Drug Saf (2013) 36:515–519
DOI 10.1007/s40264-013-0069-z

SHORT COMMUNICATION

Reports of Sexual Disorders Related to Serotonin Reuptake Inhibitors in the French Pharmacovigilance Database: An Example of Underreporting

Thierry Trenque · Géric Maura · Emmanuelle Herlem · Catherine Vallet · Elodie Sole · Pascal Auriche · Moustapha Drame

Published online: 1 June 2013

Abstract
Background Depressive disorders and use of antidepressants are associated with adverse effects on sexual function. In pharmacoepidemiological studies, sexual disorders are reported by more than 50 % of patients taking serotonin reuptake inhibitors (SRIs).
Objective The aim of this study was to determine the reporting rate of sexual disorders in association with SRIs, and to investigate the association between reported cases and the use of SRIs.
Methods All cases of adverse drug reactions (ADRs) involving sexual disorders, spontaneously reported to the French Pharmacovigilance Database from 1 January 1985 to December 2009, were reviewed. Cases of sexual disorders in SRI users were described. We calculated the rate of reported sexual disorders as a percentage of the total ADRs reported for each drug. The association between reported cases and the use of SRIs was assessed using reporting odds ratios (ROR) with 95 % confidence intervals (CIs).
Results A total of 11,863 ADRs in association with SRIs were collected, of which 98 (0.83 %) were spontaneous reports of sexual disorders. Subjects were, on average, 45.0 ± 10.6 years of age and mainly male. Sexual disorders were associated with the use of SRI antidepressants (ROR 4.47; 95 % CI 3.61–5.53), milnacipran (ROR 11.72; 95 % CI 5.79–23.72), fluvoxamine (ROR 6.91; 95 % CI 3.79–12.58), paroxetine (ROR 5.54; 95 % CI 3.92–7.83), venlafaxine (ROR 3.50; 95 % CI 1.93–6.36), fluoxetine (ROR 3.46; 95 % CI 2.26–5.29), citalopram (ROR 2.69; 95 % CI 1.28–5.67) and sertraline (ROR 2.49; 95 % CI 1.03–6.01).
Conclusion It is likely that there are instances of underreporting, particularly for ADRs that are embarrassing to talk about spontaneously. Despite the likely underreporting of this well-described adverse effect, this case/non-case study performed in a large national pharmacovigilance database confirms the existence of the risk of sexual disorders associated with SRIs, and is an example of the lack of sensitivity of spontaneous notification to measure ADRs. Minimization of antidepressant-induced sexual dysfunction could be an important factor to avoid unsuccessful treatment. Physicians should advise their patients on the possible sexual adverse effects.

T. Trenque (✉) · G. Maura · E. Herlem · C. Vallet · E. Sole
Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Reims University Teaching Hospitals, Avenue du General Koenig, 51092 Reims, France
e-mail: ttrenque@chu-reims.fr

T. Trenque · M. Drame
Faculty of Medicine, University of Reims Champagne-Ardenne, EA3797 Reims, France

P. Auriche
Pharmacovigilance Department, ANSM, Saint-Denis, France

M. Drame
Department of Research and Innovation, Reims University Hospitals, Reims, France

1 Background

Sexual dysfunction may be a symptom of major depression in both men and women. Montgomery et al. [1] showed that the rate of sexual dysfunction was higher in patients treated with antidepressants than in untreated depressed patients, and that both these groups had a higher prevalence of sexual dysfunction than the control group. Effective treatment of depression can restore normal sexual desire;

however, given the high prevalence of sexual dysfunction among patients with depressive disorders, it may be difficult to evaluate adverse drug reactions (ADRs) related to antidepressant therapy. Indeed, many antidepressants have been associated with sexual dysfunction, in particular tricyclic antidepressants [2].

Serotonin reuptake inhibitors (SRIs) enhance serotonin activity by inhibiting central nervous system neuron serotonin reuptake, and they also interact with other neurotransmitters, such as dopamine and norepinephrine. Sexual disorders are frequently observed in patients treated with SRIs, and manifest mainly as decreased libido and anorgasmia in women, and erectile dysfunction in men [3]. Sexual disorders associated with SRIs are reportedly more frequent in men than in women [3].

In pharmacovigilance, the phenomenon of underreporting is well known [4–6], but reporting rates depend, amongst other things, on the frequency with which ADRs occur. Given the high rate of sexual disorders reported in association with SRI therapy in clinical trials, a high reporting rate of the same ADRs would not be unexpected in a database of spontaneous reports.

Thus, the aim of this study was to determine the reporting rate of sexual disorders in association with SRIs, and to investigate the association between exposure to SRIs and sexual disorders, using data from the French National Pharmacovigilance Database.

2 Methods

This study used data from the French National Pharmacovigilance Database, of all ADRs spontaneously reported for commercially approved drugs in France.

The database was established in 1985 to register all ADRs spontaneously reported by healthcare professionals to the French Pharmacovigilance System, but not those reported to manufacturers. The national database comprises data from 31 regional pharmacovigilance centres. Reports are reviewed by medically qualified personnel in the regional centres before being entered into the national database.

ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, version 12.1[1]) [7].

The seriousness of the reaction is also recorded in the pharmacovigilance database: ADRs are considered serious when they result in death, are life threatening, require in-patient hospitalization or prolongation of existing hospitalization, or any reaction that results in persistent or significant disability or incapacity, congenital anomaly or birth defect.

Observations reported from 1 January 1985 to 31 December 2009 were reviewed using the following MedDRA® high-level terms (HLT) 'orgasmic disorders and disturbances', 'sexual dysfunction and fertility disorders', 'sexual desire disorders' and 'erection and ejaculation conditions and disorders'.

We calculated the rate of reported sexual disorders as a percentage of the total ADRs reported for each drug. The case/non-case method was used to measure disproportionality of the combination between a drug and a particular ADR in the pharmacovigilance database [8], and the reporting odds ratio (ROR) was calculated. Exposed cases were defined as reports of sexual disorders occurring in association with any one or more of the SRIs currently marketed in France, namely fluoxetine, duloxetine, paroxetine, escitalopram, citalopram, venlafaxine, fluvoxamine, sertraline and milnacipran. Non-cases were considered as all other reported ADRs occurring in association with any SRI. All cases were assessed from the computerized data and reviewed by two pharmacovigilance specialists (TT, EH).

For each sexual ADR reported, we studied the patient's characteristics (age, sex and underlying disease) and the characteristics of the ADR (clinical symptoms, seriousness, mean onset delay, evolution). The data in the French Pharmacovigilance Database are anonymous.

The ROR is the ratio of reporting of one specific event versus all other events for a given drug compound [9]. The 95 % confidence intervals (CIs) were calculated using the Woolf method [10]. A p-value <0.05 was considered statistically significant. All analyses were performed using SAS software version 9.1 (SAS System, SAS Institute Inc., Cary, NC, USA).

3 Results

Up to 31 December 2009, a total of 369,778 ADR reports had been recorded in the French National Pharmacovigilance Database, among which 11,863 mentioned SRIs as the suspected medication. Overall, there were a total of 764 cases of reported sexual disorders, of which 98 concerned SRIs, corresponding to a total of 109 sexual adverse effects. No serious sexual ADRs were reported. The adverse effects were all low-level terms ejaculation failure ($n = 48$), impotence ($n = 22$), anorgasmia ($n = 17$), erectile dysfunction ($n = 7$), delayed ejaculation ($n = 6$), decreased libido ($n = 6$) and libido disorders ($n = 3$). The characteristics of the patients presenting with sexual disorders in association with SRIs are presented in Table 1.

[1] MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH).

The average age of patients reporting sexual disorders was 45.0 ± 10.6 years, with a female to male sex ratio of 0.2. The average time to occurrence of symptoms was 1.82 ± 3.8 months. Overall, we noted an increased risk of sexual disorders in association with SRI therapy (ROR 4.47; 95 % CI 3.61–5.53). With SRIs, reporting rates of sexual disorders were higher than the other drugs, except for duloxetine and escitalopram.

No cases of anorgasmia were reported with duloxetine, escitalopram or milnacipran, and no cases of decreased libido were reported with escitalopram, duloxetine, milnacipran or fluvoxamine.

The event was considered resolved in 56 patients, with symptoms disappearing in 40 of these patients after the interruption of treatment. At the time of writing this report, 27/98 patients had not yet recovered.

In 50 patients (51 %), the SRI was the only drug cited as the potential cause of the ADR. Among the remaining 48 patients, frequently associated drugs were benzodiazepines [e.g. alprazolam, bromazepam, prazepam and clorazepate] (17 patients) and antiepileptic drugs (6 patients) or antipsychotic drugs (6 patients).

4 Discussion

France has the highest level of antidepressant consumption in the world [11], thus making it possible to collect a considerable number of reports of sexual disorders relating to the use of these medications. Our study confirms that there is an increased risk of sexual disorders during treatment with SRIs. Although in our study no sexual ADR was reported with duloxetine and escitalopram, all other SRIs were found to be significantly associated with sexual disorders. Proportionally, sexual ADRs were more frequently reported with milnacipran, fluvoxamine and paroxetine than with the other SRIs. The fact that no ADRs were reported with duloxetine and escitalopram may be partially explained by the fact they had not been on the market for very long (escitalopram was first made available on the market in France in May 2005, and duloxetine in January 2009). However, overall, sexual disorders represented less than 1 % of all ADRs reported to occur in association with SRI therapy.

Classically, global spontaneous reporting levels of ADRs are estimated to represent no more than 5–10 % of the real incidence [12, 13]. Regardless of the methodology used (surveys, scales of measure, pharmacoepidemiological studies), the rate of sexual disorders reported to occur in association with SRIs varies widely from 25 % to over 80 % [2, 14–19]. Several such studies have used a self-administered questionnaire to collect data on ADRs occurring during treatment. In one Internet study that included 1187 patients, Kikuchi et al. [19] showed that sexual disorders in association with SRI therapy represented the ADR for which underreporting was greatest, particularly among women. In another study of 401 patients treated with SRIs, Hu et al. [20] described the results of a telephone interview with patients taking SRIs, and 83 % of patients reported that they were still experiencing sexual disorders related to their treatment at the time of interview. In two studies evaluating sexual disorders in association with SRI therapy, Montejo-Gonzales et al. [21] and Landen et al. [22] both observed higher

Table 1 Spontaneous reports of sexual disorders among patients taking serotonin reuptake inhibitors in the French National Pharmacovigilance Database (FPVD) from 1 January 1985 to December 2009

Drug	ADRs in FPVD (no. of patients)	Sexual disorders (total patients [no. of M])	% of all ADRs	Patient characteristics			ROR	95 % CI[a]
				F to M ratio	Onset delay (mean ± SD [months])	Age (mean ± SD [years])		
Citalopram	1,271	7 [6]	0.55	0.2	2.2 ± 2.4	42.7 ± 11.4	2.69	1.28–5.67
Duloxetine	225	0	0	0	0	–	0	0
Escitalopram	440	0	0	0	0	–	0	0
Fluoxetine	3,161	22 [16]	0.69	0.4	4.2 ± 7.8	43.2 ± 10.0	3.46	2.26–5.29
Fluvoxamine	789	11 [9]	1.39	0.2	0.5 ± 0.0	44.9 ± 12.4	6.91	3.79–12.58
Milnacipran	341	8 M	2.34	0	1.1 ± 2.4	51.1 ± 15.1	11.72	5.79–23.72
Paroxetine	3,113	34 [32]	1.09	0.1	1.0 ± 1.5	45.3 ± 0.6	5.54	3.92–7.83
Sertraline	978	5 [3]	0.51	0.7	0.3 ± 0.1	46.8 ± 6.8	2.49	1.03–6.01
Venlafaxine	1,545	11 [10]	0.71	0.1	1.8 ± 2.3	43.4 ± 7.8	3.50	1.93–6.36
Total	*11,863*	*98 [84]*	*0.83*	*0.2*	*1.8 ± 3.8*	*45.0 ± 10.6*	*4.47*	*3.61–5.53*

ADRs adverse drug reactions, *F* females, *M* males, *ROR* reporting odds ratio, *SD* standard deviation

[a] Woolf's method [10]

patient-reported rates of sexual disorders in response to direct questions (58 % and 41 %, respectively) versus rates notified spontaneously (14 % and 6 %, respectively). However, it is likely that the underreporting is of similar magnitude for all SRI molecules when compared using a spontaneous-reporting database.

Underreporting is a major problem with passive surveillance systems. The degree of underreporting varies according to the ADR, with a particular underreporting problem for conditions such as sexual disorders that are embarrassing to talk about or bring up in a conversation with the physician.

Our epidemiological study based on the French National Pharmacovigilance Database is, to the best of our knowledge, the largest study to date to explore the relation between SRI treatment and the occurrence of sexual disorders. The case/non-case design confirms that there is an increased risk of sexual disorders in association with SRIs despite the underreporting. These findings confirm the conclusions of Van der Heijden et al. [23], who showed that underreporting problems played no role in the assessment of ADRs from spontaneous reporting systems with a case/non-case design. As also stated by Mannesse et al. [24], non-selective under- and overreporting do not have any significant influence on the ROR estimation, since they affect both the numerator and the denominator.

Antidepressant-induced sexual dysfunction is an important issue in the clinical management of depression. However, the problem is highly complex because sexual dysfunction may be independently associated with the depressive illness or with other non-psychiatric aetiologies. In addition, the SRIs are also likely to cause sexual adverse effects. Discontinuation of the offending medication is usually sufficient to eliminate clinical and biological signs. In patients with depression who present with sexual disorders, the sexual dysfunction may not necessarily be linked to the depression, but rather may be an adverse effect of the medical therapy being prescribed for depression. Therefore, the drug prescribed should be taken into account when evaluating the aetiology of sexual disorders in patients with depression. Physicians need to assess sexual function during initial evaluation and throughout treatment. Although depressed patients do care about their sexual function, they may be reluctant, for fear of embarrassment, to report sexual disorders spontaneously to their physicians.

Sexual activity mobilizes a number of neurotransmitters, including dopaminergic, serotoninergic, muscarinic and adrenergic receptors [25]. In different regions of the brain, serotonin (5-HT) regulates different components of sexual behaviour [25]. At least three serotonin receptors have been identified as having a role in ejaculation, namely 5-HT_{1a}, 5-HT_{1b} and 5-HT_{1c} [26]. Classically, drugs that enhance serotonin or block dopamine tend to decrease sexual activity, whereas drugs that increase dopamine or block specific serotonin receptors tend to enhance sexual activity [21]. The mechanisms of SRI-related ADRs are not well understood. The inhibition of serotonin reuptake causes an increase in intrasynaptic serotonin, which in turns leads to stimulation of the 5-HT_{1c} receptor, causing late ejaculation. An alteration in serotonin concentrations or in the sensitivity of serotonin receptors in the central nervous system could be at the origin of ejaculation disorders [25, 27]. It is also postulated that SRIs could cause a reduction in the metabolism of progesterone, with a reduction in 3-alpha, 5-alpha tetrahydroprogesterone [28]. Soga et al. [25] suggested that citalopram-induced inhibition of sexual behaviour involves the modulation of RF-amide-related peptide (RF-amide is a neuropeptide characterized by a common carboxy-terminal arginine [R] and an amidated phenylalanine [F]) through serotonin receptors in the dorsomedial hypothalamus.

In view of the sexual disorders that can occur under treatment with SRIs, their use for the treatment of premature ejaculation has been envisaged [29, 30]. However, these molecules also have other adverse effects on sexual activity that may outweigh the benefits on one particular function, such as premature ejaculation. The importance of sexual function to sexually active patients with depression should be weighed carefully when planning antidepressant therapy.

Some limitations of this study deserve to be mentioned. There are several potential pitfalls inherent to the use of disproportionality of measures in spontaneous reporting databases to estimate risk. For example, selection bias due to spontaneous reporting [31, 32] (such as underreporting and notoriety bias), as well as Weber's effect [33], could have altered our results. Secondly, the incidence of sexual disorders mentioned in the labelling of the different drugs is highly variable because it is based solely on spontaneous notifications or postmarketing studies [34]. This could have influenced our results in that it is known than when a potential adverse effect is mentioned in the drug labelling, it is less likely to be spontaneously reported as an ADR.

5 Conclusion

According to research, sexual ADRs are common in patients taking SRIs, but these effects are grossly underreported by patients. Similarly, despite their prevalence, the frequency of sexual disorders occurring in association with SRI therapy is underestimated by healthcare professionals, and data from spontaneous reporting cannot be relied upon to reflect the true incidence in the population. Patients are reluctant to discuss such problems with their physician, and physicians may be reluctant to report this

type of ADR. These results underline the low sensitivity of spontaneous reporting systems for specific conditions such as sexual disorders.

Conversely, this underreporting does not affect the risk, and our study confirms the existence of an association between SRIs and reported sexual disorders in a national pharmacovigilance database, using a case/non-case design.

Acknowledgments The MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) on behalf of the ICH. The authors would like to thank all 31 regional centres of the French Pharmacovigilance System, and to Fiona Ecarnot for translation and editorial assistance.

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflicts of interest Thierry Trenque, Géric Maura, Emmanuelle Herlem, Catherine Vallet, Elodie Sole, Pascal Auriche and Moustapha Drame have no conflicts of interest to declare that are directly relevant to the content of this study.

References

1. Montgomery SA, Baldwin DS, Riley A. Antidepressant medications: a review of the evidence for drug-induced sexual dysfunction. J Affect Disord. 2002;69(1–3):119–40.
2. Werneke U, Northey S, Bhugra D. Antidepressants and sexual dysfunction. Acta Psychiatr Scand. 2006;114(6):384–97.
3. Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. J Affect Disord. 2006;91(1):27–32.
4. McGettigan P, Golden J, Conroy RM, et al. Reporting of adverse drug reactions by hospital doctors and the response to intervention. Br J Clin Pharmacol. 1997;44(1):98–100.
5. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reactions in a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol. 1996; 42(4):423–9.
6. Ribeiro-Vaz I, Santos C, da Costa-Pereira A, et al. Promoting spontaneous adverse drug reaction reporting in hospitals using a hyperlink to the online reporting form: an ecological study in Portugal. Drug Saf. 2012;35(5):387–94.
7. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20(2):109–17.
8. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483–6.
9. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519–23.
10. Woolf B. On estimating the relationship between blood group and disease. Ann Hum Genet. 1955;19:251–3.
11. Olie JP, Elomari F, Spadone C, et al. Antidepressants consumption in the global population in France. Encephale. 2002;28(5 Pt 1):411–7.
12. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
13. Mittmann N, Knowles SR, Gomez M, et al. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. Drug Saf. 2004;27(7):477–87.
14. Williams VS, Baldwin DS, Hogue SL, et al. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. J Clin Psychiatry. 2006;67(2):204–10.
15. Lee KU, Lee YM, Nam JM, et al. Antidepressant-induced sexual dysfunction among newer antidepressants in a naturalistic setting. Psychiatry Investig. 2010;7(1):55–9.
16. Osvath P, Fekete S, Voros V, et al. Sexual dysfunction among patients treated with antidepressants: a Hungarian retrospective study. Eur Psychiatry. 2003;18(8):412–4.
17. Balon R. SSRI-associated sexual dysfunction. Am J Psychiatry. 2006;163(9):1504–9 quiz 664.
18. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry. 2002;63(4):357–66.
19. Kikuchi T, Uchida H, Suzuki T, et al. Patients' attitudes toward side effects of antidepressants: an Internet survey. Eur Arch Psychiatry Clin Neurosci. 2011;261:103–9.
20. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. J Clin Psychiatry. 2004;65(7):959–65.
21. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther. 1997;23(3):176–94.
22. Landen M, Hogberg P, Thase ME. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. J Clin Psychiatry. 2005;66(1):100–6.
23. Van der Heijden PG, van Puijenbroek EP, van Buuren S, et al. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. Stat Med. 2002;21(14):2027–44.
24. Mannesse CK, van Puijenbroek EP, Jansen PA, et al. Hyponatraemia as an adverse drug reaction of antipsychotic drugs: a case-control study in VigiBase. Drug Saf. 2010;33(7):569–78.
25. Soga T, Wong DW, Clarke IJ, et al. Citalopram (antidepressant) administration causes sexual dysfunction in male mice through RF-amide related peptide in the dorsomedial hypothalamus. Neuropharmacology. 2010;59(1–2):77–85.
26. Hellstrom WJ. Emerging treatments for premature ejaculation: focus on dapoxetine. Neuropsychiatr Dis Treat. 2009;5:37–46.
27. Wolters JP, Hellstrom WJ. Current concepts in ejaculatory dysfunction. Rev Urol. 2006;8(Suppl. 4):S18–25.
28. Frye CA, Rhodes ME. Fluoxetine-induced decrements in sexual responses of female rats and hamsters are reversed by 3alpha,5alpha-THP. J Sex Med. 2010;7:2670–80.
29. Linton KD, Wylie KR. Recent advances in the treatment of premature ejaculation. Drug Des Dev Ther. 2010;4:1–6.
30. Rowland D, McMahon CG, Abdo C, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.
31. Moore N, Hall G, Sturkenboom M, et al. Biases affecting the proportional reporting ratio (PPR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf. 2003;12(4):271–81.
32. Pariente A, Gregoire F, Fourrier-Reglat A, et al. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30(10):891–8.
33. Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, editors. Advances in inflammatory research. New York: Raven Press; 1984. p. 1–7.
34. Patterson WM. Fluoxetine-induced sexual dysfunction. J Clin Psychiatry. 1993;54(2):71.