

Medicines Adverse Reactions Committee

Meeting date	12/09/2019	Agenda item	3.2.2
Title	Serotonin reuptake inhibitors and persistent sexual dysfunction after discontinued treatment		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	Product name	Sponsor	
SSRIs			
Citalopram	Cipramil	Pharmacy Retailing (New Zealand) Limited t/a Healthcare Logistics	
	Citalopram	PSM Healthcare Limited t/a API Consumer Brands	
Escitalopram	Escitalopram Lexapro	Air Flow Products Limited Pharmacy Retailing (New Zealand) Limited t/a Healthcare Logistics	
	Loxalate	Mylan New Zealand Limited	
Fluoxetine	Arrow-Fluoxetine Arrow-Fluoxetine Dispersible Fluoxetine-AFT Prozac 20	Teva Pharma (New Zealand) Limited Teva Pharma (New Zealand) Limited AFT Pharmaceuticals Limited Eli Lilly and Company (New Zealand) Limited	
Paroxetine	Apo-Paroxetine Aropax Loxamine	Apotex New Zealand Limited GlaxoSmithKline (New Zealand) Limited Mylan New Zealand Limited	
Sertraline	Arrow-Sertraline Setrona Zoloft	Teva Pharma (New Zealand) Limited Douglas Pharmaceuticals Limited Pfizer New Zealand Limited	
SNRIs			
Venlafaxine	Arrow-Venlafaxine Efexor-XR Enlafax-XR	Teva Pharma (New Zealand) Limited Pfizer New Zealand Limited Mylan New Zealand Limited	
PHARMAC funding	Products funded by PHARMAC and on the Hospital Medicines List (in bold)		
Previous MARC meetings	None		
International action	EMA PRAC meeting on 13-16 May 2019 – Having considered the available evidence from EudraVigilance, literature, social media and cumulative reviews provided by Marketing Authorisation Holders, product information for SSRIs and SNRIs should be amended to include information on persistent sexual dysfunction after drug withdrawal ¹ .		
<i>Prescriber Update</i>	Sexual dysfunction associated with antidepressants and antipsychotics – March 2015 ² .		
Classification	Prescription medicine		

Usage data	<p>Table 1: The number of people who received a dispensing of Serotonin Reuptake Inhibitors in 2018 (From DataPharm³):</p> <table border="1" data-bbox="406 286 1324 712"> <thead> <tr> <th data-bbox="406 286 635 338">SSRI</th> <th data-bbox="635 286 1324 338">Number of people who received a dispensing in 2018</th> </tr> </thead> <tbody> <tr> <td data-bbox="406 338 635 394">Citalopram</td> <td data-bbox="635 338 1324 394">109,942</td> </tr> <tr> <td data-bbox="406 394 635 450">Escitalopram</td> <td data-bbox="635 394 1324 450">59,128</td> </tr> <tr> <td data-bbox="406 450 635 506">Fluoxetine</td> <td data-bbox="635 450 1324 506">81,706</td> </tr> <tr> <td data-bbox="406 506 635 562">Paroxetine</td> <td data-bbox="635 506 1324 562">31,967</td> </tr> <tr> <td data-bbox="406 562 635 618">Sertraline</td> <td data-bbox="635 562 1324 618">56,337</td> </tr> <tr> <td data-bbox="406 618 635 663">SNRI</td> <td data-bbox="635 618 1324 663"></td> </tr> <tr> <td data-bbox="406 663 635 712">Venlafaxine</td> <td data-bbox="635 663 1324 712">50,987</td> </tr> </tbody> </table>	SSRI	Number of people who received a dispensing in 2018	Citalopram	109,942	Escitalopram	59,128	Fluoxetine	81,706	Paroxetine	31,967	Sertraline	56,337	SNRI		Venlafaxine	50,987
SSRI	Number of people who received a dispensing in 2018																
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Sertraline	56,337																
SNRI																	
Venlafaxine	50,987																
Advice sought	<p>The Committee is asked to advise whether:</p> <ul data-bbox="406 772 1441 1014" style="list-style-type: none"> • there is evidence of persistent sexual dysfunction after discontinued treatment with serotonin reuptake inhibitors • updates to the New Zealand data sheets and consumer medicine information (for citalopram, escitalopram, paroxetine, sertraline and venlafaxine) should be requested • this topic requires further communication other than MARC's remarks in <i>Prescriber Update</i>. 																

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1 PURPOSE

In May 2018, Medsafe received an email from RxISK highlighting a study they had recently published in the International Journal of Risk and Safety in Medicine regarding persistent sexual dysfunction after treatment with antidepressants, 5 α -reductase inhibitors and isotretinoin⁴. A petition was also attached which has been submitted to the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Medicines and Healthcare products Regulatory Agency (MHRA), requesting changes to product information⁵.

The purpose of this paper is to review the risk of persistent sexual dysfunction after discontinued treatment with serotonin reuptake inhibitors (SRIs).

2 BACKGROUND

2.1 RxISK study and petition

The objective of the RxISK study was to investigate clinical reports of post-selective serotonin reuptake inhibitors (SSRI) sexual dysfunction, post-finasteride syndrome and persisting sexual dysfunction following antidepressants, 5 α -reductase inhibitors and isotretinoin⁴.

RxISK.org is an independent drug safety website set up by the authors and colleagues, offering an adverse event reporting facility which began collecting data on all drugs and all adverse events in 2012⁴. Data from RxISK was used to establish the clinical features, demographic details and clinical trajectories of syndromes of persistent sexual difficulties following three superficially different treatment modalities⁴.

The study reported on 300 cases of persisting sexual dysfunction from 37 countries following 14 different drugs comprised of serotonin reuptake inhibiting antidepressants, 5 α -reductase inhibitors and isotretinoin⁴. While reports of certain issues were unique to the antidepressants, such as the onset of premature ejaculation and persistent genital arousal disorder, there was also a significant overlap in symptom profile between the drug groups, with common features including genital anaesthesia, pleasureless or weak orgasm, loss of libido and impotence⁴. Secondary consequences included relationship breakdown and impaired quality of life⁴.

The authors concluded that the data point to a legacy syndrome or syndromes comprising a range of disturbances to sexual function⁴. More detailed studies will require developments in coding systems that recognise the condition(s)⁴. Further exploration of these tardive sexual syndromes may yield greater understanding of tardive syndromes in general⁴.

Following this study, a citizen petition, dated 23 April 2018, was submitted to request the Commissioner of Food and Drugs (in the US) to immediately require the addition of boxed warnings, warnings, precautions, and highlights of prescribing information to the product label for all SSRIs and serotonin and noradrenalin reuptake inhibitors (SNRIs), including branded and generic formulations⁵. The proposed additions are⁵:

1. Add WARNINGS, PRECAUTIONS, and HIGHLIGHTS OF PRESCRIBING INFORMATION to inform that the use of and withdrawal from SSRIs and SNRIs can result in genital anaesthesia, pleasureless or weak orgasm, delayed or absent orgasm, loss of libido, erectile dysfunction, decreased vaginal lubrication, reduced nipple sensitivity, flaccid glans penis during erection, reduced response to sexual stimuli, and decreased capacity to experience sexual pleasure.
2. Add WARNINGS, PRECAUTIONS, and HIGHLIGHTS OF PRESCRIBING INFORMATION to inform that the use of and withdrawal from SSRIs and SNRIs can result in persistent genital arousal disorder.
3. Add WARNINGS, PRECAUTIONS, HIGHLIGHTS OF PRESCRIBING INFORMATION, and BOXED WARNING to inform that sexual side effects can sometimes persist for years or indefinitely after discontinuation of the drug. They can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.
4. Send all manufacturers of SSRIs and SNRIs a notification letter of the need for a Risk Evaluation and Mitigation Strategy Plan.

The citizen petition has been submitted to the FDA, the EMA, and the MHRA, requesting changes to product information⁵.

Comments:

Further information about RxISK can be found on their website: <https://rxisk.org/>

The data from the RxISK study only started in 2012.

Although the RxISK study considered other products (ie, 5 α -reductase inhibitors and isotretinoin), this paper will review SSRIs and SNRIs only for brevity.

2.2 Serotonin reuptake inhibitors

2.2.1 Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are frequently used as first-line antidepressants because of their efficacy, tolerability, and general safety in overdose⁶. The SSRIs currently available in New Zealand are citalopram, escitalopram, fluoxetine, paroxetine and sertraline.

SSRIs inhibit the serotonin reuptake pump and increase postsynaptic serotonin receptor occupancy⁵. This initial action may cause subsequent changes involved in treating depression⁶. SSRIs are selective in that they have relatively little affinity for other types of receptors⁶.

The SSRIs may inhibit hepatic cytochrome P450 enzymes that metabolise other medications and cause drug-drug interactions⁶. Citalopram and escitalopram inhibit liver enzymes less than other SSRIs and are thus the SSRIs of choice for situations in which drug-drug interactions are a concern⁶.

Common SSRI side effects include sexual dysfunction, drowsiness, weight gain, insomnia, anxiety, dizziness, headache, and dry mouth⁶. In addition, observational studies suggest SSRIs may increase the risk of diabetes, abnormal bleeding, and bone loss⁶.

2.2.2 Serotonin and noradrenalin reuptake inhibitors (SNRIs)

The primary indications for SNRIs are depressive disorders (eg, unipolar major depression or persistent depressive disorder (dysthymia)) and anxiety disorders (eg, generalized anxiety disorder, panic disorder, or social anxiety disorder)⁷. The SNRI currently available in New Zealand is venlafaxine.

SNRIs appear to treat depression by initially blocking presynaptic serotonin and norepinephrine transporter proteins⁷. This inhibits reuptake of these neurotransmitters and leads to increased stimulation of postsynaptic receptors⁷. Venlafaxine is a more potent inhibitor of serotonin reuptake than norepinephrine reuptake⁷.

The pharmacokinetic parameters of SNRIs vary⁷. Duloxetine is similar to SSRIs and tricyclics in that it is highly protein bound, clearance is primarily hepatic, and <1 % of the drug is eliminated unchanged in the urine⁷. By contrast, the other SNRIs such as venlafaxine are less protein bound, renal excretion of the drugs plays a larger role in their clearance, more of the drug is excreted unchanged in urine, and dose adjustment is more likely to be required in the presence of renal disease⁷.

Common SNRI side effects include nausea, constipation, dizziness, dry mouth, and sweating⁷. With the exception of duloxetine, the SNRIs can raise blood pressure, which should be monitored⁷. All drugs that inhibit serotonin uptake can cause sexual dysfunction⁷. Chronic use (eg, ≥ 6 months) of SNRIs can lead to substantial weight gain (eg, 5 kg)⁷.

Comments:

All medicines that inhibit serotonin uptake (ie, SSRIs and SNRIs) can cause sexual dysfunctions.

2.3 Persistent sexual dysfunction

Sexual dysfunctions are syndromes that comprise the various ways in which adult people may have difficulty experiencing personally satisfying, non-coercive sexual activities⁸. Sexual response is a complex interaction of psychological, interpersonal, social, cultural and physiological processes and one or more of these factors may affect any stage of the sexual response⁸. In order to be considered a sexual dysfunction, the dysfunction must⁸:

1. occur frequently, although it may be absent on some occasions
2. have been present for at least several months; and
3. be associated with clinically significant distress.

Sexual dysfunctions that occur in women include hypoactive sexual desire dysfunction, female sexual arousal dysfunction, female orgasmic dysfunction, female genital-pelvic pain dysfunction, persistent genital arousal disorder, post-coital syndrome (post-orgasmic illness syndrome), hypohedonic orgasm and painful orgasm⁹.

Sexual dysfunctions that occur in men include male hypoactive sexual desire disorder, erectile dysfunction, premature ejaculation, primary delayed ejaculation, acquired delayed ejaculation, retrograde ejaculation, anejaculation, anhedonic ejaculation, anorgasmia, hypohedonic orgasm, painful ejaculation or orgasm and post-orgasmic illness syndrome⁹.

A literature review conducted in 2015 concluded that there are more studies on incidence and prevalence for men than for women and many more studies on prevalence than incidence for women and men¹⁰. The literature indicates that the most frequent sexual dysfunctions for women are desire and arousal dysfunctions¹⁰. For men, premature ejaculation and erectile dysfunction are the most common sexual dysfunctions, with less comorbidity across sexual dysfunctions for men compared with women¹⁰. The authors concluded that the results of their literature review need to be treated with caution because there is a high level of variability across studies caused by methodologic differences in the instruments used to assess presence of sexual dysfunction, ages of samples, nature of samples, methodology used to gather the data, and cultural differences¹⁰.

Among patients receiving SRIs, the estimated incidence of sexual dysfunction is approximately 50%¹¹.

The prevalence of persistent sexual dysfunction after discontinued treatment with SSRIs is unknown¹².

There is no definitive treatment for persistent sexual dysfunction after discontinued treatment with SSRIs¹². However, there are some proposed management options¹²:

- lowering SSRI dosage (could decrease the sexual side effects but weaken the medicine's initial treatment strategy)
- cognitive-behavioural therapy
- trazodone, donepezil, ketamine, metformin and mirtazapine have been tested as treatments, with varying degrees of success.

Comments:

Persistent sexual dysfunction is not officially recognised and does not seem to be quantified.

Medsafe published a consumer information leaflet regarding medicines for depression or other mental disorders and difficulties with sex (sexual dysfunction) in March 2016¹³. The leaflet does not refer to persistent sexual dysfunction.

2.4 Data sheets

2.4.1 New Zealand

Table 2 below shows the relevant New Zealand data sheet wording, from section 4.8 'undesirable effects', for each SRI.

Table 2: Relevant New Zealand data sheet wording for each SRI

Product name	Section 4.8 wording 'Undesirable effects'	Persistence mentioned?
Selective serotonin reuptake inhibitors (SSRIs)		
Substance		
<i>Citalopram</i>		
Cipramil ¹⁴ Citalopram – PSM ¹⁵	<p>Male and female sexual dysfunction with SSRIs</p> <p>While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with SSRIs may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with the SSRIs may be underestimated. In placebo-controlled clinical trials, the reported incidence of decreased libido for the whole population was 2.5%; ejaculation disorder (primarily ejaculatory delay), and impotence in male-depressed patients receiving citalopram (N = 423) was 5.9%, and 2.8%, respectively. In female-depressed patients receiving citalopram (N = 660), the reported incidence of anorgasmia was 0.5%. The reported incidence of decreased libido was 0.4% among depressed patients receiving placebo, whilst sex specific adverse events were not reported among male-and female-depressed patients receiving placebo.</p> <p>While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.</p> <p>Adverse events reported in clinical trials Psychiatric disorders – Libido decreased Reproductive disorders, male – Ejaculation disorders, Impotence</p> <p>Other events observed during the premarket evaluation Psychiatric disorders – Uncommon: Increased libido</p>	No
<i>Escitalopram</i>		
Escitalopram Air Flow Products ¹⁶ Lexapro ¹⁷ Loxalate ¹⁸	<p>Adverse events reported in clinical trials Psychiatric disorders – Libido decreased Reproductive disorders, female – Anorgasmia Reproductive disorders, male – Ejaculation disorder, Ejaculation failure</p> <p>Other events observed during the premarket evaluation Psychiatric disorders – Uncommon: Loss of libido Reproductive disorders, female – Uncommon: Sexual function abnormality Reproductive disorders, male – Uncommon: Ejaculation delayed</p>	No
<i>Fluoxetine</i>		
Arrow-Fluoxetine and Arrow- Fluoxetine Dispersible ¹⁹	<p>Adverse events reported in clinical trials Nervous system – Common: Libido decreased Urogenital system – Common: Abnormal ejaculation (male only), impotence (male only)</p>	Yes

Product name	Section 4.8 wording 'Undesirable effects'	Persistence mentioned?
	Uncommon: Anorgasmia, Sexual dysfunction (occasionally persisting after treatment discontinuation) Rare: Priapism (male only)	
Fluoxetine-AFT ²⁰	Adverse events reported in clinical trials Urogenital and reproductive system disorders – Common: Delayed or absent ejaculation, Impotence, Decreased libido Uncommon: Anorgasmia, Priapism/prolonged erection, Urination impaired Others: Sexual dysfunction, Enlarged clitoris, Gynaecomastia	No
Prozac 20 ²¹	Adverse events reported in clinical trials Nervous system disorders – Common: Libido decreased Reproductive system and breast disorders – Common: Abnormal ejaculation (male only), Impotence (male only) Uncommon: Anorgasmia, Sexual dysfunction (occasionally persisting after treatment discontinuation) Rare: Priapism (male only)	Yes
<i>Paroxetine</i>		
Apo-Paroxetine ²²	Summary of adverse reactions Reproductive system & breast disorders – Very common: Sexual dysfunction	No
Aropax ²³	Summary of adverse reactions Reproductive system & breast disorders – Very common: Sexual dysfunction	No
Loxamine ²⁴	Summary of adverse reactions Reproductive system & breast disorders – Very common: Sexual dysfunction	No
Paroxetine AFT ²⁵	Adverse events reported in clinical trials The most commonly observed adverse events associated with the use of paroxetine in clinical trials and not seen at an equivalent incidence among placebo treated patients were ... sexual dysfunction Nervous system – Common: Decreased libido Rare: Increased libido Genitourinary – Common: Abnormal ejaculation	No
<i>Sertraline</i>		
Arrow-Sertraline ²⁶	Clinical trial data Reproductive system and breast disorders – Sexual dysfunction (principally ejaculatory delay in males) Post-marketing data Psychiatric disorders - Libido decreased-female, Libido decreased-male Reproductive system and breast disorders – Premature ejaculation	No
Setrona ²⁷	Clinical trial data Psychiatric disorders – Libido decreased Reproductive – Sexual dysfunction (principally ejaculatory delay in males)	No
Zoloft ²⁸	Clinical trial data	No

Product name	Section 4.8 wording 'Undesirable effects'	Persistence mentioned?
	Reproductive system and breast disorders – Common: Ejaculation disorder, Sexual dysfunction Post-marketing experience Psychiatric disorders – Common: Libido decreased (male and female) Unknown: Premature ejaculation	
<i>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</i>		
Substance		
<i>Venlafaxine</i>		
Arrow-Venlafaxine XR ²⁹	Adverse effects Nervous system – Common: Decreased libido Urogenital system – Common: Abnormal ejaculation/orgasm (males), Anorgasmia, Erectile dysfunction Uncommon: Abnormal orgasm (females)	No
Efexor-XR ³⁰	Adverse effects Psychiatric disorders – Common: Libido decreased, Anorgasmia Uncommon: Abnormal orgasm Reproductive system and breast disorders – Common: Erectile dysfunction, Ejaculation disorder	No
Enlafax XR ³¹	Adverse effects Psychiatric disorders – Common: Libido decreased, Anorgasmia Uncommon: Abnormal orgasm Reproductive system and breast disorders – Common: Erectile dysfunction, Ejaculation disorder	No

Comments:

There is some variation in the text but overall the data sheets list sexual dysfunction disorders. However, the persistence of sexual dysfunction after discontinued treatment is not listed as an adverse reaction, with the exception of two fluoxetine data sheets (Arrow-Fluoxetine and Prozac 20).

Some of the data sheets include wording on withdrawal symptoms or adverse effects seen on discontinuation of SRIs. However, sexual dysfunction is not included.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Bala et al (2018)³²

Aim

The aim of the literature review was to provide coverage of the current literature on post-SSRI sexual dysfunction, update information on the pathophysiology of post-SSRI sexual dysfunction and discuss potential management options.

Methods

A literature review was performed on PubMed using the search strings post-SSRI sexual dysfunction and persistent sexual dysfunction SSRI. The authors examined 74 articles and included 33 articles that were relevant to post-SSRI sexual dysfunction.

Articles that evaluated sexual dysfunction by SSRI instead of post-SSRI sexual dysfunction were excluded. Based on reading the included results and examining their references, the authors added peer-reviewed articles on post-SSRI sexual dysfunction to their review.

Main Outcome Measures

The symptoms, classification, pathophysiology, diagnostic considerations, and management of post-SSRI sexual dysfunction were reviewed.

Results

Common post-SSRI sexual dysfunction symptoms include genital anaesthesia, pleasure-less or weak orgasm, decreased sex drive, erectile dysfunction, and premature ejaculation.

Different theories have been proposed to explain the pathophysiology of post-SSRI sexual dysfunction: epigenetic gene expression theory, cytochrome actions, dopamine-serotonin interactions, proopiomelanocortin and melanocortin effects, serotonin neurotoxicity, downregulation of 5-hydroxytryptamine receptor 1A, and hormonal changes in the central and peripheral nervous systems.

The diagnosis of post-SSRI sexual dysfunction is achieved by excluding all other etiologies of sexual dysfunction. Treating post-SSRI sexual dysfunction is challenging, and many strategies have been suggested and tried, including serotonergic antagonists and dopaminergic agonists. There is still no definitive treatment for post-SSRI sexual dysfunction. Low-power laser irradiation and phototherapy have shown some promising results.

Conclusion

Post-SSRI sexual dysfunction is a debilitating condition that adversely affects quality of life. Further studies are warranted to investigate the prevalence, pathophysiology, and treatment of post-SSRI sexual dysfunction.

Comments:

The literature review examined 74 articles but only 32 references were provided. The authors concluded that further research is required.

3.1.2 Coskuner et al (2017)³³

Aim

The aim of the literature review was to summarise the long-lasting effects of SSRIs on sexuality, starting with animal models and continuing with the clinical experience of different investigators.

Method

The literature on sexuality after SSRI exposure was reviewed through a PubMed search for articles published from January 1980 through August 2017 using the following combination of keywords: post-SSRI sexual dysfunction and SSRIs. All articles were screened based on titles and abstracts.

Main Outcome Measures

To assess the long-lasting effects of SSRIs on sexuality.

Results

Although the persistent effects of SSRIs on sexuality have been little studied in humans, animal studies suggest that SSRIs might cause permanent sexual dysfunction after ending SSRI exposure at a young age but not in adulthood in rats. There are no prospective randomized controlled trials in humans and the present evidence is derived from case reports, incidental research findings, and experiences of some internet communities.

Conclusion

There is some preclinical evidence from animal studies for enduring SSRI-induced sexual dysfunction, but the available clinical information could prevent a clear decision about the existence of post-SSRI sexual dysfunction, its pathophysiology and its management. The authors conclude more research is needed to fill in the gaps in their knowledge.

Comments:

The authors note that whilst persistent sexual dysfunction after discontinued treatment with SSRIs seems to be unrecognised by research and professional communities, it is increasingly identified in internet communities. The authors concluded that further research is required.

This literature review did not specifically state the number of articles reviewed. However, it provides evidence from animal studies.

3.1.3 Reisman (2017)³⁴

Aim

To examine the existence of post-SSRI sexual dysfunction, possible theoretical mechanisms, possible risk factors and possible treatment modalities.

Methods

Literature research and clinical experience.

Main outcome measures

Summary of the current literature with insights into possible causes and management options.

Results

Table 3 below displays the characteristics of post-SSRI sexual dysfunction cases reported in the literature.

Table 3: Characteristics of post-SSRI sexual dysfunction cases reported in the literature

Study	Year of publication	Cases, n	Sex	Age (y), mean ± SD or median (range)	Symptoms	SSRI treatment duration (mo)	PSSD duration (mo)
Bolton et al ¹⁹	2006	1	M	26	LL, OD, GA	5	72
Csoka and Shipko ²⁰	2006	3	2 M, 1 F	27 ± 3	LL, GA, ED	1–24	NR
Kauffman and Murdock ²¹	2007	1	F	32	GA, OD	1	14
Csoka et al ²²	2008	3	M	33.6 ± 9	ED, LL, GA, An	4–24	NR
Lareb Quarterly Report ²³	2012	19	13 M, 6 F	30 (20–59)	LL, OD, ED	<1–120	2–24
Stinson ²⁴	2013	9	4 M, 5 F	34.8 ± 12.3	LL, OD, GA, An	7–168	2–48
Hogan et al ²⁵	2014	90	75 M, 15 F	30.9 (15–65)	LL, ED, OD, GA	<1–120	≤18 y
Waldinger et al ²⁶	2015	1	M	NR	OD, ED, GA	30	24
Ben-Sheetrit et al ²⁷	2015	23	19 M, 4 F	32.9 ± 11.4	GA, OD	18 ± 21	1–120

An = anhedonia; ED = erectile dysfunction; F = female; GA = genital anesthesia; LL = libido loss; M = male; NR = not reported; OD = orgasmic disorder; PSSD = post-SSRI sexual dysfunction; SSRI = selective serotonin reuptake inhibitor.

The authors conclude there are some indications that antidepressant-emergent sexual dysfunctions do not always resolve after discontinuation of the medication and can persist indefinitely in some individuals. Although some or all sexual side effects that start with the use of SSRIs might continue after stopping the medication, other sexual complaints can develop. Decreased capacity to experience sexual pleasure is the most frequent characteristic of post-SSRI sexual dysfunction.

Conclusion

The research and understanding of post-SSRI sexual dysfunction remain limited and not well understood. However, the data support the existence of post-SSRI sexual dysfunction, which can have a substantial effect

on the quality of life in patients. More research is warranted to show the cause and possible mechanism of post-SSRI sexual dysfunction that could lead to the correct diagnosis and treatment.

Comments:

Another literature review with the same conclusion. There is some evidence of persistent sexual dysfunction after discontinued treatment. However, the authors concluded that more research is required.

Table 2 provides a good summary of the cases reported in the literature between 2006 and 2015. In one case, the duration of post-SSRI sexual dysfunction extended to 18 years.

3.2 International

[REDACTED]

[Redacted text block]

[REDACTED]

SNRIs/SSRIs – Persistent sexual dysfunction after drug withdrawal

Having considered the available evidence from EudraVigilance, literature, social media and cumulative reviews provided by Marketing Authorisation Holders for duloxetine, fluoxetine (Eli Lilly), citalopram, vortioxetine, escitalopram (Lundbeck), fluvoxamine (Mylan), sertraline, desvenlafaxine (Pfizer), paroxetine (GSK), venlafaxine (Almirall), milnacipram (Pierre Fabre) and clomipramine (Alfasigma) the PRAC has agreed that all Marketing Authorisation Holders of products containing citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline (SSRIs) and all Marketing Authorisation Holders of products containing duloxetine, venlafaxine, desvenlafaxine, milnacipram (SNRIs) should submit a variation within 2 months to amend the product information as described below (new text underlined):

Summary of product characteristics (ie, New Zealand data sheet)

4.4. Special warnings and precautions for use

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Package leaflet (ie, New Zealand consumer medicine information)

2. What you need to know before you take [Invented name]

Warnings and precautions

Medicines like [Invented name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have continued after stopping treatment.

Comments:

The citizen petition was targeted at the FDA, EMA and MHRA. The FDA has started their review. The EMA has concluded their review with recommended amendments to the product information. As indicated in section 3.2.4, the MHRA will follow the recommendations from the EMA's PRAC.

3.4 Company reports

[Redacted content]

[REDACTED]

Table 6: CARM reports of sexual dysfunction that appeared to persist after discontinued treatment with a SRI

Report #	Date of Report	Gender	Age	Medicine(s)			Reactions
058800	01/2004	Male	40	Citalopram			Priapism
098574	11/2011	Male	47	Citalopram			Penis disorder
034596	06/1997	Male	UNK	Fluoxetine			Ejaculation premature
042761	09/1999	Male	49	Fluoxetine			Ejaculation disorder Dysuria Hypoaesthesia Weight increase Libido decreased
046380	12/2000	Female	57	Fluoxetine Celiprolol Acetylsalicylic acid Bendrofluazide			Rash Brand switch Tremor Emotional lability Sexual function abnormal
091279	08/2010	Female	81	Fluoxetine			Orgasm abnormal
129865	09/2018	Male	40	Venlafaxine			Libido decreased Suicidal ideation Lethargy Therapeutic response decreased Brand switch
130193	09/2018	Male	56	Venlafaxine			Micturition frequency Libido decreased
130300	10/2018	Male	44	Venlafaxine			Mood swings Headache Brand switch Arthralgia Libido decreased
130458	10/2018	Female	42	Venlafaxine Nortriptyline			Night sweats Memory loss Fuzzy head Thinking abnormal Libido decreased
130472	10/2018	Male	51	Venlafaxine Valproate sodium Quetiapine Nadolol			Therapeutic response decreased Lethargy Fuzzy head Appetite decreased Libido decreased



3.6 ADIS Insight³⁵



[REDACTED]

4 DISCUSSION AND CONCLUSIONS

In May 2018, Medsafe received an email from RxISK with a study they had recently published in the International Journal of Risk and Safety in Medicine regarding persistent sexual dysfunction after treatment with antidepressants, 5 α -reductase inhibitors and isotretinoin⁴. A petition was also attached which has been submitted to the FDA, EMA, and the MHRA, requesting changes to product information⁵.

Although the RxISK study considered other products (ie, 5 α -reductase inhibitors and isotretinoin), this paper reviewed SRIs for brevity. The SSRIs currently available in New Zealand are citalopram, escitalopram, fluoxetine, paroxetine and sertraline. The SNRI currently available in New Zealand is venlafaxine.

All medicines that inhibit serotonin uptake (ie, SSRIs and SNRIs) can cause sexual dysfunctions. However, persistent sexual dysfunction is not officially recognised and does not seem to be quantified.

There is some variation in the text but overall the New Zealand data sheets list sexual dysfunction disorders. The persistence of sexual dysfunction after discontinued treatment is not listed as an adverse reaction, with the exception of two fluoxetine data sheets (Arrow-Fluoxetine and Prozac 20). Some of the data sheets include wording on withdrawal symptoms or adverse effects seen on discontinuation of SRIs. However, sexual dysfunction is not included.

Recent literature reviews conclude that there is some evidence of persistent sexual dysfunction after discontinued treatment. However, more research is required. There are also a number of case reports in the literature. Whilst case reports are hypothesis generating and useful in certain fields such as pharmacovigilance, they can't be generalised and cause and effect cannot be established. There is also confounding by indication.

In June 2019, the EMA recommended updates to the product information as described below (new text underlined):

Summary of product characteristics (ie, New Zealand data sheet)

4.4. Special warnings and precautions for use

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Package leaflet (ie, New Zealand Consumer Medicine Information)

2. What you need to know before you take [Invented name]

Warnings and precautions

Medicines like [Invented name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have continued after stopping treatment.

The EMA recommended these updates to all products containing citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline (SSRIs) and all products containing duloxetine, venlafaxine, desvenlafaxine, milnacipram (SNRIs).



Whilst there is only limited evidence of persistent sexual dysfunction after treatment with SRIs, the Committee is asked whether updates to the New Zealand data sheets and consumer medicine information are warranted at this time for those products where updates have not already been provided.

5 ADVICE SOUGHT

The Committee is asked to advise whether:

- there is evidence of persistent sexual dysfunction after discontinued treatment with SRIs
- updates to the New Zealand data sheets and consumer medicine information (for citalopram, escitalopram, paroxetine, sertraline and venlafaxine) should be requested
- this topic requires further communication other than MARC's remarks in *Prescriber Update*.

6 ANNEXES

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