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# Vilazodone does not inhibit sexual behavior in male rats in contrast to paroxetine: A role for 5-$HT_{1A}$ receptors?

Ronald S. Oosting [a, *], Johnny S.W. Chan [a], Berend Olivier [a, b, c], Pradeep Banerjee [d]

[a] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands
[b] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[c] Groningen Institute for Evolutionary Life Sciences (GELIFES), Rijksuniversiteit Groningen, The Netherlands
[d] Forest Research Institute (an Allergan affiliate), 1900 Plaza Five, Jersey City, NJ 07311, USA

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ABSTRACT

Vilazodone (VLZ) is a selective serotonin reuptake inhibitor (SSRI) and 5-$HT_{1A}$ receptor partial agonist approved for the treatment of major depressive disorder in adults. In preclinical studies, VLZ had significantly lower sexual side effects than SSRIs and reduced serotonin transporter (SERT) levels in forebrain regions. In the current study, once-daily paroxetine (PAR, 10 mg/kg), VLZ (10 mg/kg), PAR + buspirone (BUS, 3 mg/kg; a 5-$HT_{1A}$ partial agonist), or vehicle (VEH) was administered to male rats for 2 weeks then switched for 7 days (eg, PAR switched to VLZ, PAR + BUS, or VEH). Sexual behavior (eg, ejaculation frequency and latency) was evaluated 1-hr postdose on days 1, 7, 14, and 21. After 2 weeks, treatment with PAR but not VLZ resulted in a significant decrease in sexual behavior. In a 30-min test, the range of ejaculation frequency was 3.08–3.5 with VLZ and 1.00–1.92 with PAR ($P < 0.05$ vs VEH). After switching from PAR to VEH, PAR + BUS, or VEH, sexual behaviors were normalized to control levels. In contrast, the switch from VLZ to PAR resulted in reduced sexual behaviors. This preclinical study showed that unlike PAR, an SSRI with no 5-$HT_{1A}$ receptor activity, initial treatment with VLZ did not result in sexual side effects at therapeutically relevant doses. Results in male rats switched from PAR to VLZ or PAR + BUS strongly suggest that activation of 5-$HT_{1A}$ receptors may mitigate the sexual side effects associated with conventional SSRIs.



## 1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders worldwide (Bromet et al., 2011), and antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are among the most frequently prescribed drugs (Lindsley, 2012). The clinical efficacy can be limited, however, due to adverse sexual side effects that may affect up to 60% of patients treated with SSRIs (Kennedy and Rizvi, 2009). These SSRI-induced sexual side effects can lead to treatment noncompliance and discontinuation (Ashton et al., 2005), which can lower patient quality of life (Hu et al., 2004) and increase the risk of relapse and recurrence of MDD (Clayton and Montejo, 2006). Therefore, understanding the neurobiology underlying SSRI-induced sexual dysfunction and identifying treatment options with a lower risk of adverse impact on sexual function may help to optimize the management of MDD and improve patient outcomes.

Strategies used to mitigate the adverse sexual side effects of SSRIs include lowering dosage, switching class of antidepressant medication (eg, norepinephrine-dopamine reuptake inhibitor), or adding concomitant medications such as a phosphodiesterase inhibitor type 5 (PDE5; eg, sildenafil) or 5-$HT_{1A}$ receptor partial agonists (Rizvi and Kennedy, 2013).

Preclinical studies and clinical evidence support a role for 5-$HT_{1A}$ receptors in modulating sexual behavior. Buspirone and its major active metabolite, 6-OH-buspirone, act as partial agonists at presynaptic 5-$HT_{1A}$ receptors in the raphe nuclei (higher affinity) and at postsynaptic 5-$HT_{1A}$ receptors throughout the brain (lower affinity) (Wong et al., 2007). Studies in male rats have shown that 5-$HT_{1A}$ receptor agonists (8-OH-DPAT, FG-5893, flesinoxan), as well as the partial agonist buspirone, have a facilitating effect on sexual behavior (Bijlsma et al., 2014; Chan et al., 2008). In contrast, the 5-

* Corresponding author. Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands.
*E-mail address:* R.S.Oosting@uu.nl (R.S. Oosting).

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**Abbreviations**

| | |
|---|---|
| ANOVA | analysis of variance |
| BUS | buspirone |
| DA | dopamine |
| FDA | US Food and Drug Administration |
| MDD | major depressive disorder |
| MPOA | medial preoptic area |
| PAR | paroxetine |
| PDE5 | phosphodiesterase inhibitor type 5 |
| PO | orally administered |
| SEM | standard error of the mean |
| SER | sertraline |
| SERT | serotonin transporter |
| SSRI | selective serotonin reuptake inhibitor |
| VLZ | vilazodone |
| VEH | vehicle |

$HT_{1A}$ receptor antagonist WAY-100635 was found to inhibit sexual behavior when coadministered with the SSRIs citalopram and paroxetine (Olivier et al., 2011) and when administered to serotonin transporter (5-$HT_T$) knockout rats (Chan et al., 2011). In a clinical study of depressed patients, addition of the 5-$HT_{1A}$ receptor partial agonist buspirone improved sexual function in patients who had been experiencing sexual dysfunction while taking an SSRI (ie, paroxetine or citalopram) (Landen et al., 1999).

Vilazodone is an SSRI and 5-$HT_{1A}$ receptor partial agonist approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults. In clinical trials, vilazodone was associated with a low adverse impact on sexual function relative to the high prevalence of sexual dysfunction that was present in the patients at baseline (Clayton et al., 2013a). In preclinical studies, acute treatment with vilazodone showed dose-dependent occupancy of 5-$HT_T$ and 5-$HT_{1A}$ receptors in the rat cortex and hippocampus, with systemic administration of 10 mg/kg vilazodone producing ~90–100% occupancy at serotonin transporter (SERT) and 5-$HT_{1A}$ receptors and resulting in a 2-fold increase in extracellular 5-HT in the rat frontal cortex (Hughes et al., 2005). Results from another preclinical study showed that treatment with vilazodone (acute [1 d], subchronic [7 d], or chronic [14 d]) was not associated with sexual dysfunction in a rat sexual behavior model (Oosting et al., 2016). Similar treatments with the SSRIs citalopram and paroxetine were associated with sexual dysfunction, with vilazodone causing a marked decrease in 5-$HT_{1A}$ receptor levels in the cortex and hippocampus and the SSRIs causing increased receptor levels in similar regions.

The current study was conducted to investigate whether switching treatments from (chronically administered) paroxetine, an SSRI known to cause sexual dysfunction in rats, to a treatment that includes both SSRI and 5-$HT_{1A}$ receptor partial agonism (ie, vilazodone or paroxetine + buspirone coadministration) normalizes rat sexual behaviors. The doses of drugs that were administered to rats in this study (vilazodone, paroxetine, buspirone) were selected based on SERT and 5-HT receptor occupancy data (Hughes et al., 2005) and because they fall within the dose ranges for animal paradigms used to screen for antidepressant and anxiolytic activity (Adamec et al., 2004; Page et al., 2002).

## 2. Experimental procedures

### 2.1. Animals

Male (300–400 g) and female (200–300 g) Wistar rats (Charles River Laboratories, FR) were group housed (4 per cage) with food and water ad libitum. All animal cages were stored in the same room maintained at 21 °C and 55% humidity. Rats were habituated for 1 week to reversed light/dark schedule (lights off 7:00; lights on 19:00). All experiments were reviewed and approved by Utrecht University's animal welfare committee (DEC), in accordance with the European Communities Council Directive of 24 November 1986.

### 2.2. Drug administrations

Vilazodone hydrochloride was obtained in powder form from Forest Laboratories, Inc. (an Allergan affiliate). Paroxetine hydrochloride and buspirone hydrochloride tablets (Sandoz, France) were purchased from a local pharmacy in generic form. All drugs were dissolved or suspended in vehicle (1% methylcellulose and water) and orally administered (PO) between 9:00 and 15:00 (non-test days) or 1 h before testing. Doses were 10 mg/kg for vilazodone and paroxetine; 3 mg/kg buspirone was co-administered with 10 mg/kg paroxetine.

### 2.3. Sexual behavior test

The sexual behavior test was performed as previously described (Chan et al., 2010). All assessments were performed in the dark phase of the light/dark-cycle under dim red light conditions.

### 2.4. Sexual training and selection of male rats

144 male rats were trained (30 min) once weekly for 4 consecutive weeks with an estrus female that was located in an observation cage behind a clear Plexiglas front. At 36 h before the test, the female received a subcutaneous injection of 50 μg estradiol-benzoate dissolved in sesame oil to induce receptivity. Males that exhibited 2–3 ejaculations during the final three 30-min training sessions were classified as normal-performers (Pattij et al., 2005) and were included in the drug testing studies (n = 84).

### 2.5. Experimental design and testing

Male normal-performers were divided into 7 treatment groups (n = 8 per group) that consisted of 2 distinct successive pharmacological treatments (exception was vehicle-to-vehicle group). The experimental design is shown in Fig. 1. Rats received the first treatment for 14 d and were switched to the second treatment for an additional 7 d.

Male rats were placed in an observation cage (30 × 40 × 60 cm) with an estrous female on Day 1 (acute), Day 8 (subchronic), Day 15 (chronic), and Day 22 (7 d after switch) to score sexual behavior. Evaluations included the frequencies of mounts (no vaginal penetration) and intromissions (vaginal penetration) in the first ejaculation series, latency to the first ejaculation (time between the first mount or intromission to first ejaculation), and ejaculation frequency for the duration of the 30-min test. Copulatory efficiency was defined as: # intromissions/(# intromissions + # mounts) × 100%. All measurements and scoring were performed using Observer® 5.0 (Noldus, Wageningen, The Netherlands).

### 2.6. Statistical analysis

Data for each sexual behavior test day (acute, subchronic,