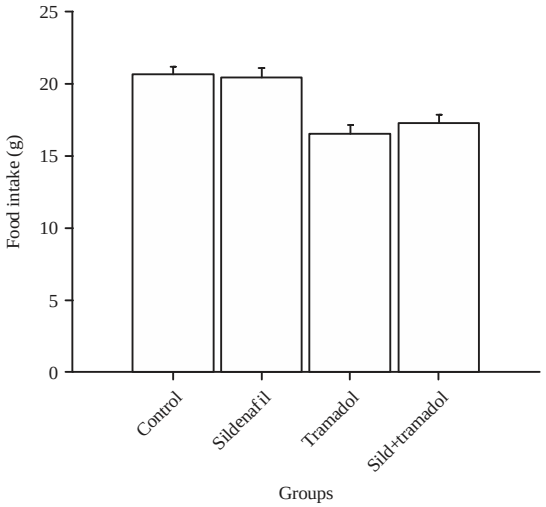


Fig. 1: Comparison of mean daily food intake in the different experimental groups. Values are Mean±SEM, n = 5, *p<0.05 vs. control

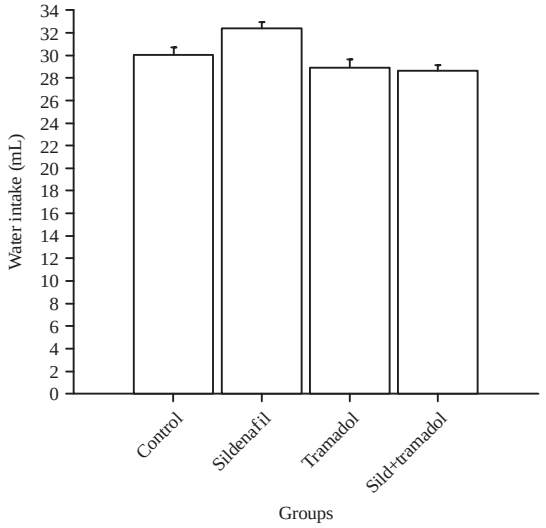


Fig. 2: Comparison of mean daily water intake in the different experimental groups. Values are Mean±SEM, n = 5

sildenafil (202±3.4 g) and sildenafil+tramadol (205±2.2 g) decreased significantly ($p<0.01$) on the 3rd week, compared with control (220±4.3 g), while animals treated with tramadol (212±3.7 g) had an insignificantly different body weight compared with control. On the 4th week, the body weight of animals in the control, sildenafil-treated, tramadol-treated and sildenafil+tramadol-treated group was 227±3.9, 213±5.0, 221.0±2.5 and 222.0±3.4 g, respectively. Sildenafil-treated group had a significantly ($p<0.05$) lower body weight, compared with control (Fig. 3).

Body weight change for sildenafil-treated (17±2.6 g) and sildenafil+ tramadol-treated (27±2.0 g) groups were significantly ($p<0.001$, $p<0.05$) lower than control (35±1.9 g). Body weight change was significantly ($p<0.01$) higher in tramadol-treated (29±2.5 g) and sildenafil+tramadol-treated groups, compared with sildenafil-treated group (Fig. 4).

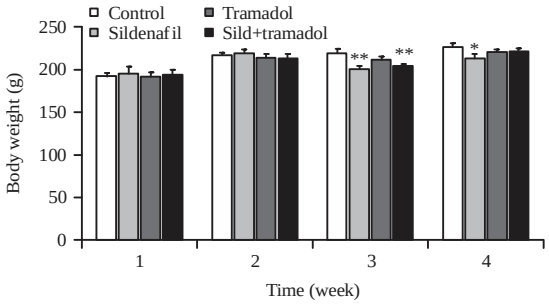


Fig. 3: Comparison of weekly body weight in the different experimental groups. Values are Mean±SEM, n = 5. *p<0.05, **p<0.01 vs. control

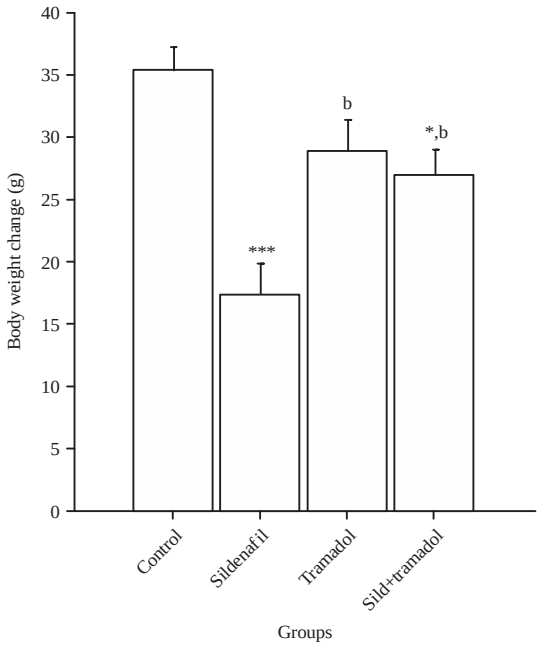


Fig. 4: Comparison of body weight change in the different experimental groups. Values are Mean±SEM, n = 5, *p<0.05, ***p<0.001 vs. control; b = p<0.01 vs. sildenafil

**Basal metabolic rate:** Figure 5 shows the study groups (control, sildenafil-treated, tramadol-treated and sildenafil+tramadol-treated) with BMR (mL $h^{-1}$ $g^{-1}$) 0.76±0.04, 0.76±0.05, 0.74±0.03 and 0.73±0.03, respectively,with non-significant differences among them after the first week (acclimatization) of the study. Basal metabolic rate (mL $h^{-1}$ $g^{-1}$) increased in weeks 2 and 3 in sildenafil-treated (0.97±0.11, 0.93±0.10), tramadol-treated (0.91±0.05, 0.85±0.02) and sildenafil+tramadol-treated (1.00±0.07; 1.04±0.07) groups, while that of control (0.78±0.06, 0.76±0.04) was comparatively low. On the 4th week, BMR reduced in all treated groups (0.79±0.03, 0.51±0.03, 0.69±0.07 and 0.77±0.04, for control, sildenafil-treated, tramadol-treated and sildenafil+tramadol-treated groups, respectively) relative to the 1st, 2nd and 3rd weeks. On the 3rd week, BMR was significantly (p<0.01) higher in sildenafil+tramadol-treated group, compared with control and significantly (p<0.01) higher in sildenafil+tramadol-treated group, compared with sildenafil- treated group on the 4th week. Sildenafil-treated group recorded a significantly (p<0.01) lower BMR, compared with control (Fig. 5).

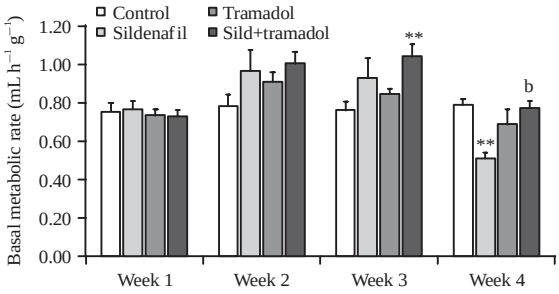


Fig. 5: Comparison of weekly basal metabolic rate in the different experimental groups. Values are Mean±SEM, n = 5, **p<0.01 vs control, b = p<0.01 vs. sildenafil

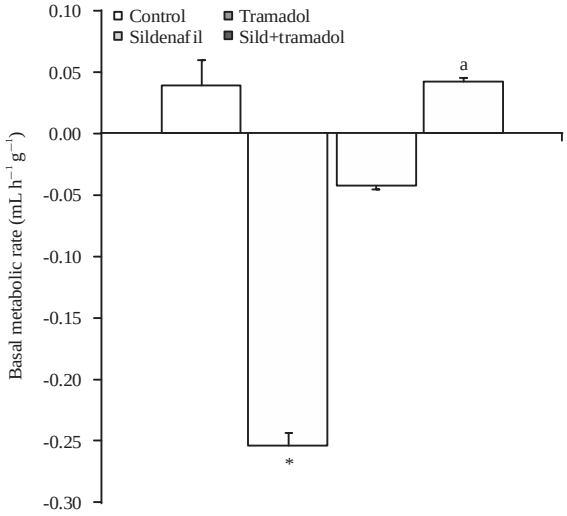


Fig. 6: Comparison of change in basal metabolic rate in the different experimental groups. Values are Mean±SEM, n = 5, *p<0.05 vs. control, a = p<0.05 vs. sildenafil

Figure 6 shows the change in basal metabolic rate (mL $h^{-1}$ $g^{-1}$) in the control, sildenafil, tramadol and sildenafil+tramadol-treated groups which were 0.04±0.02, -0.25±0.06, -0.04±0.01 and 0.04±0.01, respectively. Change in BMR was significantly ($p<0.05$) lower in sildenafil treated group, compared with control. Change in BMR for sildenafil+tramadol-treated group was significantly ($p<0.05$) higher than that of sildenafil-treated group.

**Serum triiodothyronine ($T_3$) concentration:** Serum $T_3$ concentration (ng $mL^{-1}$) for tramadol-treated (0.78±0.04) and sildenafil+tramadol-treated (0.92±0.03) groups were significantly ($p<0.001$) higher than control (0.52±0.002) and sildenafil (0.40±0.05) treated group. The sildenafil-treated group had a decreased $T_3$ concentration compared to control, but was not significant ($p>0.05$) (Fig. 7).

**Serum cortisol concentration:** Serum cortisol concentration (ng $mL^{-1}$) significantly ($p<0.001$) decreased in sildenafil-treated (72.16±1.15), tramadol-treated (81.14±3.36) and sildenafil+tramadol-

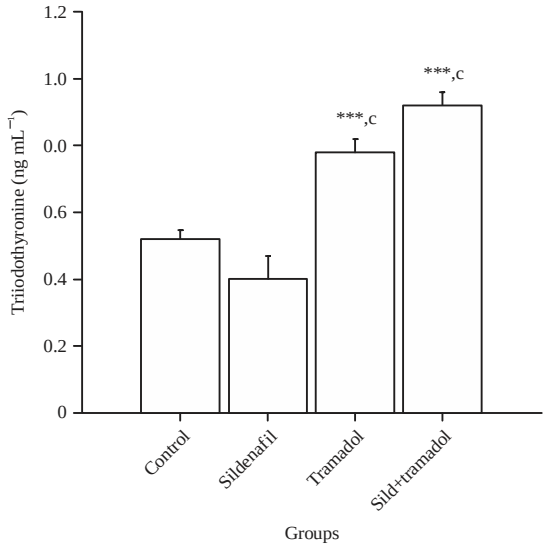


Fig. 7: Comparison of T3 concentration in the different experimental groups. Values are Mean±SEM, n = 5, ***p<0.001 vs. control, c = p<0.001 vs. sildenafil

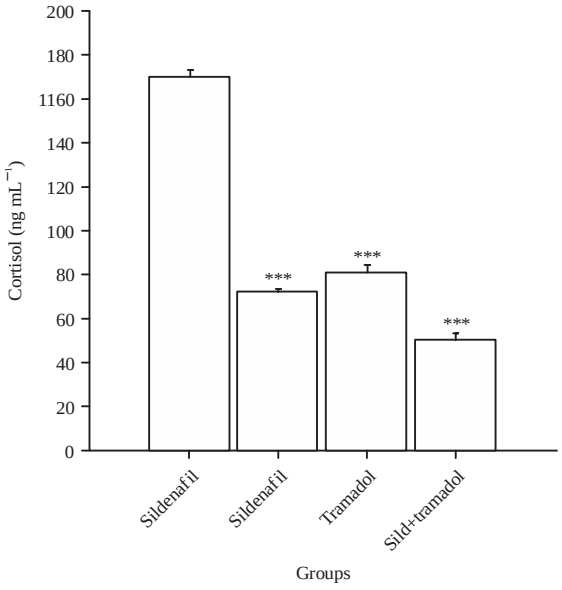


Fig. 8: Comparison of cortisol concentration in the different experimental groups. Values are Mean±SEM, n = 5, ***p<0.001 vs. control

treated (50.4±2.89) groups, compared with control (170.0±3.32). Serum cortisol concentration was lowest in sildenafil+tramadol-treated group (Fig. 8).

## DISCUSSION

Basal metabolic rate reflects the amount of energy spent at rest and is measured 12-14 h after the last meal (Guyton and Hall, 2000). The effect of sildenafil citrate and tramadol administered separately and in combination on BMR in albino wistar rats was studied. In addition, the study also

investigated the effect of the above drugs on food intake, water intake, serum $T_3$ and cortisol concentrations. At the end of the 1st week (end of acclimatization), there was no significant difference in BMR. Following treatment with sildenafil and tramadol, all treated groups showed increased BMR on the 2nd and 3rd weeks compared to control. This increase was only significant in sildenafil + tramadol-treated group, compared with control on the 3rd week. The BMR decreased on the 4th week in all treated groups, compared to the preceding weeks but tramadol and sildenafil+tramadol-treated groups still had a slightly higher BMR compared with sildenafil- treated group. These results can be explained both in terms of the food intake and the body weight on the one hand and $T_3$ levels on the other hand. Food intake and body weight were both decreased in tramadol-treated and sildenafil+tramadol-treated groups. A decrease in food intake lowers the metabolic rate and eventually lowers body weight. It has been documented that weight loss results in a loss of metabolically active tissue and therefore, decreases BMR (Leibel *et al*., 1995). There is a possibility that administration of tramadol alone and in combination with sildenafil have inhibitory effects on the appetite centers of the hypothalamus which may explain the low food intake in these groups.

Increased $T_3$ concentration increases BMR (Guyton and Hall, 2000; Welcker *et al*., 2013) and breaks down glucose and fatty acids from their stores to generate fuel for metabolic activities (De Lange *et al*., 2008). This may be a reason for the increase in BMR and reduction in weight change seen in tramadol-treated and sildenafil+tramadol-treated groups, compared to control. The decrease in BMR seen in sildenafil-treated group on the 4th week agrees with the result of this group for $T_3$ levels which showed a reduction in $T_3$. Triiodothyronine is the major metabolic hormone which increases metabolic rate by 60-100% (Guyton and Hall, 2000). Serum concentration of $T_3$, body weight change and change in BMR were lowest in the group treated with sildenafil alone. This again, explains the interplay between $T_3$, body weight and BMR.

Documented report has shown that elevated levels of cortisol decrease BMR and increase body weight (Talbott and Kraemer, 2007). However, in this present study, serum cortisol level was significantly reduced in all treated groups, with sildenafil+tramadol-treated group having the lowest concentration. The result observed in sildenafil+tramadol-treated group is not surprising since, both drugs separately reduced serum cortisol concentration. This observed effect may be attributed to potentiating effect of one drug over the other. The decreased serum cortisol concentration in all the treated groups compared to control could also be a contributory factor to the higher change in BMR and reduced weight gain observed in these groups.

## CONCLUSION

Sildenafil citrate decreased body weight, BMR, serum $T_3$ and cortisol concentrations, while tramadol increased BMR and serum $T_3$ concentration, but decreased body weight and serum cortisol concentration in rats. Sildenafil and tramadol administered together tends to cause the same effects as tramadol alone does. Basal metabolic rate was mostly affected by sildenafil administration. The results of this present study explain the exhaustion and weakness previously reported by chronic users of these drugs.

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