ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 10, Issue 2, 2017

Online - 2455-3891
Print - 0974-2441

Research Article

# EFFECT OF YOHIMBINE ON CLOMIPRAMINE-INDUCED SEXUAL DYSFUNCTION IN MALE RATS

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***Received: 20 May 2016, Revised and Accepted: 05 November 2016***

**ABSTRACT**

**Object:** The present investigation has been carried out to find out the effect of yohimbine on clomipramine-induced sexual dysfunction in male rats.

**Methods:** The male rats were treated with clomipramine and yohimbine simultaneously for 60 days. During the treatment, all the male rats were challenged with the female rats which are in estrous phase and their sexual behavior was observed under dim red light. Half of the animals in each group and remaining on 60$^{th}$ day were sacrificed, blood was collected and serum separated. Testis was collected and preserved in 10% formalin for subsequent histopathological examination.

**Results:** The study reveals that yohimbine failed to antagonize the clomipramine-induced sexual dysfunction in male rats in all aspects, except the partial improvement in the sexual behavior.

**Conclusion:** Yohimbine a well-known aphrodisiac failed to antagonize the clomipramine-induced sexual dysfunction in male rats. The decrease in testosterone levels, a decrease in spermatozoa count were continued even in the presence of yohimbine except improvement in the sexual behavior parameters. Hence, yohimbine could not be a safe antidote against clomipramine-induced sexual dysfunction in male rats.

**Keywords:** Yohimbine, Clomipramine, Testosterone, Male rat sexual competence, Testicular damage.

 DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i2.12970

## INTRODUCTION

Psychic depression is a disorder that requires treatment for longer periods. It is known to be precipitated because of excessive metabolism of centrally located monoamines, particularly serotonin. Hence, monoamine oxidase inhibitors, tricyclic antidepressants, and specific serotonin inhibitors (SSRI) are used for its treatment. The antidepressants elevate the monoamines, particularly serotonin for its effect in the treatment of depression. In doing so, they produce sexual dysfunction as a rise in central serotonin leads to decreased libido. Clomipramine (Clmp) is the imipramine analog of chlorpromazine. Due to its action against anxiety disorders and panic attacks, it is the only drug with 2 entries in the essential drugs list of the WHO. Regarding the compulsive disorders, it is now the "gold standard" of therapy against which other drugs are measured [1,2]. In addition to SSRI, action clomipramine can block adrenergic, cholinergic, and dopaminergic receptors which also contribute for sexual dysfunction [3]. It was shown that 96% of males and females on clomipramine suffered from delayed orgasm representing the highest rate of antidepressant-induced sexual dysfunction with any medication and it was consistent with clomipramine's potent serotonergic activity [4,5].

The sexual function involves central, and peripheral neuronal activity, hormonal activity, and peripheral cellular activity. Compared to other tricyclic antidepressants, it has a greater effect on dopamine blockade and serotonin reuptake inhibition [6]. These implicate for prolactin release [7]and orgasmic dysfunction mediated through 5-$HT_2$ receptors [8]. Moreover, peripheral antimuscarinic and α adrenergic blockade [9-12], effects have been implicated in the clomipramine-induced sexual dysfunction. It was also reported in our studies that clmp dose-and time-dependently decreased the testosterone levels, sexual competence of male rats and damaged the testes [13]. In another study, amantadine failed to antagonize Clomipramine-induced sexual dysfunction in male rats [14]. Various treatment strategies exist for antidepressant-induced sexual dysfunction. They are (1) try waiting (which does not really work)for spontaneous remission of symptoms as tolerance to the drug may develop, (2) decreasing the dose of the current antidepressant or (3) switching to a different antidepressant [15]. Although sometimes effective these strategies scare patients as switching to a different antidepressant that works in one may not work as well in another. The decrease in the dose of the current drug and/or taking a drug holiday (Purposely skipping medication for a period when sexual activity is anticipated) may cause a relapse of depression. The prevention of the relapse/worsening of depression are of utmost importance to the patient even more so than a healthy sex life. Therefore, the most promising treatment is to stick to the current effective antidepressant and add another medication (or antidote) by a trial and error method to suppress sexual side effects. However, no perfect solution exists to date as these antidotes have their own adverse effects, and hence the search for proper medication be continued [16].

The drug yohimbine is known as adrenergic α2 receptor blocker and as an aphrodisiac since a long time. Some of the textbooks in pharmacology mention that it is claimed as aphrodisiac without scientific support. The α2 activity being associated with autoregulation of noradrenaline, its blockade led to increased secretion and increased the level of noradrenaline which is known to be associated with improved sexual function. The recent literature reports on yohimbine indicate that it improved erectile dysfunction in aged male rats [17]. Other reports indicated that it improved sexual function in male rats mostly through dopamine-related activity rather than α2 adrenergic blocking activity which improves central adrenergic activity. The net result of the recent reports was that it improves sexual function and as per one report, it improves sexual function even in sexually satiated rats [18].

As per the literature, yohimbine improves sexual activity by involving noradrenaline and dopamine of central origin and improves sexual behavioral parameters [19]. However, its activity on the hormonal

and histological parameters of testes is not known. An aphrodisiac can be clinically well-accepted if it works well centrally and peripherally. Hence, to know more about the influence of yohimbine on sexual activity on clomipramine-induced sexual dysfunction the present study was undertaken.

## METHODS

- Yohimbine Hcl: John Baker Inc., Colorado, U.S.A
- Clomipramine Hcl: Psychotropic India Ltd, Ghaziabad
- Carboxymethyl cellulose: Nice chemicals, Cochin
- Diethyl ether: Nice chemicals, Cochin
- Estradiol benzoate: Sigma-Aldrich, U.S.A
- Eosin: Nice chemicals, Cochin
- Hematoxylin: Nice chemicals, Cochin
- Progesterone: Glen mark, Mumbai
- Sesame oil: N. Ravindra Company, Mumbai
- Rat feed: Saidurga animal feeds, Bengaluru
- Testosterone and prolactin kits: DPC, New York, USA.

### Preparation of drug solution

*Clomipramine solution*

The maximum human therapeutic dose of clomipramine was 300 mg/daily. From this ½ therapeutic dose and therapeutic dose were calculated based on body surface area and was found to be 13.5 mg/kg and 27 mg/kg [20]. The control group received vehicle. Yohimbine dose used was as per the earlier studies 2 mg/kg.

### Animal preparation

A total of 36 male and 36 female Sprauge-Dawley albino rats were purchased from central animal house NIMHANS, Bengaluru. All animals were housed in a group of four males and females separately in plexiglass cages (62×40×21) in an acclimatized colony room (25±0.5°C) maintained on a 12/12 hrs light/dark cycle. The rats were 4 months old. They were weighed around 200-300 g each and females 250-350 g each. They were fed on commercial pellet feed and water was available ad libitum. Prior approval was obtained from the institutional ethical committee for conducting the studies.

### Animal treatment

The male rats were randomly divided into three groups of 12 rats in each. Group I served as control, Groups II and III were treated with yohimbine (2 mg/kg) orally, 30 minutes later they were treated with clomipramine13.5 mg/kg and 27 mg/Kg body weight, respectively, for 60 days. The control group received vehicle. All the drugs were given by oral route.

### Procedure for overiectomization

Ovariectomy was necessary to make the female non-pregnant when mated with male rats and to reuse them repeatedly during the period of experimentation [21]. To bring them to oestrous phase, they were given 12 µg/rat of estrodiol benzoate (sesame oil) S.C. 56 hrs before and 500 µg (sesame oil) of progesterone 4-6 hrs before the copulatory test [22].

The drugs were administered orally to male rats and the animals were observed for their sexual behavior. Female rats were prepared for sexual receptivity as described earlier. Male rat sexual behavior was studied as explained elsewhere [23]. The drugs were administered orally to male rats and the animals were observed for their sexual behavior. Female rats were prepared for sexual receptivity as described earlier. Then, the highly receptive female was introduced into the male's cage a rectangular glass observation cage (62 cm × 40 cm × 21 cm) in which male acclimatizes for 2 hrs. They were observed in the cage for 30 minutes under dim red light. When there was no mount latency, intromission, ejaculation, and post ejaculation pause their total latent period was taken as 1800 seconds. Tests were terminated immediately after the first post-ejaculatory intromission/mount.

### Collection of blood sample and testes

Half of the animals in each group on the 30$^{th}$ day and remaining on the 60$^{th}$ day were sacrificed for blood sample collection and histopathological examination of testes. Blood was collected through cardiac puncture using a 16 no needle under mild ether anesthesia and allowed to settle for some time. After centrifugation serum was separated and stored at −20° for subsequent hormonal estimation. Testes were also collected and processed for the histopathological studies [24].

## RESULTS

1. Influence of yohimbine on clomipramine-induced decline in sexual competence in male rats
   Yohimbine significantly increased the number of rats intromitting and ejaculating in both ½ TD and TD of clmp.
   A significant decrease in mount latency, intromission latency, ejaculation latency, post ejaculation pause was observed. Increase in the copulating efficiency and decrease the inter-copulating interval was observed at both doses of clmp.
   Hence, to conclude yohimbine significantly retained the sexual behavior of male rats treated with clomipramine, but still failed to maintain the normal sexual competence.
   Results indicate that the number of rats mounted, intromitted, and ejaculated was significantly more in combination with clomipramine. There was a decrease in the inter-copulatory interval and increased copulatory efficiency. The number of mounts, number of intromissions and ejaculations were more than that of the clomipramine alone treated groups. A significant decrease in the post-ejaculatory interval was also observed. However, yohimbine also failed to prevent the sexual dysfunction completely in the male rats treated with clomipramine. Results were tabulated in Table 1.
2. Influence of yohimbine and clomipramine on serum testosterone
   At the end of 30 and 60 days treatment, no improvement in the testosterone level was observed. Yohimbine failed to antagonize clmp induced decline in serum testosterone levels. The results were tabulated in Table 2.
3. Histological studies of testes
   The decrease in the sperm cells counted namely spermatogonia, preleptotene, pachytene, and secondary spermatocytes was continued with the yohimbine +27 mg/kg clmp treatment at the end of 30 days and 60 days indicating that yohimbine did not prevent the testes from the damage induced by clmp. Results were tabulated in Tables 3 and 4 testicular damage was shown in Figs. 1-5.

## DISCUSSION

The sexual response is the result of neuronal (both central and peripheral), hormonal and peripheral activities. The central activity is influenced by several mediators, the notable among them being noradrenaline, dopamine, and serotonin.

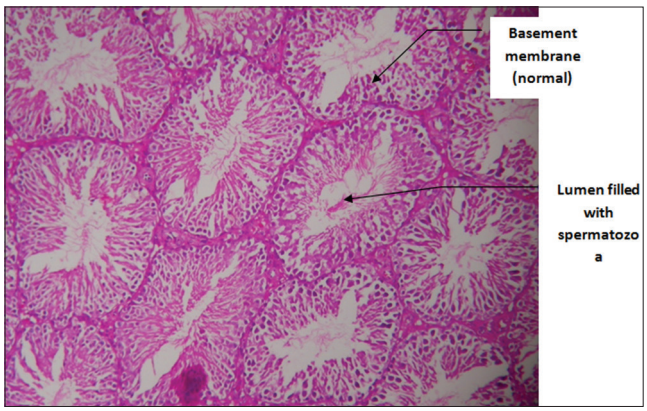


**Fig. 1: Cross section of seminiferous tubules. Control ×400**

**Table 1: Effect of chronic oral administration of yohimbine and clomipramine on sexual behavior parameters of male rats (Data given as mean±SEM)**

| Parameter studied | Control | | | | Yohimbine + clomipramine 13.5 mg/kg | | | | Yohimbine + clomipramine 27 mg/kg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | 0 | 15 | 30 | 60 | 0 | 15 | 30 | 60 | 0 | 15 | 30 | 60 |
| % Mounted | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| % Intromitted | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| % Ejaculated | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 50 | 50 | 50 |
| Mount latency | 5.37±0.84 | 8.5±1.29 | 8.87±1.02 | 7.5±0.8 | 11.8±1.2** | 12.6±0.7* | 10.5±1.4 | 8.5±0.5 | 12.5±0.95** | 14.4±1.6** | 11±1 | 12.5±1.4* |
| Intromission latency | 23.5±4.9 | 20.65±4.8 | 18.62±1.4 | 20.5±1.8 | 51.25±6.8** | 152.5±6.8** | 173.75±2.6** | 210±30* | 75±4.6** | 198.7±9.71** | 236.25±19.08** | 653.7±382.1* |
| Ejaculation latency | 360±18.4 | 375.5±9.4 | 372.5±8.8 | 375±6.45 | 622.5±25.1** | 772.5±23.8** | 592.5±31.1** | 8855±75* | 742.5±50.63** | 1305±146.42** | 1515±139.2** | 1620±180* |
| Number of intromissions | 15.625±0.3 | 15.625±0.3 | 15.37±0.2 | 15.5±0.2 | 19.5±0.5** | 19.375±0.4** | 19.6±0.4** | 18±0.7* | 22.5±0.45** | 16.25±2.34 | 19.12±3.5 | 13.75±5.7 |
| Number of mounts | 2.5±0.32 | 2.25±0.36 | 2.62±0.4 | 3.5±1.08 | 2.7.5±0.59 | 2.87±0.39 | 2.37±0.18 | 2.5±0.5 | 3.25±0.67 | 4.5±0.7* | 7.125±1.7* | 12.25±3.01* |
| Post ejaculation Pause | 262.5±10.9 | 290±30.9 | 225±15.0 | 270±19.14 | 340±22** | 351.2±25.4** | 390±21.9** | 385±45.7* | 340±24.78** | 901.25±263.58* | 1127.5±254.36** | 1475±325.00* |
| Copulatory efficiency | 0.85±0.01 | 0.86±0.2 | 0.85±0.03 | 0.82±0.04 | 0.84±0.02 | 0.87±0.01 | 0.88±0.08 | 0.87±0.05 | 0.86±0.02 | 0.75±0.06 | 0.73±0.05 | 0.39±0.18 |
| Inter copulatory interval | 23.13±1.43 | 24.15±0.5 | 24.29±0.8 | 24.2±0.7 | 32.34±0.6** | 39.96±1.38** | 30±1.92* | 47.3±3.7* | 33.5±2.51** | 119.1±40.018** | 110.82±2.9** | 129.5±41.3 |

Significant at p<0.05*, 0.01** compared to control (Mann Whitney U-test)




**Fig. 2: Cross section of seminiferous tubules. Yohimbine + clomipramine 13.5 mg/kg 30 days treatment ×400**




**Fig. 3:**




**Fig. 4: Cross section of seminiferous tubules. Yohimbine + clomipramine 27 mg/kg 30 days treatment**

In the CNS, antagonism of adrenergic α2 receptors by other drugs appears to be the most probable mechanism for the important role of norephinephrine (NE) in enhancing sexual functions especially arousal [25,26]. Direct administration of the α2 agonist clonidine to the median preoptic area in male rats demonstrated increased latency to ejaculate and longer inter-couplatory interval. Clonidine action could be reversed by yohimbine a α2 antagonist. α2 antagonism can be understood as blocking the inhibitory activities of autoreceptors, leading to increased noradrenaline transmission resulting in C N S prosexual effects [27].

Blocking catecholamine (CA) synthesis with the CA synthesis inhibitor α- methylP-tyrosine, markedly reduced masculine sexual behavior pointed to a fundamental role of the catecholaminergic system in the expression of sexual behavior [28].

Guanethidine, an adrenergic neuronal blocking agent, exerts its antihypertensive effect by preventing the intraneuronal storage

**Table 2: Influence of yohimbine and clomipramine (30 days and 60 days) on serum testosterone (Data given as mean+SEM, n=6)**

| Treatment | Testosterone ng/ml after 30 days | Testosterone ng/ml after 60 days |
|---|---|---|
| Control 1 ml/kg CMC suspension | 6.55±0.66 | 5.07±0.3 |
| Yohimbine + clomipramine 13.5 mg/kg | 8.57±0.39 | 8.5±0.65 |
| Yohimbine + clomipramine 27 mg/kg | 3.27±0.351** | 2.5±0.52** |

Significant at p<0.05*, 0.01** compared to control (student *t*-test), CMC: Carboxy methyl cellulose

**Table 3: Yohimbine and clomipramine treatment (30 days) influence on histology of testes (data given as mean+SEM n=6)**

| Treatment (30 days) | Sertoli cells | SP Gonia | Preleptotene | Pachytene | S.spermotocytes |
|---|---|---|---|---|---|
| Control 1 ml/kg CMC suspension | 3.5±0.288 | 8.25±0.4 | 21.25±0.8 | 27±0.4 | 48.75±0.75 |
| Yohimbine + clomipramine 13.5 mg/kg | 3.25±0.25 | 8.25±0.47 | 22.7±0.4 | 29.5±1.19 | 54.5±1.25 |
| Yohimbine + clomipramine 27 mg/kg | 2.5±0.28 | 6±0.4** | 17.25±0.7** | 23.5±0.40** | 37.5±1.56** |

Significant at p<0.05*, 0.01** compared to control (student *t*-test), CMC: Carboxy methyl cellulose

**Table 4: Yohimbine and clomipramine treatment (60 days) influence on histology of testes (data given as mean+SEM n=6)**

| Treatment (30 days) | Sertoli cells | SP Gonia | Preleptotene | Pachytene | Secondary spermatocytes |
|---|---|---|---|---|---|
| Control | 3.5±0.288 | 8.25±0.4 | 21.25±0.8 | 27±0.4 | 48.75±0.75 |
| Yohimbine + clomipramine 13.5 mg/kg | 3±0.4 | 7.5±0.28 | 23±0.8 | 28±1.08 | 54.75±2.4 |
| Yohimbine + clomipramine 27 mg/kg | 3±0.2 | 7.5±0.2 | 16±0.4** | 22.75±0.80** | 31.25±0.8** |

Significant at p<0.05*, 0.01** compared to control (student *t*-test)

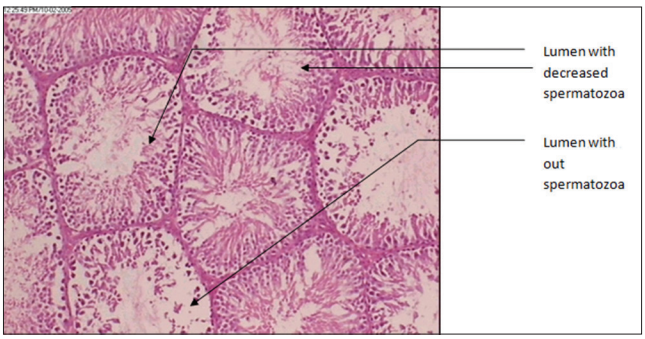


**Fig. 5: Cross section of seminiferous tubules. Yohimbine + clomipramine 27 mg/kg 60 days treatment**

granule reuptake of NE, thereby blocking sympathetic neuronal activity. Methyldopa, a centrally acting sympatholytic agent, is metabolized to the false neurotransmitter α methyl NE. α methyl NE decreases the sympathetic outflow from the brain by competing with NE in sympathetic axons and by stimulating α receptor sites in the CNS. The common side effects of methyldopa are impotence, decreased libido, ejaculatory difficulties, and gynecomastia [29]. Since yohimbine is known to influence adrenergic function by blockade of α2 adrenergic receptors and is claimed to be aphrodisiac, its activity on the sexual function was evaluated in the present model in the presence of clomipramine.

The observed improvement in the male rat sexual competence may be due to its action on both the noradrenergic and dopaminergic system. It increases the turnover of rat cerebral noradrenaline, through the interaction with α2 adrenoreceptors [30]. The alkaloid also increases brain dopamine turnover an effect attributed to an indirect action of the drug on dopaminergic neurons exerted through changes in noradrenaline transmission [31]. The same effect of yohimbine has been observed in mice and was proposed to be exerted by the selective blockade of α2 autoreceptors [32].

Regarding the noradrenergic system, it was reported that yohimbine significantly increased the proportion of sexually exhausted rats showing mating behavior 24 hrs after the copulation to exhaustion session [33]. In addition, it was reported that the neurotoxic lesion of the noradrenergic system blocks the ability of the 5-HT1$_A$ agonist 8 - hydroxyl - 2- (Di- n. propylamine) tetralin (8 - OH. DPAT) and the μ and δ opioid receptor antagonist, naloxone to induce mating behavior in sexually satiated rats [34]. These findings suggest that the integrity of the noradrenergic system is essential for the pharmacological establishment of copulatory behavior. The central and peripheral effects of yohimbine+clomipramine associated with sexual function were given in Table 1 and represented graphically in.

Tonic adrenergic tone at α1 and α2 receptors act to keep the penis in a flaccid state and α1 blockers can produce prolonged erection and priapism [35]. This erection preventing norepinephrine-induced penile vascular smooth muscle contractility is blocked by either α1 antagonist, for example, prazocin or α2 antagonist yohimbine [36,37]. By a mechanism not clear and presumably under the influence of nitric oxide and vasoactive intestinal polypeptide (VIP). Adrenergic stimulation ceases to be inhibitory after sexual stimulation and was associated with increasing arousal in both men and women [38].

In our experiments, change in sexual behavior parameters was observed without change in the hormonal (testosterone), histological parameters (testicular) in the presence of the treatment with yohimbine. It clearly showed that it affected the adrenergic α2 receptors and its related activities also. It is well-established that α2 receptor blocking activity is associated with central and peripheral noradrenergic activity and also with associated dopamine function, both leading to behavioral sexual improvement. The results also indicated that yohimbine does not influence the testosterone or the peripheral histological parameters and its main action was due to its influence on adrenergic and associated dopaminergic system. Yohimbine, an antagonist at inhibitory noradrenergic α2 receptors, has been used to increase the limbic levels of norepinephrine. Yohimbine also increases parasympathetic activity [39,40].

Ultimately yohimbine appears to improve sexual behavior through its α2- blockade action which is reported to be associated with increased central and peripheral noradrenergic, dopaminergic functions and peripheral parasympathetic functions through NO and VIP.

The study indicated that yohimbine can be a supportive drug to antagonize sexual dysfunction produced by antidepressant clomipramine. It cannot be used alone to totally antagonize the sexual dysfunction of clomipramine as it did not prevent the hormonal and cellular changes.

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