International Journal of Risk & Safety in Medicine 28 (2016) 1–12
DOI 10.3233/JRS-160668
IOS Press



Review Article

# Persistent sexual dysfunction after early exposure to SSRIs: Systematic review of animal studies

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Received 13 October 2015
Accepted 10 January 2016

**Abstract.**
**BACKGROUND:** Sexual dysfunction is a common adverse effect of selective serotonin reuptake inhibitors (SSRIs) and there is a concern that the sexual harms might persist after discontinuation of therapy.
**OBJECTIVE:** To assess whether the use of SSRIs in animals can lead to persistent sexual dysfunction.
**METHODS:** Systematic review of animal studies measuring sexual behaviour after end of treatment with SSRIs or serotonin norepinephrine reuptake inhibitors.
**DATA SOURCES:** We searched PubMed and EMBASE.
**RESULTS:** We included 14 studies. The general quality of the studies was poor. Only four studies reported use of randomisation and none mentioned allocation concealment. All studies used placebo and were therefore blinded. For rats exposed to SSRIs compared with those exposed to placebo, we found a higher risk of no mounting behaviour (RR = 0.73; 95% CI = 0.62–0.86), no intromission behaviour (RR = 0.74; 95% CI = 0.60–0.92) and no ejaculation behaviour (RR = 0.49, 95% CI = 0.24–1.00).
**CONCLUSION:** Our results showed substantial and lasting effects on sexual behaviour in rats after exposure to an SSRI early in life on important sexual outcomes.

Keywords: Selective serotonin reuptake inhibitors (SSRIs), long lasting harm, permanent sexual dysfunction, animal studies, systematic review

## 1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have become one of the most prescribed medicines in the world. They have many approved indications and are often used off-label for dubious purposes [1–3].

One of the many effects of SSRIs is to increase serotonin, which plays a key role for many functions, including sexual behaviour [4]. It is well documented that SSRIs can cause sexual dysfunction [5–8]. The drug companies have claimed that very few patients become sexually disturbed, e.g. only 1.9% in the registration application for fluoxetine [9, 10], but the prevalence has varied from 27% to 80% in

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different studies [5, 6, 11–13]. A study of 1,022 patients who all had a normal sex life before they started on antidepressants found sexual dysfunction in 59% of the patients [6] on direct questioning; only 20% reported such effects spontaneously [6]. The weighted average occurrence of sexual problems for the five most commonly used drugs was: 57% experienced decreased libido; 57% experienced delayed orgasm or ejaculation; 46% experienced no orgasm or ejaculation; and 31% experienced erectile dysfunction or decreased vaginal lubrication [2]. About 40% of the patients considered their sexual dysfunction unacceptable [6].

There is concern that the sexual harms might persist after discontinuation of therapy. Two studies with three cases each reported on persistent sexual dysfunction long after discontinuation of SSRIs [14, 15]. Another paper listed 120 cases of enduring sexual dysfunction following drug treatment reported to RxISK.org, and 101 of these were related to SSRIs and similar drugs [16]. The length of treatment prior to the dysfunction ranged from 3 days to 15 years, and in many instances these problems first occurred when treatment was stopped [16]. In the internet community, SSRIsex@yahoogroups.com, with over 3500 members, patients also complain about sexual problems that persist long after the end of therapy.

The persistent effects of SSRIs on sexuality have been little studied in humans, and patients might not associate them with a drug they no longer take. Animal studies suggest that SSRIs might cause permanent sexual dysfunction after ending SSRI exposure at an early age [17–21]. Unfortunately, the methodological quality of animal studies is generally poor [22–24]. The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs; http://www.nc3rs.org.uk/), a UK government sponsored organization, found that most studies did not use randomization (87%) or blinding (86%) [22].

Initiatives have been undertaken to promote the use of similar standards for systematic reviews of animal studies as those used in Cochrane reviews of human studies, e.g. The Collaborative Approach to Meta-analysis and Review of Animal Data from Experimental Studies (CAMARADES; www.Camarades.info) and the Systematic Review Centre for Laboratory animal Experimentation research group (SYRCLE; www.umcn.nl/Research/Departments/cdl/SYRCLE).

Systematic reviews of animal studies could make significant contributions to healthcare [25] and could also identify biasing factors in these studies [26, 27]. We have not found any systematic reviews of sexual dysfunction in animal studies after early exposure to SSRIs and therefore decided to perform our own.

## 2. Methods

### *2.1. Search strategy*

Guided by two university librarians, we did preliminary searches in PubMed, Embase, Biosis, Zoological Records, Web of Science and PsycINFO in order to identify the most relevant search criteria and databases. We did our final searches in PubMed and Embase. PubMed is the biggest database of medical animal studies; two other big databases of animal studies are Embase and Web of Science. We chose Embase because of its good search options, map terms, and its inclusion of many European and pharmacological journals not found in PubMed. We excluded PsycINFO, Web of Science, Biosis and Zoological Records, as it has never been shown that it adds anything to search in multiple databases, compared to searching only two and track references in the included articles.

We searched the two databases for selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs) combined with sexual dysfunction and animal using appropriate subheadings.

#### 2.1.1. Search strategy in PubMed

("Sexual Dysfunction, Physiological"[Mesh] OR "Sexual Dysfunctions, Psychological"[Mesh] OR "Erectile Dysfunction"[Mesh] OR "Sexual Behavior, Animal"[Mesh] OR "Disorders of Sex Development"[Mesh])

AND ("Serotonin Uptake Inhibitors"[Mesh] OR "Serotonin Uptake Inhibitors"[Pharmacological Action])

AND Other animals (search filter).

#### 2.1.2. Search strategy in EMBASE

Sexual dysfunction/ or sexual behaviour/ or sexual development/

AND serotonin noradrenalin reuptake inhibitor/ or serotonin uptake inhibitor/ or duloxetine/ or paroxetine/ or fluoxetine/

AND Limit to animal studies (limits in advanced search)

AND Exclude MEDLINE journals (limits in advanced search).

The results returned from the searches of each of the electronic databases were exported to a single folder in Mendeley. Duplicate references were deleted.

### 2.2. Eligibility and data extraction

According to our predefined protocol, we included laboratory studies in all mammal species and strains, regardless of age and sex, with an untreated control group. The studies should measure sexual behaviour after end of treatment with SSRIs or SNRIs.

Two investigators decided on inclusion of articles and performed data extraction independently; disagreements were resolved by discussion. Potentially eligible studies were read in full. Data were recorded in an Excel sheet.

The primary outcome was sexual dysfunction of any kind. Data from each included study were extracted according to the reporting guidelines for preclinical systematic reviews [27–30]. We extracted information about study design, randomisation and blinding procedures, size of experimental and control groups, interventions, dose, route and timing of drug administration, length of follow-up after discontinuation of drug, timing of assessments, and outcome measures.

We also extracted information about the animals: species, strain, age and developmental stage at treatment start and at final assessment, sex, conditions for experimental and control groups, and number of excluded animals and reasons during the various phases of the trial.

We noted whether there were any statement about conflicts of interest and funding. We contacted the corresponding authors when data were missing, but those few that responded said they didn't had the time to help us or couldn't find the data.

### 2.3. Quantitative data synthesis

We included outcomes for analysis when more than two studies had available data. Many authors did not include data or did not mention the exact number of animals used. When the exact number of animals was not known in relation to the analyses, we used the lowest number for both the treatment and the control group. When the outcome was measured at several time points, we used the last measurement. When studies had several treatment groups [20, 31, 32], we split the control group to avoid using the control group animals more than once in our meta-analyses [20, 31].

We performed random effects meta-analyses with Review Manager [33] on risk ratios for binary data. We had also planned to meta-analyse continuous data but their distributions were too skew to allow this. We also skipped our planned subgroup analyses because we had too little data to justify this.

## 3. Results

### 3.1. Result of the searches

In our searches, we identified 154 citations; 145 in PubMed and 9 additional ones in Embase. We excluded 140 for various reasons: not an SSRI or SNRI, no follow-up period without drug, not an animal study, not measuring sexual behaviour. We excluded two more studies; one because it was not based on mammals but on fruit flies (Drosophila melanogaster) and another because the female mice assessed were hormonally primed. We found two additional studies from other sources. This gave us a total of 14 animal studies for our systematic review [17–21, 31, 32, 34–40].

### 3.2. Study characteristics

All 14 studies were published in English from 2006 to 2013. All studies used an SSRI, most commonly fluoxetine or citalopram, and all had a placebo treated control group. In 7 studies, the drug was given subcutaneously [17, 19, 20, 31, 36, 38, 39], in 6 orally [18, 21, 32, 34, 35, 40] and 1 intraperitoneally [37]. The animals were treated in the prenatal period in 3 studies [18, 35, 38], in the neonatal period in 7 studies (between day 1 and 21) [17, 19, 20, 31, 34, 36, 39], in one study in both the prenatal and neonatal period [21], in the adolescent period in 2 studies (between days 33 and 62) [32, 37] and as adults (8 weeks old) in one study [40]. All studies assessed sexual behaviour in adults, which were rodents in all studies: 12 used rats (5 Long-Evans rats, 5 Wistar rats, 2 Sprague Dawley rats) and 2 used mice (1 C57 BL/6N mice and 1 Swiss mice) [18, 19]. The size of experimental and control groups varied from 5 to 22.

### 3.3. Quality assessment

The general quality of the included studies was poor. Only 4 studies reported use of randomisation, but gave no further explanation [34, 37, 38, 40]; which makes allocation concealment unclear in all studies. All studies used placebo control groups and were therefore blinded; four mentioned explicitly the use of blinded outcome assessment [31, 34, 37, 39]. Nine articles had no conflicts of interest section; in the remaining 5 studies, the authors declared to have no conflict of interest [17, 20, 21, 34, 35]. One study didn't mention funding [38], two studies were funded by pharmaceutical companies [32, 40] whereas the remaining 11 studies were publicly funded. Ten studies did not mention whether any animals were excluded; in two studies, animals were excluded if they had no sexual activity [19, 21]; one study did not mention the reasons why some animals were excluded [18]; and one study mentioned that no animals were excluded [32].

### 3.4. Quantitative data synthesis

#### 3.4.1. Binary data

All studies with binary data had used rats treated prenatally or neonatally, assessed as adults. They examined the effect of citalopram or fluoxetine at different concentrations [17, 20, 21, 31, 36, 39]. For rats exposed to SSRIs compared with those exposed to placebo, we found a higher risk of no mounting behaviour (RR = 0.73; 95% CI = 0.62–0.86; 5 studies, with 106 rats in the SSRI groups and 54 in the placebo groups), (Fig. 1), no intromission behaviour (RR = 0.74; 95% CI = 0.60–0.92; 4 studies, with 106 versus 53 rats) (Fig. 2), and no ejaculation behaviour (RR = 0.49, 95% CI = 0.24–1.00; 3 studies, with 92 versus 42 rats) (Fig. 3).

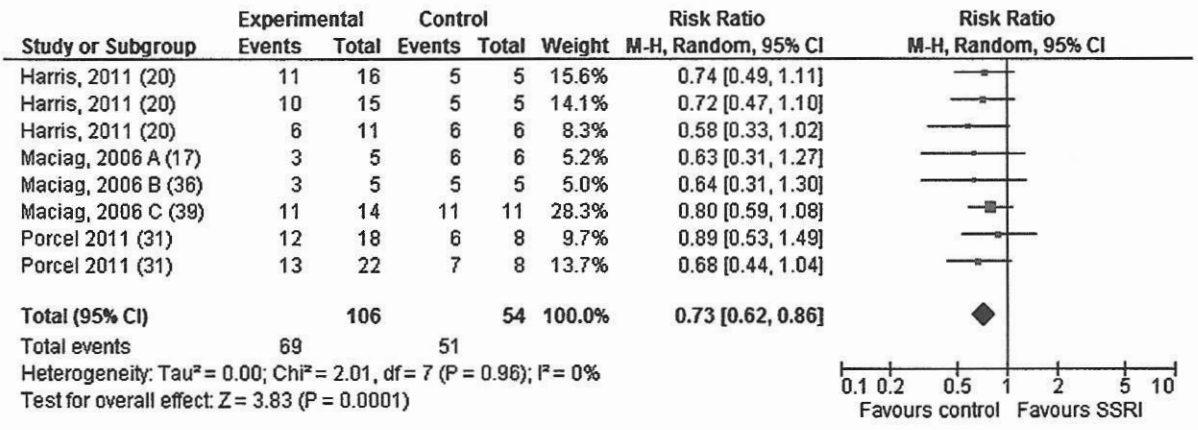


Fig. 1. Number of animals (events) showing mounting behaviour out of the total number of animals. Year indicates the year of publication.

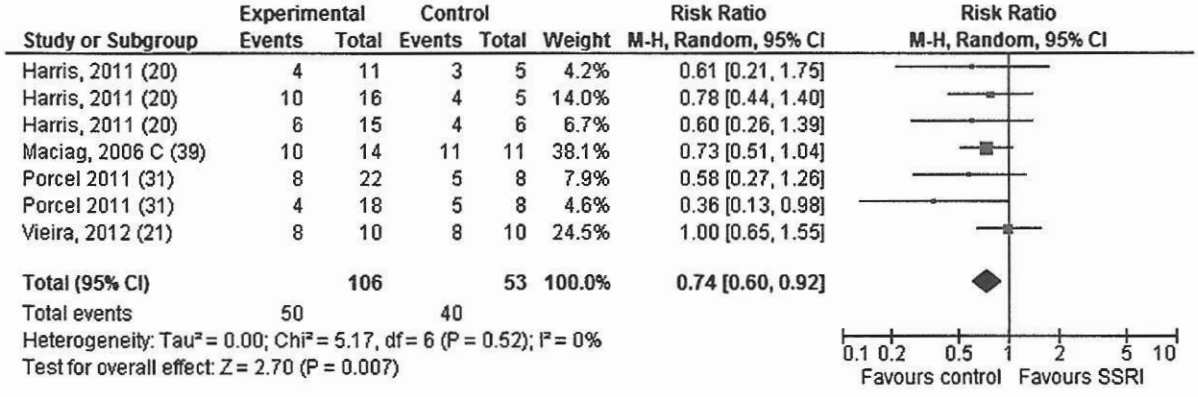


Fig. 2. Number of animals (events) showing intromission behaviour out of a total number of animals. Year indicates the year of publication.

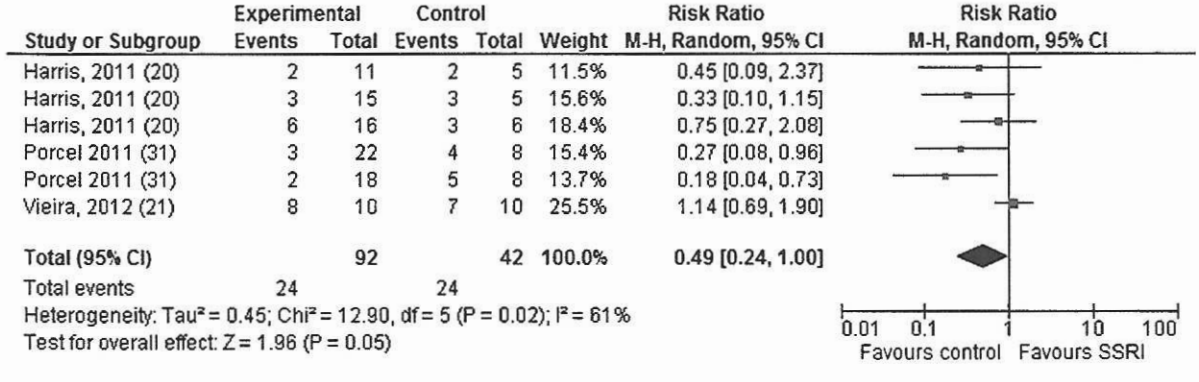


Fig. 3. Number of animals (events) showing ejaculation behaviour out of a total number of animals. Year indicates the year of publication.

### *3.4.2. Continuous data*

The distributions of the data were very skewed and, compared to the means, the standard deviations were far too large to allow us to do meta-analyses. We therefore only show the means in the tables

Table 1
Mean number or rate of mountings at longest follow-up

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 8,1 | 12 | 12 |
| de Jong T, 2006 [32] | PAR/15 mg/kg | 16 | 19 | 7,6 | 16 |
| de Jong T, 2006 [32] | FLUV/30 mg/kg | 16 | 13 | 7,6 | 16 |
| Gouvêa, 2008 [18] | FLX/7,5 mg/kg | 9 | 4,9 | 5,6 | 7 |
| Harris, 2011 [20] | CTM/20 mg/kg | 11 | 9 | 31 | 16 |
| Harris, 2011 [20] | CTM/10 mg/kg | 15 | 9,4 | 31 | 16 |
| Harris, 2011 [20] | CTM/5 mg/kg | 16 | 18 | 31 | 16 |
| Maciag, 2006 B [36] | CTM/5 mg/kg | 5 | 35 | 49 | 5 |
| Maciag, 2006 C [39] | CTM/5 mg/kg | 14 | 24 | 46 | 11 |
| Olivier, 2011 [35] | FLX/12 mg/kg | 9 | 1,2 | 0,92 | 11 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 5,3 | 8,7 | 10 |
| Soga T, 2012 [19] | CTM/10 mg/kg | 15 | 20 | 43 | 15 |

The boxes indicate that the data comes from the same control group. Chan and de Jong were sponsored by a drug company, all other studies in the table were public funded [32, 40].

below. The data rather consistently showed permanent impairment of sexual function in terms of number of or average rates of mounting, intromission and ejaculation (Tables 1–3) and time to first mounting, intromission and ejaculation (Tables 4–6). Trials sponsored by the drug industry tended to show markedly different results than other trials, in some cases reporting an improvement in sexual function while other trials showed an impairment.

For the number of or average rates of intromission and ejaculations, one study, which did not find significant differences, provided no data [35]. For time to first mounting, one study found a significant increased latency when comparing citalopram 20 mg/kg to control, but not for 10 and 5 mg/kg, but provided no data [20]. For time to intromission, two studies found no significant difference but provided no data [17, 20]; and for time to ejaculation, one study provided no data [20].

## 4. Discussion

### *4.1. Study strengths and limitations*

It was a strength that the included studies were similar in many ways; all used rodents, most animals were treated in the prenatal or neonatal period and were assessed as adults, most studies assessed the effect of citalopram or fluoxetine, and all of them studied SSRIs. Compared to studies in humans, the risk of introducing bias after the randomisation is lower, i.e. there are usually no potentially distorting factors such as concomitant medication, concurrent illnesses, or differential exposure to environmental factors due to the effects of the experimental drug [41]. It was a strength that all studies were placebo controlled, which suggests that outcome assessment was blinded, as there would otherwise be no good reason to blind the treatments. Another strength was that only two studies were funded by pharmaceutical companies (these reported more positive results for the drugs than other studies).

Table 2
Mean number or frequency of intromissions at longest follow-up

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 4,9 | 4,4 | 12 |
| de Jong T, 2006 [32] | PAR/15 mg/kg | 16 | 10 | 8 | 16 |
| de Jong T, 2006 [32] | FLUV/30 mg/kg | 16 | 8,5 | 8 | 16 |
| Gouvêa, 2008 [18] | FLX/7,5 mg/kg | 9 | 27 | 33 | 7 |
| Harris, 2011 [20] | CTM/20 mg/kg | 11 | 2,9 | 7,7 | 16 |
| Harris, 2011 [20] | CTM/10 mg/kg | 15 | 3,2 | 7,7 | 16 |
| Harris, 2011 [20] | CTM/5 mg/kg | 16 | 5,8 | 7,7 | 16 |
| Maciag, 2006 A [17] | CTM/5 mg/kg | 5 | 3 | 40 | 6 |
| Maciag, 2006 B [36] | CTM/5 mg/kg | 5 | 2 | 40 | 5 |
| Maciag, 2006 C [39] | CTM/5 mg/kg | 14 | 22 | 42 | 11 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 11 | 43 | 10 |
| Soga T, 2012 [19] | CTM/10 mg/kg | 16 | 0,88 | 1,2 | 15 |
| Vieira, 2012 [21] | FLX/7,5 mg/kg | 10 | 19 | 19 | 10 |

The boxes indicate that the data comes from the same control group, compared to different treatments or different concentrations of the same treatment. Chan and de Jong were sponsored by drug companies, all other studies in the table were public funded [32, 40].

Table 3
Mean number or frequency of ejaculations at longest follow-up

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 2,3 | 2 | 12 |
| de Jong T, 2006 [32] | PAR/15 mg/kg | 16 | 2 | 3 | 16 |
| de Jong T, 2006 [32] | FLUV/30 mg/kg | 16 | 2 | 3 | 16 |
| Harris, 2011 [20] | CTM/20 mg/kg | 11 | 0,39 | 0,84 | 16 |
| Harris, 2011 [20] | CTM/10 mg/kg | 15 | 0,19 | 0,84 | 16 |
| Harris, 2011 [20] | CTM/5 mg/kg | 16 | 0,97 | 0,84 | 16 |
| Iñiguez, 2010 [37] | FLX/ 10mg/kg | 10 | 1 | 3,6 | 10 |
| Maciag, 2006 A [17] | CTM/5 mg/kg | 5 | 0 | 3,6 | 6 |
| Maciag, 2006 B [36] | CTM/5 mg/kg | 5 | 0,13 | 3 | 5 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 0,43 | 2 | 10 |
| Vieira, 2012 [21] | FLX/7,5 mg/kg | 10 | 1,8 | 1,9 | 10 |

The boxes indicate that the data comes from the same control group, compared to different treatments or different concentrations of the same treatment. Chan and de Jong were sponsored by drug companies, all other studies in the table were public funded [32, 40].

Table 4

Mean time to first mounting at longest follow-up. Data in the table are given in seconds. Chan were sponsored by drug companies, all other studies in the table were public funded [40]

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 35 | 19 | 12 |
| Gouvêa, 2008 [18] | FLX/7,5 mg/kg | 9 | 380 | 282 | 7 |
| Iñiguez, 2010 [37] | FLX/ 10mg/kg | 10 | 1790 | 158 | 10 |
| Maciag, 2006 B [36] | CTM/5 mg/kg | 5 | 1532 | 40 | 5 |
| Maciag, 2006 C [39] | CTM/5 mg/kg | 14 | 1053 | 179 | 11 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 1607 | 1131 | 10 |
| Soga T, 2012 [19] | CTM/10 mg/kg | 16 | 230 | 218 | 15 |

Table 5

Mean latency to first intromission at longest follow-up. Data in the table are given in seconds. Chan were sponsored by drug companies, all other studies in the table were public funded [40]

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 229 | 39 | 12 |
| Gouvêa, 2008 [18] | FLX/7,5 mg/kg | 9 | 454 | 421 | 7 |
| Maciag, 2006 C [39] | CTM/5 mg/kg | 14 | 1373 | 273 | 11 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 2286 | 1071 | 10 |
| Soga T, 2012 [19] | CTM/10 mg/kg | 16 | 841 | 490 | 15 |
| Vieira, 2012 [21] | FLX/7,5 mg/kg | 10 | 154 | 243 | 10 |

Table 6

Mean latency to first ejaculation at longest follow-up

| | | Experimental | | Control | |
|---|---|---|---|---|---|
| Study | Treatment/conc. | Total | Mean | Mean | Total |
| Chan, 2009 [40] | PAR/10 mg/kg | 12 | 633 | 661 | 12 |
| de Jong T, 2006 [32] | PAR/15 mg/kg | 16 | 4 | 3 | 16 |
| de Jong T, 2006 [32] | FLUV/30 mg/kg | 16 | 6 | 3 | 16 |
| Iñiguez, 2010 [37] | FLX/ 10mg/kg | 10 | 4308 | 1385 | 10 |
| Olivier, 2011 [35] | FLX/12 mg/kg | 9 | 325 | 275 | 11 |
| Rayen I, 2013 [34] | FLX/5 mg/kg | 10 | 3333 | 2381 | 10 |
| Soga T, 2012 [19] | CTM/10 mg/kg | 16 | 32 | 45 | 15 |
| Vieira, 2012 [21] | FLX/7,5 mg/kg | 10 | 772 | 911 | 10 |

The boxes indicate that the data comes from the same control group, compared to different treatments or different concentrations of the same treatment. Data in the table are given in seconds. Chan and de Jong were sponsored by drug companies, all other studies in the table were public funded [32, 40].

There are several limitations in our study. The sample sizes were small and only four of the 14 studies were described as randomised. We would have liked to search for unpublished studies, but it was not clear to us how this could be done for animal studies.

### *4.2. Interpretation*

Our results showed substantial and lasting effects on sexual behaviour in rats after exposure to an SSRI early in life on important outcomes: mounting, intromission and ejaculation behaviours. These findings provide support to the many reports about sexual dysfunction in humans that persist long after the patients came off their SSRI. Taken together, the research suggests that SSRIs can cause permanent impairment of sexual function. This problem is likely much underestimated, both because patients and clinicians will likely not know that it can happen, and because both parties may feel uncomfortable about discussing sexual problems [42]. Another aspect that might contribute to underreporting is the adverse effects of SSRIs, which include emotional indifference and withdrawal from former important relationships and activities [9].

During our work on this study, we found three placebo controlled randomised trials of SSRIs as a treatment for premature ejaculation in humans that included a post treatment follow-up. Safarinejad and Hosseini compared 29 patients on citalopram with 29 patients on placebo, and Safarienjad alone made a similar study, with 138 patients receiving escitalopram and 138 receiving placebo, all, non-depressed, psychologically and physically healthy men with premature ejaculation as their only sexual complaint. The studies demonstrated significantly delayed ejaculation, which persisted after the end of treatment at three and six months follow-up [43, 44]. A third study by Arafa and Shamloul, compared 77 men with no physical or psychiatric illness but with premature ejaculation receiving sertraline with 70 men receiving placebo and found that 43% had persistent benefit six months after cessation of treatment [45]. These lasting effects can be either due to SSRI induced permanent brain impairment or they might be due to a more permanent psychological benefit from more successful intercourses. Whether these trials are fully reliable should be considered, however. For example, the trial that had Safarinejad as the only author reported three cases of erectile dysfunction in the placebo group of 138 patients and none in the treatment group of the same size [44], which is surprising since SSRIs can cause erectile dysfunction [6]. Unfortunately, none of these trials assessed or reported on other outcomes related to sexual dysfunction.

### *4.3. Implications*

Our results suggest that patients should be informed before they are being prescribed SSRIs, that these drugs may cause long-lasting or perhaps even permanent harm on sexual function that persists after the patients have come off the drugs. Our results also provide support to reports about other permanent harms caused by SSRIs, e.g. tardive dysphoria [46], tardive dyskinesia and tardive dystonia [47–49]. These harms lower the quality of life and should be taken into consideration when prescribing these drugs and during follow-up of patients in treatment.

## Acknowledgments

We thank Lisbeth W. Børgesen, MSc and PhD, university librarian, information specialist Susie Andersen, and Jesper Mørch, information specialist and expert in reference tools, all at the University of Copenhagen.

## Conflict of interest

Authors have declared they have no financial conflicts of interest.

## Funding

This study was carried out without any specific funding at the Nordic Cochrane Centre.

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