We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 4

Sexual Dysfunction, Depression and Antidepressants: A Translational Approach

Jocelien D.A. Olivier, Diana C. Esquivel Franco, Marcel D. Waldinger and Berend Olivier

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69105

Abstract

Major depression is frequently associated with sexual dysfunctions. Most antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), induce additional sexual side effects and, although effective antidepressants, deteriorate sexual symptoms, which are the main reason that patients stop antidepressant treatment. Many strategies have been used to circumvent the additional sexual side effects, but results are rather disappointing. Recently, new antidepressants have been introduced, vilazodone and vortioxetine, which seem to lack sexual side effects in the early registration trials. Much research with large numbers of depressed patients and adequate methodological tools still has to confirm in daily use the absence of sexual side effects of new antidepressants. Animal models that in an early phase of drug development may predict putative sexual side effects of new antidepressants are extremely useful and could speed up development of new antidepressants. A rat model of sexual behavior is described that has a very high predictive validity for sexual side effects in man. Several characteristics of present antidepressants with regard to sexual dysfunctions are also present in the rat model and establish its validity. The animal model can also be used in the search for new psychotropics without sexual side effects or for drugs with sexual stimulating activity.

Keywords: depression, sexual dysfunction, antidepressants, sexual side effects, SSRI, animal model

1. Introduction: depression and sexual (dys)function

Sexual functioning in humans is a very complex phenomenon and involves many interacting processes that have been conceptualized as desire, arousal, and orgasm [1]. It is

INTECH
open science | open minds

© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

plausible to imagine that disturbances in the networks steering the appropriate processes may lead to disturbances in various aspects of sexual behavior or even to sexual dysfunction.

Major depression is often associated with sexual dysfunctions [2, 3]. Treatment of the depression with antidepressants complicates the situation considerably. Whereas some aspects of sexual functioning may improve, especially libido, others, notably erection and ejaculation may deteriorate. It is often difficult or impossible to ascertain what is caused by depression and what caused by the antidepressant, their interaction or even other factors. Lahon et al. [4] suggest that a complaint by a patient of sexual dysfunction might either indicate a failure to respond to treatment or the side effects of the drug. The large majority of commonly prescribed antidepressants are associated with sexual side effects, which often lead to noncompliance to the treatment. In an early study, Monteiro et al. [5] described that approx. 20% of patients treated with the tricyclic antidepressant clomipramine did stop treatment due to anorgasmia or delayed ejaculation. Although some clinicians were aware that antidepressants like tricyclics and monoamine oxidase (MAO) inhibitors induce sexual side effects [6], most clinicians were clearly unaware of such side effects. In the first decades of antidepressant use, other side effects like sedation, dizziness, hypotension, nausea, and anticholinergic effects were prominent. Only with the introduction of the serotonin reuptake inhibitors (SSRIs), these "old" side effects were no longer troublesome leading to an "explosive" use of this new, safe antidepressant class. Gradually, it became clear that SSRI use was associated with sexual side effects [7]. In the last decade, attempts were made to develop and introduce new antidepressants with low(er) sexual side effects, e.g., vilazodone and vortioxetine.

Clinically, drug-induced sexual dysfunction should be recognized because of noncompliance to the treatment [8], but on the other side, it also may complicate recovery from depression, e.g., by decreasing patient's self-esteem, self-worth, and competence and may put additional stress on relationships [9]. The latter authors give an excellent and extensive review on antidepressant-induced sexual dysfunction in men. This is an extremely complicated area because of the methodology used, the changes in the methodology over time, and the pharmacological differences in the various antidepressants and doses used. One of the most clear-cut differences, in the incidence of sexual side effects reported, has to do with instruments used to inquire about them. Montejo-González et al. [10] showed a fourfold difference in the percentage of patients reporting sexual dysfunction spontaneously versus reporting after direct inquiry by the clinician. Almost all double-blind, placebo-controlled drug trials of antidepressants are performed by pharmaceutical companies. They often compare their product with a competitive drug already present in the market. If sexual side effect incidence is an important factor in the future marketing of the drug, the pharmaceutical company often uses a competing antidepressant with a known, high propensity to induce sexual side effects. Although this may lead to the suggestion of a lower propensity to induce such effects, in later clinical practice realistic data are materialized and often lead to a different profile. Many more serious issues cloud the interpretations of many studies into the sexual side effects of antidepressants [9].

http://dx.doi.org/10.5772/intechopen.69105

2. What are the sexual side effects of antidepressants in men?

Early antidepressants (tricyclic (TCA), heterocyclic, and (irreversible) monoamine oxidase inhibitors (MAOI)) have not very well been investigated regarding associated sexual side effects. Many case reports and small clinical studies have been performed, and the data suggested various sexual side effects [8]. Only two placebo-controlled studies were performed. Imipramine (a TCA) induced delayed orgasms in approx. 20–30% of the patients and phenelzine (an irreversible MAOI) in approx. 30–37% [11]. Monteiro et al. [5] found that after taking clomipramine, more than 90% of patients had difficulty in achieving orgasm. This study was performed in obsessive-compulsive disorder patients, a disorder not associated with basic sexual dysfunction itself. Although all these "classic" antidepressants have a polypharmacological mode of action, the high incidence of sexual side effects after clomipramine, the most "serotonergic" TCA known, pointed to an important role of serotonin in the induction of such effects.

Not surprisingly, most controlled (placebo-controlled, randomized trials often with comparator drug) studies on antidepressants have been performed by pharmaceutical companies during the initial phases of drug development. If such trials were specifically aimed for sexual side effects, often a comparator drug was included that either displayed considerable sexual side effects (an SSRI) or had a low sexual side effect profile, like bupropion [12], an antidepressant that blocks noradrenergic and dopaminergic (DA) reuptake sites without any effect on the serotonin transporter (SERT). In comparator antidepressant studies of SSRIs versus bupropion, the SSRIs always have a higher incidence of sexual complaints than bupropion. Coleman et al. [13] reported 30% sexual complaints on fluoxetine compared to 10% on bupropion in a placebo-controlled study. In a double-blind, placebo-controlled study on sertraline and bupropion in major depressed patients [14], sertraline induced far higher sexual complaints than bupropion (52% versus 8%). This was also found in studies on sertraline versus bupropion [15], paroxetine versus bupropion [16], escitalopram versus bupropion [17], and venlafaxine (a noradrenaline/serotonin reuptake blocker-SNRI) versus bupropion [18]. Recently, new SSRIs with additional serotonergic mechanisms like vilazodone and vortioxetine were introduced. Vilazodone, an SSRI with 5-HT_{1A} receptor agonistic effects, showed a low propensity to induce sexual dysfunction. Although a statistically significant decrease in libido was reported, no or minimal differences were reported in sexual side effects in pooled data from three randomized, double-blind, placebo-controlled studies in almost 500 depressed adult patients [19–21]. Vortioxetine is an SSRI that also exerts agonistic activity at 5-HT_{1A} and 5-HT_{1B} receptors and antagonistic activity at 5-HT_{3}, 5-HT_{7}, and 5-HT_{1D} receptors [22, 23]. Vortioxetine is an efficient antidepressant and has a low sexual side effect profile [21, 22]. The additional mechanisms in the mode of action of vilazodone (5-HT_{1A} agonist) and vortioxetine (5-$HT_{1A/1B}$ agonist and 5-$HT_{3/7/1D}$ antagonist) apparently antagonize the sexual inhibitory actions of the SSRI-moiety of the respective molecules. These additional mechanisms do not clearly jeopardize the antidepressant effects that probably are caused by the SSRI activity. This may lead to the hypothesis that the antidepressant effects and the sexual side effects induced by an SSRI are caused by different mechanisms in the brain that can be separately influenced by other (serotonergic) mechanisms and may lead to selective antagonizing of the sexual side effects. It

is extremely difficult if not impossible to elucidate the exact underlying mechanisms of such complex acting antidepressants in humans. Combination of two (or more) separate drugs, e.g., an SSRI combined with reboxetine (a noradrenalin reuptake inhibitor-NRI) or bupropion a noradrenalin-dopamine reuptake inhibitor (NDRI) could lead to some answers but the combination is accompanied by several complicated interactions, not only at the level of side effects, but also at pharmacokinetic and metabolism levels. Such studies suffer always from complicated results that are often not clear-cut at all. Development of new antidepressants with less or no sexual side effects (as they appear the main reason for stopping treatment at long-term use) seems an important way to go.

The need for new and effective treatment of depression is clearly influenced by the need for less or milder side effects (not only sexual ones). Moreover, additional benefits like a fast onset of action of the antidepressant activity (days instead of weeks), a higher efficacy (present antidepressants are only working in 40–60% of the depressed patients), and a reasonable price may lead to new antidepressants that have enormous advantages over the existing "low cost" antidepressants (TCAs and SSRIs).

3. Translational studies into the putative sexual side effects of novel antidepressants

From all the human studies on antidepressants and sexual side effects, a strong pattern emerges: SSRIs, drugs that block serotonergic transporters at serotonergic neurons, have intrinsic effects on sexual behavior. Other antidepressants, like bupropion that lack serotonergic activity, have no or less sexual side effects and may even be beneficially in alleviating the often already lowered libido of depressed patients [24]. In the search for new and better antidepressants, an animal model with a high predictive validity for sexual (side) effects is an indispensable asset. It is of paramount importance that such an animal model should be as predictive as possible for the human (depressed) patient. An ideal animal model should follow the human course of the emergence of sexual side effects of present SSRIs: not acute, but after (sub) chronic administration. The emergence of the sexual side effects more or less parallels the emergence of the antidepressant activity that takes weeks to develop gradually. The animal model has also to be able to detect prosexual effects of drugs, as this may be an important factor in the treatment of either the SSRI-induced sexual dysfunctions or in the improvement of the basically lowered sexual drive (libido) associated with the depression itself. Ideally, the model should also be able to determine a fast(er) onset of action of new antidepressants, whereas long-term efficacy (years) is a must because antidepressant treatment lasts often for a very long time.

4. The actual animal model

Several years ago we noticed that upon testing of young adult male outbred (Wistar strain) rats on their sexual performance against a female rat brought into behavioral estrus, individual

http://dx.doi.org/10.5772/intechopen.69105

males exhibited variable levels of sexual activity. Some rats were sexually very active, some not at all and the rest with a variety of intermediate levels [25]. We standardly test all males subsequently for four weekly tests of 30 minutes, which generates very stable levels of sexual behavior in individual males. At the third to fourth test individual rats have a very stable and long-lasting level of sexual performance. The number of ejaculations per 30 min is a very reliable and predictive measure of the sexual performance of male rats and we hypothesized that male rats display sexual endophenotypes [26]. Over the last decade we tested (trained) more than 2000 male rats (of the Wistar outbred strain) in this way and we established that such rats might be distributed according to their sexual endophenotype [27, 28] in slow (sluggish), average (normal), and fast ejaculators. On average 20–30% of the rats are "slow" performers (0–1 ejaculation/30 min) and 10% are fast performers (4–5 ejaculations per 30 min). Animals with 2–3 ejaculations per test are regarded as "average" or normal ejaculators and constitute the bulk of all rats (60–70%). We hypothesized that male rats notoriously low in sexual performance might model delayed or retarded (an) ejaculation in human males, and those with four or more ejaculations per test reflecting premature ejaculation in men [26].

In the present contribution we focus on average ejaculating rats. They are ideally suited to test the effects of antidepressants or other psychotropic drugs on sexual behavior because both inhibitory and stimulatory (prosexual) properties can be detected.

To assess putative sexual side effects of psychotropic drugs we designed an experimental drug test consisting of 14 days of daily drug treatment followed by a week washout to judge the reversibility of a putative drug effect [28]. Sexual behavior is measured for 30 min after acute, sub-chronic (1 week), and chronic (2 weeks) treatment and a week after stopping treatment (washout).

Critical factors in using an animal model over time (years) are the reproducibility and stability of the model. Our standard control SSRI that we always used as positive control reference drug in our studies is paroxetine, an SSRI with rather severe sexual side effects in humans. We analyzed the effects of one dose of paroxetine (10 mg/kg p.o.) in seven subsequent experiments performed over several years using the protocol as described by Chan et al. [28]. After placing an estrus female into the cage of a sexually trained rat the male starts sniffing and following the female. Ensuing, the female responds by displaying the typical proceptive behaviors hopping and darting, upon which the male starts mounting and intromitting the female, finally leading to an ejaculation. Usually a series of mounts and intromissions occurs (introductory male sexual behavior) leading to the consummatory phase, ejaculation, which is followed by a rest period (postejaculatory interval) after which the male resumes the next series of mounts and intromissions and finally again ejaculation (**Figure 1**). Most males show around 2–3 ejaculations per 30 min, but this number may vary from 0 to 5 ejaculations.

Figure 2 shows the number of ejaculations per test (30 min) of sexually trained rats with an average ejaculation rate (2–3 ejaculations/30 min) after vehicle or paroxetine (10 mg/kg p.o.) treatment. The sexual behavior of all animals was measured acutely (30 min after administration), sub-chronically (after 1 week administration), chronically (after 2 weeks administration), and after washout (1 week after stopping treatment). Overall, the vehicle treated animals did not differ over tests (time) significantly in ejaculation frequency ($F_{18,171} = 1253$ n.s.) and latency to the first

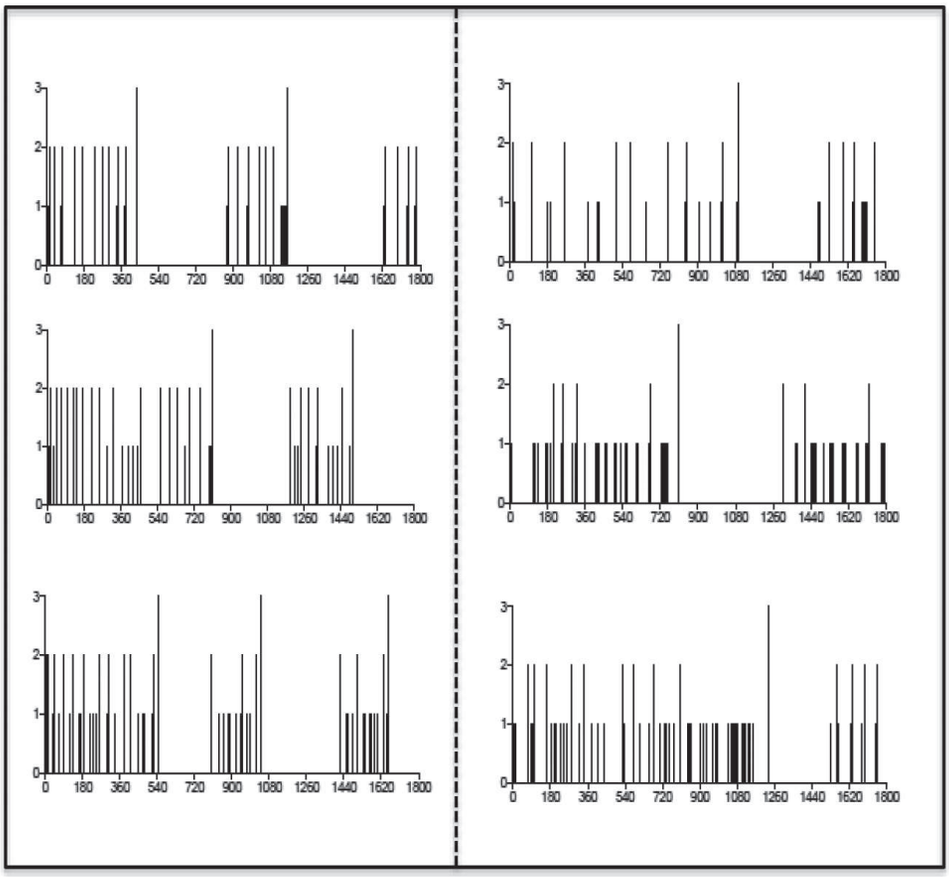


Figure 1. Representative examples of sexual behavior pattern of experienced male Wistar rats chronically treated with vehicle (left) or paroxetine (right) during a 30 min test with an estrus female. 1 = mount, 2 = intromission, 3 = ejaculation.

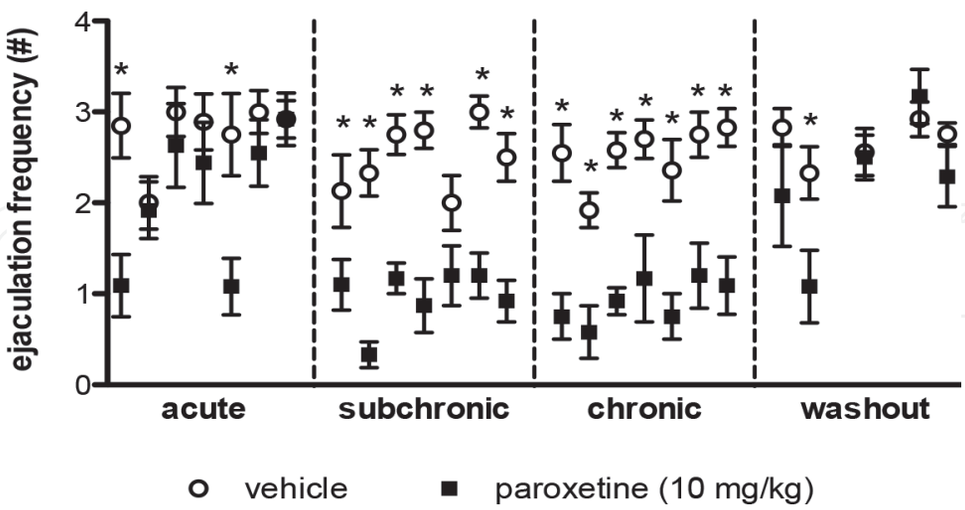


Figure 2. The ejaculation frequencies of seven cohorts of male rats tested against an estrus female rat during a 30 min test. The independent seven cohorts were tested over a time span of approx. 4 years. The data of the vehicle groups (open circles) and the paroxetine groups (10 mg/kg p.o.) are shown after acute, sub-chronic, and chronic treatment with either vehicle or paroxetine. One week after cessation of treatment a last sexual test was performed in order to study whether the sexual behavior returned to the original level. Asterisk (*) indicates significant difference between the vehicle and paroxetine group.

ejaculation ($F_{15,168}$ = 1360 n.s.) showing the stability of male sexual behavior across experiments and time. Paroxetine showed a very stable reduction in the number of ejaculation (**Figure 2**) and increase in the latency to ejaculate (not shown) after 1 and 2 weeks of administration compared to vehicle treatment. One week after cessation of treatment (washout) paroxetine pretreated groups returned to normal levels (in four of five experiments), and there were no differences between the acute treatment and the washout data.

These data confirm the reliability and stability of the paradigm used for measuring sexual behavior and drug effects. This allows the direct comparison of different psychotropic drugs tested in separate experiments.

5. Dose-dependency of drug effects on sexual behavior

Sexual side effects in humans are dose-dependent, although human studies often do not investigate several doses (dose-dependency) in one experiment. In general, higher doses of antidepressants lead to much more serious side effects, including sexual effects. Therefore, in our animal model we always tried to test increasing doses in order to possibly generate a dose-response curve. In case of paroxetine, doses of 2.5, 5, and 10 mg/kg (p.o.) were tested using our standard experimental design.

Figure 3 (left column; top figure) shows the results. Paroxetine acutely given did not affect the ejaculation frequency but showed a dose-dependent effect after sub-chronic and chronic administration, although the 5-mg/kg dose did not significantly differ from the highest dose (10 mg/kg). Although not shown here, other parameters measured (e.g., latency to ejaculation and post-ejaculatory latency) also showed the inhibitory profile of paroxetine. This pattern of paroxetine's inhibitory action in rat's sexual behavior parallels the human situation where at least 1 week of administration is needed to induce sexual dysfunctions [29, 30]. Looking into the structure of the sexual performance in rats, paroxetine changes the sexual behavior pattern after sub-chronic and chronic dosing. More mounts are needed to reach the same amount of intromissions, reflected in the increased intromission latency and increased mount frequency and the decreased copulatory efficiency. Rats show a decreased "hit rate," i.e., attempts to reach vaginal penetration. This is also evident in the increased ejaculation latency (for details see Table 1 and Figure 4 in [31]).

All SSRIs share the inhibitory action on male sexual behavior after (sub) chronic but not acute administration (**Table 1**). This pattern clearly follows the antidepressant profile which also emerges only after some delay after starting treatment. Apparently, the mechanisms underlying the inhibitory effects of SSRIs after repeated administration reflect changes in the serotonergic system which become manifest only after sustained administration. The underlying hypothesis, increased serotonin-mediated tonic inhibition, suggests that chronic SSRI treatment influences underlying circuitry mediating sexual behavior by enhancing 5-HT activity in projection areas [32]. Although it is not at all clear that how this mechanism specifically acts at various brain levels, it is evident that a very complex network in the brain and spinal cord is

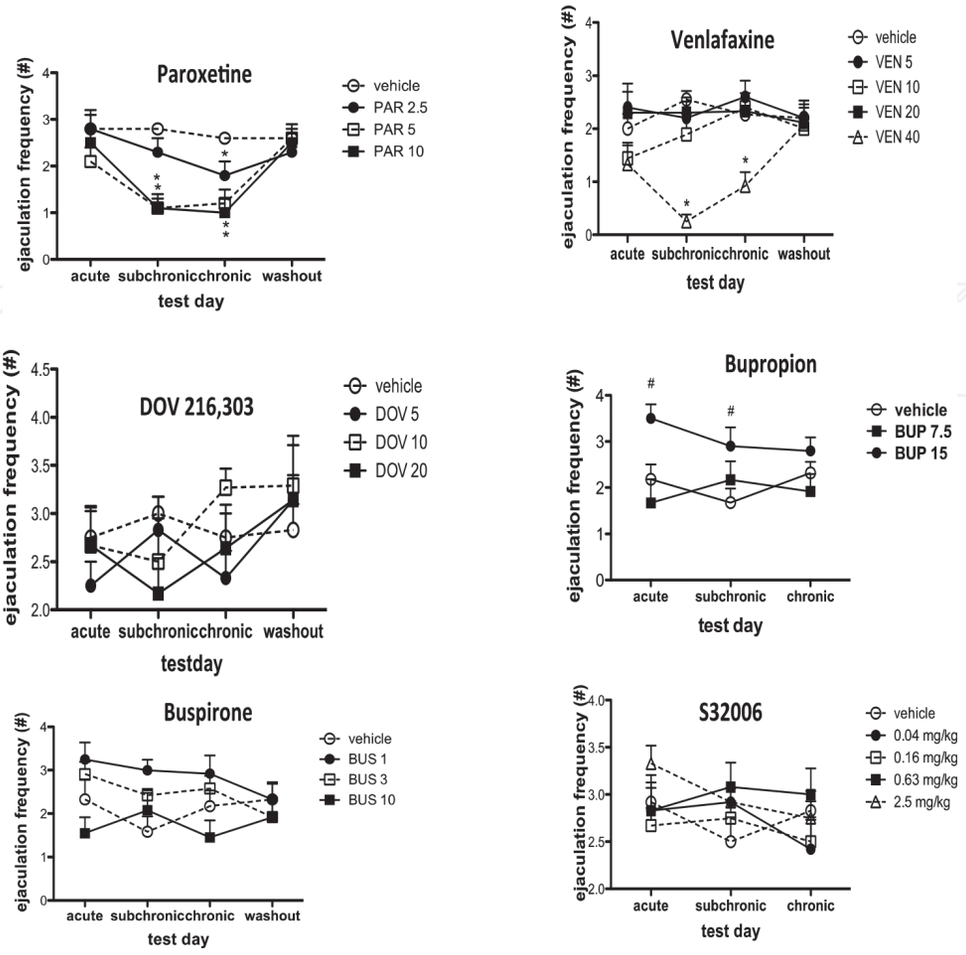


Figure 3. The effects of paroxetine (left, top), venlafaxine (right, top), DOV 216,303 (left, middle), bupropion (right, middle), buspirone (left, bottom), and S32006 (right, bottom) on the ejaculation frequency are shown after acute, subchronic, and chronic administration as well as after 1 week of washout.

involved in this serotonergically induced action, including important roles for noradrenergic, dopaminergic, and glutamatergic systems [33].

The serotonin-noradrenalin reuptake inhibitor (SNRI) venlafaxine affects male sexual behavior at relatively high doses (**Figure 3**, right column, top). Because noradrenaline exerts facilitatory effects in sexual behavior in humans [31], one might hypothetically expect that this may contrast the inhibitory effects of the SSRI-component in venlafaxine. Although at lower doses (that are antidepressant in animal depression models) venlafaxine does not affect sexual behavior, at the higher dose tested it does, indicating that the SSRI activity becomes dominant in venlafaxine's action.

The dopaminergic (DA) system plays an important role in the facilitation of sexual behavior [34]. DA activity in mesolimbic areas is involved in motivational and copulatory aspects of sexual behavior. There is a strong 5-HT/DA interaction in the brain, which modulates motivational aspects of sexual performance [31] and adding a dopaminergic stimulating mechanism to an inhibiting serotonergic mechanism (e.g., SSRI) might result in amelioration of the inhibitory action of the latter [31]. DOV 216,303 is a triple monoaminergic reuptake inhibitor (TRI) that blocks noradrenergic, serotonergic, and dopaminergic transporters [35, 36].

One of the core symptoms of depression, anhedonia, is connected to a lowered mesolimbic DA neurotransmission and the original rationale for development of TRIs was to alleviate anhedonia in depression [36]. An additional advantage might be that the dopaminergic stimulation by DA-reuptake inhibition might reverse sexual side effects. No data are available on the sexual side effect profile of TRIs, but a recent trial with a TRI (the DOV 216,303 isomer amitifadine) showed no worsening of sexual functioning after chronic treatment of depressed patients [37]. The preclinical data (**Figure 3** left column, middle) confirm the lack of sexual side effects of DOV 216,303 at doses that exert antidepressant effects in animal models of depression [36, 38–40]. This clearly suggests that 5-HT mediated inhibition of sexual behavior can be overcome by stimulating dopaminergic neurotransmission via dopamine transporter (DAT)-blockade, although a role for noradrenaline cannot be excluded.

Bupropion is well known for its counteractive effects on SSRI-induced sexual dysfunctions [17]. Bupropion facilitates noradrenergic and dopaminergic mechanisms (it is a noradrenalin transporter(NET) and DAT antagonist) and we expected a rather strong prosexual effect of bupropion in our animal model. Bupropion had a slight stimulating effect on sexual behavior, but only at the higher dose and only after acute and (marginally) sub-chronic dosing, but not at chronic administration (**Figure 3**, right column; middle). This small and short-living facilitatory effect of bupropion was rather unexpected. Apomorphine [41], a mixed dopamine D_2/D_3 receptor agonist showed a comparable profile in a similar experiment (**Table 1**),

Drug	Mechanism of action	Acute	Sub-chronic	Chronic	Washout	Reference
Paroxetine	SSRI	0	↓	↓	0	[31]
Fluvoxamine	SSRI	0	0	↓	nt	[59]
Citalopram	SSRI	0 (↓)	↓	↓	0	[57, 60]
Fluoxetine	SSRI	0	↓	↓	nt	[61]
Venlafaxine	SNRI	0	0	↓	0	[31]
Bupropion	NDRI	↑	0	0	0	[31]
DOV 216,303	TRI	0	0	↓	0	[31]
Buspirone	5-HT_{1A} R Agonist	↑	0	0	0	[31]
Vilazodone	SSRI/5-HT_{1A} R agonist	0	0	0	0	[56, 57]
Vortioxetine	SSRI/5-$HT_{1A,1B}$ R agonist; 5-$HT_{3,7,1D}$ R antagonist	0	0	0	0	[58]
Tramadol	SNRI/μ-opioid R agonist	0↓	nt	nt	nt	[62]
Apomorphine	DA-$D_{2/3}$ R agonist	↑	↑	↑	nt	[41]
S32006	5-HT_{2C} R antagonist	0	0	0	0	[31]
WAY100,635	5-HT_{1A} R antagonist	0	0	0	nt	[60]

↓: inhibition; ↑: stimulation; 0: no effect; nt: not tested. SSRI: selective serotonergic reuptake inhibitor; SNRI: serotonergic and noradrenergic reuptake inhibitor; NDRI: noradrenergic and dopaminergic reuptake inhibitor; TRI: triple monoaminergic reuptake inhibitor; R: receptor.

Table 1. Summary of effects of various drugs on male sexual behavior after acute, sub-chronic, or chronic treatment.

although it had a somewhat stronger prosexual effect than bupropion. Apparently, the relatively weak DAT-blockade of bupropion might be not strong enough to permanently stimulate sexual behavior in healthy subjects (like our rats), leaving open the possibility that in "depressed" brains with an extra SSRI-induced sexual dysfunction, bupropion might be very effective as an "add-on" medication. We have not tried bupropion in our SSRI (paroxetine)-treated model as an add-on yet.

When an SSRI is given (either to man or animal) the pharmacological mechanism, blockade of the SERT on the neuron induces an increase in the level of 5-HT in the synaptic cleft [42]. 5-HT is the endogenous ligand of all 14 different 5-HT receptors and it is very likely that some but not all 5-HT receptors are involved in serotonin's action in sexual behavior. One of the receptors involved is the 5-HT_{1A} receptor, located as a somatodendritic autoreceptor on 5-HT cell bodies and as postsynaptic heteroreceptor on many nonserotonergic neurons in various brain areas [42]. 5-HT_{1A} receptor agonists including buspirone have prosexual activity in rats upon acute administration [43, 44]. Extensive evidence suggests that this prosexual activity of 5-HT_{1A} R agonists is most likely due to activation of postsynaptic 5-HT_{1A} receptors that probably mediate dopaminergic activation in brain areas that decrease the ejaculation threshold [44]. Clinically, the only available (partial) 5-HT_{1A} receptor agonist buspirone (also a dopamine D_2 receptor antagonist) is used as an antidepressant and has not been associated with sexual side effects [45, 46]. In our model in rats, low doses of buspirone which are also exerting antidepressant effects in animal depression models have mild prosexual activity (**Figure 3** left column; lower panel). Our rat data are in line with (limited) human data which indicate that buspirone does not exert sexual side effects as well as it is not a very strong add-on drug in combination with SSRIs. The absence of prosexual effects at the highest dose could reveal the dopamine D_2 receptor blocking activity of buspirone which certainly comes in action at this dose. Dopamine D_2 receptor blockade has strong inhibitory effects on sexual behavior and interferes at higher doses with the prosexual activity of the 5-HT_{1A} receptor stimulation.

We have tested a selective 5-HT_{2C} receptor antagonist (S32006) in our rat model (**Figure 3**, right column; bottom panel). 5-HT_{2C} receptor agonists induce penile erections in rats and facilitate ejaculation via 5-HT_{2C} receptor activation in the lumbosacral spinal cord [47, 48]. Because 5-HT_{2C} receptor activation by d-LSD and quipazine induce increased ejaculation latencies, it has been suggested that the inhibition pattern by SSRIs has resemblance to that of 5-HT_{2C} receptor activation [49]. Novel nonSSRI antidepressants like agomelatine and mirtazapine lack sexual side effects [50]. Augmentation therapy with mirtazapine seems to decrease the sexual side effects of SSRIs [51, 52] supporting the notion of SSRI-induced sexual dysfunction mediated via 5-HT_{2C} receptors. S32006 is a very selective 5-HT_{2C} receptor antagonist, has antidepressant effects in preclinical depression models and elevates extracellular DA and NA, but not 5-HT [53, 54]. S32006 was completely devoid of any effect on sexual behavior after acute, sub-chronic and chronic administration [31], suggesting that 5-HT_{2C} receptors are not (directly) involved in sexual effects induced by SSRIs.

Recently, some new antidepressants were introduced in the market, vilazodone and vortioxetine. Vilazodone is an SSRI and a partial 5-HT_{1A} receptor agonist that has antidepressant activity in man and rat. Although much more clinical research is needed, the initial clinical trials suggested the absence of (additional) sexual side effects during treatment of the depressed patients [55].

We tested vilazodone (1, 3, and 10 mg/kg p.o.) and as reference drugs citalopram (10 and 30 mg/kg p.o.) and paroxetine (10 mg/kg p.o.) in our standard rat model [56]. Vilazodone did not affect sexual behavior at any dose or after acute, sub-chronic, or chronic administration, whereas both citalopram and paroxetine showed the typical SSRI profile: no acute effects but inhibitory effects at sub-chronic and chronic administration. In a subsequent experiment [57] once daily paroxetine (10 mg/kg p.o.), vilazodone (10 mg/kg p.o.), paroxetine (10 mg/kg p.o.) plus buspirone (3 mg/kg p.o.) or vehicle were given for 14 days to male rats and then switched for 7 days to various treatments. Vehicle, paroxetine, and vilazodone pretreated groups were switched to vehicle; paroxetine pretreated groups were switched to vilazodone, paroxetine plus buspirone or vehicle and the paroxetine plus buspirone group was switched to paroxetine alone. Sexual behavior was scored acutely (1 h after dosing), after 7 days dosing and after 14 days dosing as well as after 7 days after switching. The combination of paroxetine plus buspirone, like vilazodone alone, did not have an effect on sexual behavior, while paroxetine alone reduced it considerably. Switching to paroxetine in both the paroxetine plus buspirone group as well as in the vilazodone group resulted in clear sexual inhibitory effects. These studies strongly suggest that the 5-HT_{1A} receptor agonistic activity in the vilazodone molecule counteracts the inhibitory action of the SSRI part. These preclinical data strongly support the clinical studies that suggest absence of sexual side effects due to the antidepressant. The findings also suggest that adding a 5-HT_{1A} receptor agonist (like buspirone) to an SSRI may indeed counteract the SSRI-induced sexual dysfunctions.

Another recently developed and introduced antidepressant, vortioxetine, is an SSRI with an additional complex profile. Next to inhibiting the SERT, it exerts agonistic activity at 5-HT_{1A} and 5-HT_{1B} receptors and antagonistic activity at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors [22].

Vortioxetine (1 and 10 mg/kg, p.o.) did not affect sexual behavior in male rats, neither after acute, sub-chronic, and chronic dosing [58]. The doses used led to, respectively, 50% (1 mg/kg) and 90% (10 mg/kg) SERT occupation. In the same experiment, the reference paroxetine (at 10 mg/kg) had a comparable SERT occupancy of 90% as the highest vortioxetine dose, indicative that at least at the highest dose tested vortioxetine showed sufficient SERT occupancy to induce sexual side effects. It is therefore clear that the remaining mechanisms in vortioxetine (5-$HT_{3,7,1A,1B,1D}$) in some as yet not understood way counteract the SSRI-induced inhibitory effects. Ongoing research tries to further unravel this mechanism. Based on our finding in rats, vortioxetine is predicted being devoid of (extra) sexual side effects in depressed patients. Clinical findings, although not explicitly aimed to study the sexual side effects of vortioxetine (e.g., in healthy people), indeed hint to a low propensity of vortioxetine in this area [22].

6. Discussion

Serotonin is critically involved in the mechanisms underlying various aspects of sexual behavior, both in men and male rats. Nowadays, the main treatment of depression uses SSRIs. They are strongly associated with sexual side effects that frequently lead to stopping the antidepressant treatment. SSRIs increase the serotonergic tone in the central nervous system, leading to

a cascade, although largely unknown, of neurochemical changes that in some way or another lead to sexual dysfunctions, in particular, after longer (weeks) treatment. The antidepressant quality of SSRIs is generally considered as reasonable whereas other side effects of SSRIs (like dizziness, nausea) are tolerable and disappear upon continuous treatment. The sexual side effects do not disappear and are troublesome. Thus, there is a great need to get rid of these effects and newly developed antidepressants are scrutinized for their induction of sexual dysfunction. Recently, two new antidepressants, vilazodone and vortioxetine have been introduced and both compounds claim a low propensity to induce sexual side effects. Both compounds have an important SSRI function in their mechanism of action that more or less guarantees antidepressant effects, and also have additional inherent pharmacological mechanisms that presumably antagonize the inhibitory sexual effects caused by the SSRI mechanism. The clinical use of both drugs over the coming years will further elucidate their propensity to induce sexual side effects.

Over the last decade, we have developed a male rat sexual behavior paradigm that models to a large extent the human situation. Classic SSRIs (fluoxetine, paroxetine, fluvoxamine, citalopram, escitalopram, sertraline) have sexual behavior inhibiting effects, not after acute but after (sub) chronic administration. This mimics the human situation where such effects emerge after longer (weeks) administration and do not disappear upon continuous use (months, years), which is also the case in our rat model. Some compounds (e.g., buspirone, bupropion) are active after acute administration. Whether this is also the case in humans is unknown because of lack of studies. Our model is also fit to measure the effects of psychotropics in addition to antidepressants. We have studied various drugs, e.g., apomorphine, tramadol [62], and several serotonergic drugs and have found inhibitory, facilitatory, or no effects. The model is very useful to study the brain mechanisms underlying various aspects of sexual behavior and of sexual dysfunction. The most remarkable characteristics of the model are its reliability and reproducibility. Each male rat appears to have an endophenotype with regard to its sexual behavior that becomes very stable after a number of sexual training sessions. Whether such sexual endophenotypes are present in men is unclear but the presence of lifelong premature ejaculation suggests that possibility. It is at least clear that much more research is needed to unravel such hypotheses in humans.

7. Conclusion

Sexual side effects are a major concern in presently used antidepressants, especially the SSRIs. Several strategies have been used to circumvent these problems but are rather disappointing. Newly developed antidepressants like vortioxetine and vilazodone seem to be devoid of sexual side effects in humans, although large scale data are not yet available. In the search for new antidepressants that lack sexual side effects, animal models can play an important role. A rat model of sexual (dys)function is illustrated, which seems to fulfill the face, predictive, and construct validities for a valuable animal model. The model can also be used to investigate underlying mechanisms in the control of sexual functions and dysfunctions.

Author details

Jocelien D.A. Olivier[1], Diana C. Esquivel Franco[1], Marcel D. Waldinger[2] and Berend Olivier[1,3,4]*

*Address all correspondence to: b.olivier@uu.nl

1 Groningen Institute for Evolutionary Life Sciences, Faculty of Science and Engineering, Rijksuniversiteit Groningen, Groningen, The Netherlands

2 Department of Pharmacology and Physiology, Drexell University College of Medicine, Philadelphia, USA

3 Department of Psychopharmacology, Science Faculty, Utrecht University, Utrecht, The Netherlands

4 Department of Psychiatry, Yale University School of Medicine, New Haven, USA

References

[1] Pfaus JG. Pathways of sexual desire. The Journal of Sexual Medicine. 2009;**6**:1506-1533. DOI: 10.1111/j.1743-6109.2009.01309.x

[2] Makhlouf A, Kparker A, Niederberger CS. Depression and erectile dysfunction. The Urologic Clinics of North America. 2007;**34**:565-574

[3] Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: Impact, effects, and treatment. Drug Health Patient Safety. 2010;**2**:141-150. DOI: 10.2147/DHPS.S7634

[4] Lahon K, Shetty HM, Paramel A, Sharma G. Sexual dysfunction with the use of antidepressants in a tertiary care mental health setting—A retrospective case series. The Journal of Pharmacology & Pharmacotherapeutics. 2011;**2**:128-131. DOI: 10.4103/0976-500X.81913

[5] Monteiro WO, Noshirvani HF, Marks IM, Lelliott PT. Anorgasmia from clomipramine in obsessive-compulsive disorder. A controlled trial. The British Journal of Psychiatry. 1987;**151**:107-112

[6] Beaumont G. Sexual side-effects of clomipramine (Anafranil). The Journal of International Medical Research. 1977;**5**:37-44

[7] Balon R. Depression, antidepressants and human sexuality. Primary Psychiatry. 2007;**14**:42-50

[8] Segraves RT. Sexual dysfunction associated with antidepressant therapy. The Urologic clinics of North America. 2007;**34**:575-579

[9] Segraves RT, Balon R. Antidepressant-induced sexual dysfunction in men. Pharmacology, Biochemistry and Behavior. 2014;**121**:132-137. DOI: 10.1016/j.pbb.2013.11.003

[10] Montejo-González AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, De la Gandara J, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez JM, Sanchez S, Vicens E. SSRI-induced sexual dysfunction: Fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. Journal of Sex & Marital Therapy. 1997;**23**:176-194

[11] Harrison WM, Rabkin JG, Ehrhardt AA, Stewart JW, McGrath PJ, Ross D, Quitkin FM. Effects of antidepressant medication on sexual function: A controlled study. Journal of Clinical Psychopharmacology. 1986;**6**:144-149

[12] Latorre A, Guipponi G, Duffy D, Conca A. Sexual dysfunction related to psychoptropic drugs: A critical review-part 1: Antidepressants. Pharmacopsychiatry. 2013;**46**:191-199

[13] Coleman CC1, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, Ascher J, Batey S, Jamerson B, Metz A. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clinical Therapeutics. 2001;**23**:1040-1058

[14] Segraves RT, Kavoussi R, Hughes AR, Batey SR, Johnston JA, Donahue R, Ascher JA. Evaluation of sexual functioning in depressed outpatients: A double-blind comparison of sustained-release bupropion and sertraline treatment. Journal of Clinical Psychopharmacology. 2000;**20**:122-128

[15] Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clinical Therapeutics. 1999;**21**:643-658

[16] Kennedy SH, Fulton KA, Bagby RM, Greene AL, Cohen NL, Rafi-Tari S. Sexual function during bupropion or paroxetine treatment of major depressive disorder. The Canadian Journal of Psychiatry. 2006;**51**:234-242

[17] Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG. Bupropion extended release compared with escitalopram: Effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. The Journal of Clinical Psychiatry. 2006;**67**:736-746

[18] Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: Sexual functioning, antidepressant efficacy, and tolerability. Journal of Clinical Psychopharmacology. 2006;**26**:482-488

[19] Khan A, Cutler AJ, Kajdasz DK, Gallipoli S, Athanasiou M, Robinson DS, Whalen H, Reed CR. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. The Journal of Clinical Psychiatry. 2011;**72**:441-447. DOI: 10.4088/JCP.10m06596

[20] Clayton AH, Kennedy SH, Edwards JB, Gallipoli S, Reed CR. The effect of vilazodone on sexual function during the treatment of major depressive disorder. The Journal of Sexual Medicine. 2013;**10**:2465-2476. DOI: 10.1111/jsm.12004

[21] Deardorff WJ, Grossberg GT. A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine. Expert Opinion on Pharmacotherapy. 2014;**15**:25-42. DOI: 10.1517/14656566.2014.960842

[22] Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. Pharmacology & Therapeutics. 2015;**145**:43-57. DOI: 10.1016/j.pharmthera.2014.07.001

[23] Gibb AI, Deeks ED. Vortioxetine: First global approval. Drugs. 2014;**74**:135-145. DOI: 10.1007/s40265-013-0161-9

[24] Dorevitch A, Davis H. Fluvoxamine-associated sexual dysfunction. The Annals of pharmacotherapy. 1994;**28**:872-874

[25] Pattij T, de Jong TR, Uitterdijk A, Waldinger MD, Veening JG, Cools AR, van der Graaf PH, Olivier B. Individual differences in male rat ejaculatory behaviour: Searching for models to study ejaculation disorders. The European Journal of Neuroscience. 2005;**22**:724-734

[26] Olivier B, Chan JS, Pattij T, de Jong TR, Oosting RS, Veening JG, Waldinger MD. Psychopharmacology of male rat sexual behavior: Modeling human sexual dysfunctions?. International Journal of Impotence Research. 2006;**18**(1):423

[27] Chan JS, Olivier B, de Jong TR, Snoeren EM, Kooijman E, van Hasselt FN, Limpens JH, Kas MJ, Waldinger MD, Oosting RS. Translational research into sexual disorders: pharmacology and genomics. European Journal of Pharmacology. 2008;**585**:426-435. DOI: 10.1016/j.ejphar.2008.02.098

[28] Chan JS, Waldinger MD, Olivier B, Oosting RS. Drug-induced sexual dysfunction in rats. Current Protocols in Neuroscience. 2010;**Chapter 9**:Unit 9.34. DOI: 10.1002/0471142301.ns0934s53

[29] Balon R. Modifications of the serotonin system by antidepressant treatments: Implications for the therapeutic response in major depression. The American Journal of Psychiatry. 2006;**163**:1504-1509

[30] Waldinger MD, Zwinderman AH, Olivier B. SSRIs and ejaculation: A double-blind, randomized, fixed-dose study with paroxetine and citalopram. Journal of Clinical Psychopharmacology. 2001;**21**:556-560

[31] Bijlsma EY, Chan JS, Olivier B, Veening JG, Millan MJ, Waldinger MD, Oosting RS. Sexual side effects of serotonergic antidepressants: Mediated by inhibition of serotonin on central dopamine release? Pharmacology, Biochemistry and Behavior. 2014;**121**:88-101. DOI: 10.1016/j.pbb.2013.10.004

[32] Blier P, de Montigny C, Chaput Y. Modifications of the serotonin system by antidepressant treatments: Implications for the therapeutic response in major depression. Journal of Clinical Psychopharmacology. 1987;**7**(6 Suppl):24S-35S

[33] Will RG, Hull M, Dominguez JM. Influences of dopamine and glutamate in the medial preoptic area on male sexual behavior. Pharmacology Biochemistry & Behavior. 2014;**121**:115-123. DOI: 10.1016/j.pbb.2014.02.005

[34] Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: Influences on male sexual behavior. Physiology & Behavior. 2004;**83**:291-307

[35] Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. Antidepressant-like actions of DOV 21,947: A "triple" reuptake inhibitor. European Journal of Pharmacology. 2003;**461**:99-104

[36] Skolnick P, Krieter P, Tizzano J, Basile A, Popik P, Czobor P, Lippa A. Preclinical and clinical pharmacology of DOV 216,303, a "triple" reuptake inhibitor. CNS Drug Reviews. 2006;**12**:123-134

[37] Tran PI, Skolnick P, Czobor P, Huang NY, Bradshaw M, McKinney A, Fava M. Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Journal of Psychiatric Research. 2012;**46**:64-71. DOI: 10.1016/j.jpsychires.2011.09.003

[38] Breuer ME, Chan JS, Oosting RS, Groenink L, Korte SM, Campbell U, Schreiber R, Hanania T, Snoeren EM, Waldinger M, Olivier B. The triple monoaminergic reuptake inhibitor DOV 216,303 has antidepressant effects in the rat olfactory bulbectomy model and lacks sexual side effects. European Neuropsychopharmacology. 2008;**18**:908-916. DOI: 10.1016/j.euroneuro.2008.07.011

[39] Caldarone BJ1, Paterson NE, Zhou J, Brunner D, Kozikowski AP, Westphal KG, Korte-Bouws GA, Prins J, Korte SM, Olivier B, Ghavami AJ. The novel triple reuptake inhibitor JZAD-IV-22 exhibits an antidepressant pharmacological profile without locomotor stimulant or sensitization properties. Journal of Pharmacology and Experimental Therapeutics. 2010;**335**:762-770. DOI: 10.1124/jpet.110.174011

[40] Paterson NE, Balci F, Campbell U, Olivier BE, Hanania T. The triple reuptake inhibitor DOV216,303 exhibits limited antidepressant-like properties in the differential reinforcement of low-rate 72-second responding assay, likely due to dopamine reuptake inhibition. Journal of Psychopharmacology. 2011;**25**:1357-1364. DOI: 10.1177/0269881110364272

[41] Olivier JD, de Jong TR, Jos Dederen P, van Oorschot R, Heeren D, Pattij T, Waldinger MD, Coolen LM, Cools AR, Olivier B, Veening JG. Effects of acute and chronic apomorphine on sex behavior and copulation-induced neural activation in the male rat. European Journal of Pharmacology. 2007;**576**:61-76

[42] Olivier B. Serotonin: A never-ending story. European Journal of Pharmacology. 2015;**753**: 2-18. DOI: 10.1016/j.ejphar.2014.10.031

[43] Åhlenius S, Larsson K, Svensson L, Hjorth S, Carlsson A, Lindberg P, Wikström H, Sanchez D, Arvidsson LE, Hacksell U, Nilsson JL. Effects of a new type of 5-HT receptor agonist on male rat sexual behavior. Pharmacology, Biochemistry and Behavior. 1981;**15**:785-792

[44] Snoeren EM, Veening JG, Olivier B, Oosting RS. Serotonin 1A receptors and sexual behavior in female rats: A review. Pharmacology, Biochemistry and Behavior. 2014;**121**:43-52. DOI: 10.1016/j.pbb.2013.11.017

[45] Landén M, Eriksson E, Agren H, Fahlén T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. Journal of Clinical Psychopharmacology. 1999;**19**:268-271

[46] Landén M, Högberg P, Thase ME. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. The Journal of Clinical Psychiatry. 2005;**66**:100-106

[47] Stafford SA, Tang K, Coote JH. Activation of lumbosacral 5-HT2C receptors induces bursts of rhythmic activity in sympathetic nerves to the vas deferens in male rats. British Journal of Pharmacology. 2006;**148**:1083-1090

[48] Yonezawa A, Yoshizumi M, Ebiko M, Ise SN, Watanabe C, Mizoguchi H, Kimura Y, Sakurada S. Ejaculatory response induced by a 5-HT2 receptor agonist m-CPP in rats: Differential roles of 5-HT2 receptor subtypes. Pharmacology, Biochemistry and Behavior. 2008;**88**:367-373

[49] Waldinger MD, Olivier B. Selective serotonin reuptake inhibitor-induced sexual dysfunction: Clinical and research considerations. International Clinical Psychopharmacology. 1998;**13**(Suppl 6):S27-33

[50] Millan MJ. Multi-target strategies for the improved treatment of depressive states: Conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacology & Therapeutics. 2006;**110**:135-370

[51] Atmaca M, Korkmaz S, Topuz M, Mermi O. Mirtazapine augmentation for selective serotonin reuptake inhibitor-induced sexual dysfunction: A retrospective investigation. Psychiatry Investigation. 2011;**8**:55-57. DOI: 10.4306/pi.2011.8.1.55

[52] Ozmenler NK, Karlidere T, Bozkurt A, Yetkin S, Doruk A, Sutcigil L, Cansever A, Uzun O, Ozgen F, Ozsahin A. Mirtazapine augmentation in depressed patients with sexual dysfunction due to selective serotonin reuptake inhibitors. Human Psychopharmacology. 2008;**23**:321-326. DOI: 10.1002/hup.929

[53] Dekeyne A, Mannoury la Cour C, Gobert A, Brocco M, Lejeune F, Serres F, Sharp T, Daszuta A, Soumier A, Papp M, Rivet JM, Flik G, Cremers TI, Muller O, Lavielle G, Millan MJ. S32006, a novel 5-HT2C receptor antagonist displaying broad-based antidepressant and anxiolytic properties in rodent models. Psychopharmacology (Berlin). 2008;**199**:549-568. DOI: 10.1007/s00213-008-1177-9

[54] Millan MJ1, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: Role of 5-HT_{2C} receptor blockade. Psychopharmacology (Berlin). 2005;**177**:448-458

[55] Clayton AH, Gommoll C, Chen D, Nunez R, Mathews M. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: Results from a phase IV clinical trial. International Clinical Psychopharmacology. 2015;**30**:216-223. DOI: 10.1097/YIC.0000000000000075

[56] Oosting RS, Chan JS, Olivier B, Banerjee P. Vilazodone does not inhibit sexual behavior in male rats in contrast to paroxetine: A role for 5-HT1A receptors? Neuropharmacology. 2016;**107**:271-277. DOI: 10.1016/j.neuropharm.2016.03.045

[57] Oosting RS, Chan JS, Olivier B, Banerjee P, Choi YK, Tarazi F. Differential effects of vilazodone versus citalopram and paroxetine on sexual behaviors and serotonin transporter and receptors in male rats. Psychopharmacology (Berlin). 2016;**233**:1025-34. DOI: 10.1007/s00213-015-4198-1

[58] Li Y, Pehrson AL, Oosting RS, Gulinello M, Olivier B, Sanchez C. A study on time-and sex-dependent effects of vortioxetine on rat sexual behavior: possible role of direct receptor modulation. Neuropharmacology. 2017;**121**:89-99. DOI:10.1016/j.neuropharm.2017.04.017

[59] de Jong TR, Pattij T, Veening JG, Waldinger MD, Cools AR, Olivier B. Effects of chronic selective serotonin reuptake inhibitors on 8-OH-DPAT-induced facilitation of ejaculation in rats: Comparison of fluvoxamine and paroxetine. Psychopharmacology (Berlin). 2005;**179**:509-515

[60] de Jong TR, Pattij T, Veening JG, Dederen PJ, Waldinger MD, Cools AR, Olivier B. Citalopram combined with WAY 100635 inhibits ejaculation and ejaculation-related Fos immunoreactivity. European Journal of Pharmacology. 2005;**509**:49-59

[61] Vega Matuszcyk JI, Larsson K, Eriksson E. The selective serotonin reuptake inhibitor fluoxetine reduces sexual motivation in male rats. Pharmacology, Biochemistry and Behavior. 1998;**60**:527-32

[62] Olivier JDA, Esquivel Franco DC, Oosting RS, Waldinger MD, Sarnyai Z, Olivier B. Tramadol: Effects on sexual behavior in male rats are mainly caused by its 5-HT reuptake blocking effects. Neuropharmacology. 2017;**11**6:50-58. DOI: 10.1016/j.neuropharm.2016.11.020

IntechOpen