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Pharmacovigilance and Epidemiology Department

Serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors and other antidepressants and persistent sexual dysfunction

EudraVigilance analysis

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Abbreviations

EV	EudraVigilance
HLGT	High-level group term
HLT	High-level term
MedDRA	Medical Dictionary for Regulatory Activities
NEC	Not elsewhere classified
PT	Preferred term
PSSD	Post-SSRI/SNRI sexual dysfunction
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitor

1. Roles and responsibilities

Role	Responsible
Lead investigator	Luis Pinheiro
Investigator	Julie Durand, Izabela Skibicka-Stepien
Procedure/topic lead	Izabela Skibicka-Stepien
Data extraction	Luis Pinheiro, Gianmario Candore
Data validation	Julie Durand
Peer review	Jim Slattery, Alexandra Pacurariu, Daniel Zondag
Sign-off	Peter Arlett

2. Milestones

Milestone	Planned	Actual
Data analysis plan	4 December 2018	7 December 2018
Internal report	30 January 2019	21 February 2019
Peer-review	6 February 2019	22 February 2019
Implementation of corrections	11 February 2019	26 February 2019
Submission	13 February 2019	26 February 2019

3. Objectives

The objectives of the EudraVigilance analysis are:

- To describe the case reports of sexual dysfunctions to selected antidepressants;
- To identify, assess and characterise case reports of persistent sexual dysfunctions to selected antidepressants;
- To describe the duration between suspension of antidepressants and resolution of the sexual dysfunctions reported to selected antidepressants.

4. Methodology

4.1. Database

The database used was EudraVigilance. The period of interest is from start of data collection (i.e. 1995) to 31 December 2018.

4.2. Exposure

The exposure was defined in accordance with the scope of the signal procedure and thus includes the following substances: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (desvenlafaxine, duloxetine, milnacipran, venlafaxine), clomipramine and vortioxetine.

See Annex I for additional details.

4.3. Outcomes

4.3.1. Primary outcome

4.3.1.1. Sexual dysfunctions

Sexual dysfunctions are defined as all MedDRA PTs under the HLTs Orgasmic disorders and disturbances, Paraphilias and paraphilic disorders, Sexual and gender identity disorders NEC, Sexual arousal disorders, Sexual desire disorders, Erection and ejaculation conditions and disorders and Sexual function and fertility disorders NEC.

4.3.1.2. Post-SSRI sexual dysfunction

This study is specifically addressed to post-SSRI sexual dysfunctions. There is scarce literature on the case definition of post-SSRI sexual dysfunction. Available literature[1,2] clarifies that PSSD, while nominally referring to SSRIs, applies to antidepressants in general. PSSD is, thus, a misnomer and better defined as post-antidepressant sexual dysfunctions.

PSSD is classified as sexual dysfunction disorders, which manifest days or weeks after beginning antidepressants and persist after discontinuation. The sexual dysfunction disorders that make up PSSD in the literature seem to be selected based on frequency of occurrence.

These signs and symptoms are: genital hypoaesthesia, loss of libido, libido decreased, female sexual arousal disorder, anorgasmia, female orgasmic disorder, male orgasmic disorder, orgasm abnormal, orgasmic sensation decreased, premature ejaculation, ejaculation delayed, ejaculation failure, vulvovaginal dryness, nipple hypoaesthesia , nipple hypoesthesia .

4.3.1.3. Persistent sexual dysfunctions

As seen above, formally, PSSD can be considered a subset of sexual dysfunctions (4.3.1.1.), which persist for an undefined period after suspension of the offending antidepressant, i.e. "persisting after discontinuation" has no minimum time-duration threshold.

For comparison and reproducibility, this study defines a disorder as *persistent* if after discontinuation of the antidepressant a reaction persists beyond the following thresholds, which are based on the half-life of the antidepressants:

- Fluoxetine – 40 days or longer;
- All other antidepressants – 30 days or longer.

[1] Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI Sexual Dysfunction: A Literature Review. Sex Med Rev. 2018 Jan;6(1):29-34. doi: 10.1016/j.sxmr.2017.07.002. Epub 2017 Aug 1. Review. PubMed PMID: 28778697.
[2] Ben-Sheetrit J, Aizenberg D, Csoka AB, Weizman A, Hermesh H. Post-SSRI Sexual Dysfunction: Clinical Characterization and Preliminary Assessment of Contributory Factors and Dose-Response Relationship. J Clin Psychopharmacol. 2015 Jun;35(3):273-8. doi: 10.1097/JCP.0000000000000300. PubMed PMID: 25815755.

Individual case review was performed solely on cases of persistent sexual dysfunction. To ensure high recall of cases (sensitivity), three distinct methods of determining whether a case referred to persistent sexual dysfunctions were employed:

Calculation of the time from discontinuation to recovery: defined as the difference between the latest date of discontinuation of an antidepressant [ICH E2B(R3) G.k.4.r.5] and the latest date of end of reaction(s) [ICH E2B(R3) E.i.5].

Calculation of time from discontinuation to receive date, where reaction is ongoing: defined as the difference between the receive date of the report [ICH E2B(R3) C.1.4] and the latest date of discontinuation of the medicinal product [ICH E2B(R3) G.k.4.r.5], if the reaction was ongoing/had not been resolved/resulted in sequelae.

Text mining of the narratives in the line listing using natural language processing: Text mining using regular expressions was performed on the narratives in the line listing of the case reports. The patterns "persis", "chroni", "ongoin", "prolong" were identified, as these may be related to persistent reactions and the complete sentence that included them was extracted. These selected sentences were then manually reviewed to confirm whether the term was referring to persistent PSSD.

See annex III for additional details.

4.3.2. Secondary outcome

4.3.2.1. Persistent genital arousal disorder

Persistent genital arousal disorder is a reasonably new preferred term in MedDRA, included from version 20.0, and the only one term within the spectrum of sexual disorders that includes in its denomination a reference to long duration.

Considering the above, and that up until MedDRA v20.0 persistent genital arousal disorder was being coded as different term(s), PGAD was assessed as a secondary endpoint.

4.4. Analytical plan

4.4.1. Descriptive statistics of sexual dysfunctions

Descriptive statistics were run on the totality of the cases with sexual dysfunctions, by reporter type, by substance, by class, by indication, by country, by age, gender and by previous medical history of sexual dysfunction.

Results by reaction were stratified by core PSSD (see 4.3.1.2.), extended terms, which are the remaining terms from the sexual dysfunction case definition (see 4.3.1.1.) and secondary terms as per annex II.

4.4.2. Individual case safety review

Two investigators (ISS, LP) independently review case reports of persistent sexual dysfunction (see 4.3.1.3.) and perform a narrative review of the cases to assess the causal association between the persistent sexual dysfunction and the drugs of interest.

For the selected cases with at least possible causal association, histogram and density plots of duration between discontinuation of the drug and persistence of the sexual dysfunction will be plotted, if enough data is available. Different thresholds as described above will be applied.

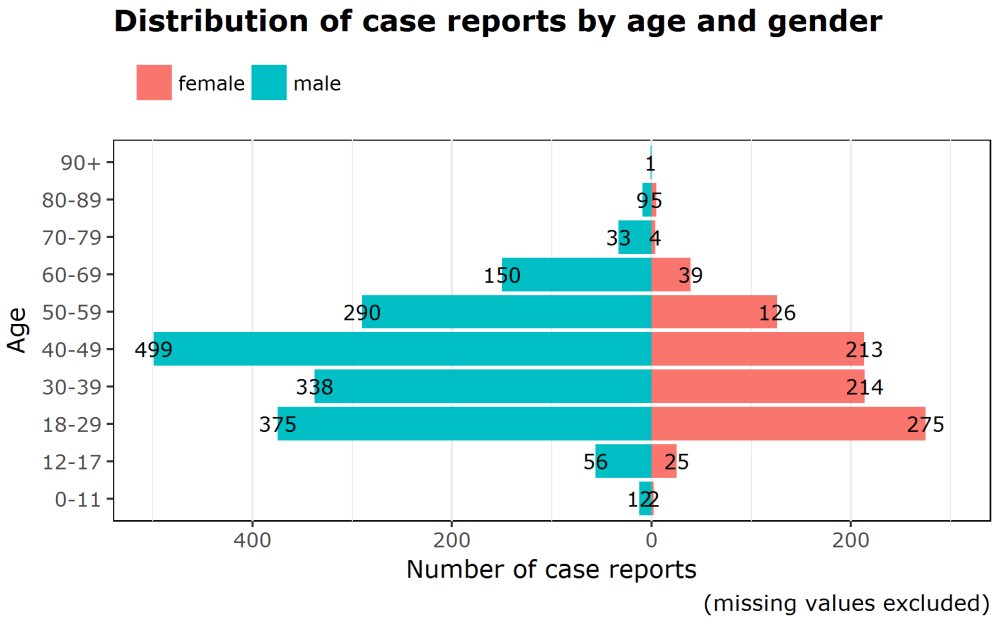
5. Results

5.1. Descriptive analysis of sexual dysfunctions

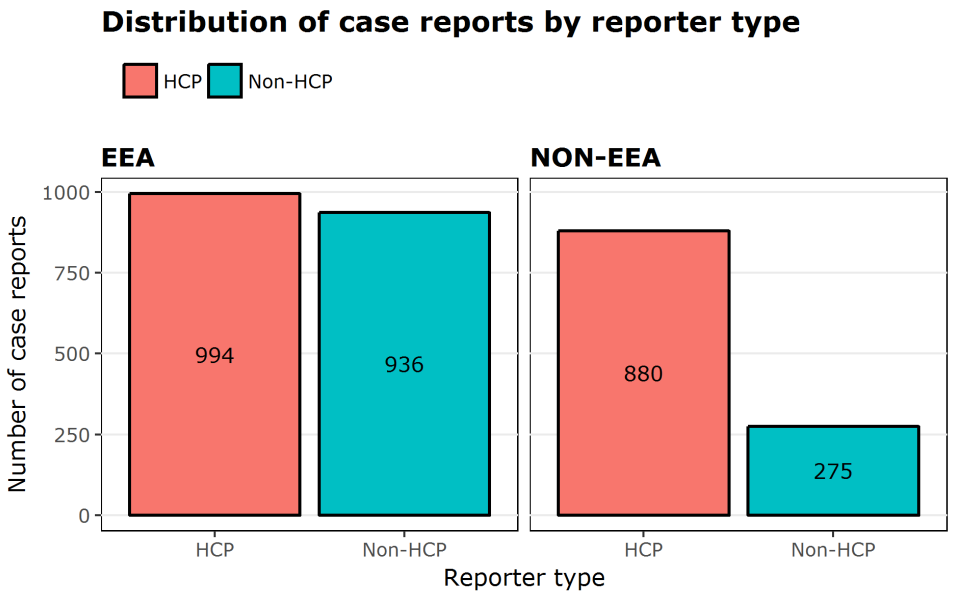
There are 3,210 individual case reports of sexual dysfunction with the antidepressants of interest in EudraVigilance. These cases have not been manually screened for duplicates.

A history of sexual dysfunction was only reported in 79 cases.

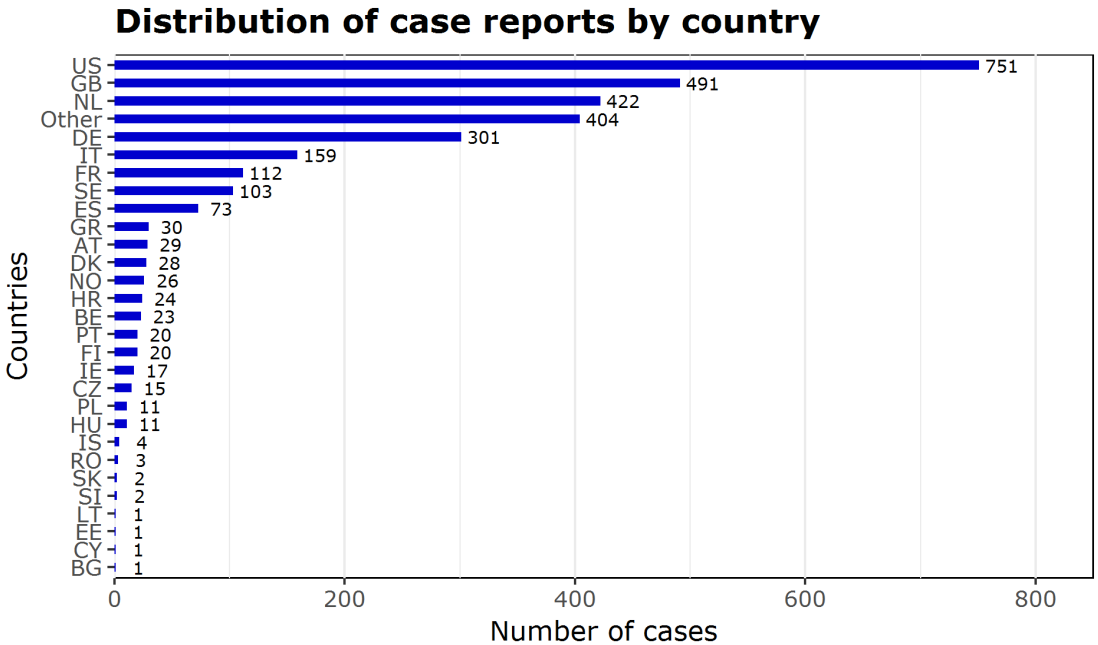
The majority of reports (66.2%) concern male patients. Most reports are in patients aged 18 to 49 years (60%) with the highest frequency in the 40-49 age group (22.3%). Of note, age is missing from 528 of all reports (16.4%).



Cases reported by non-healthcare professionals account for 38.4% of all reports, and nearly half (47.9%) of reports originating from EEA countries. Amongst non-EEA countries, only 22.7% of cases were reported by non-healthcare professionals.

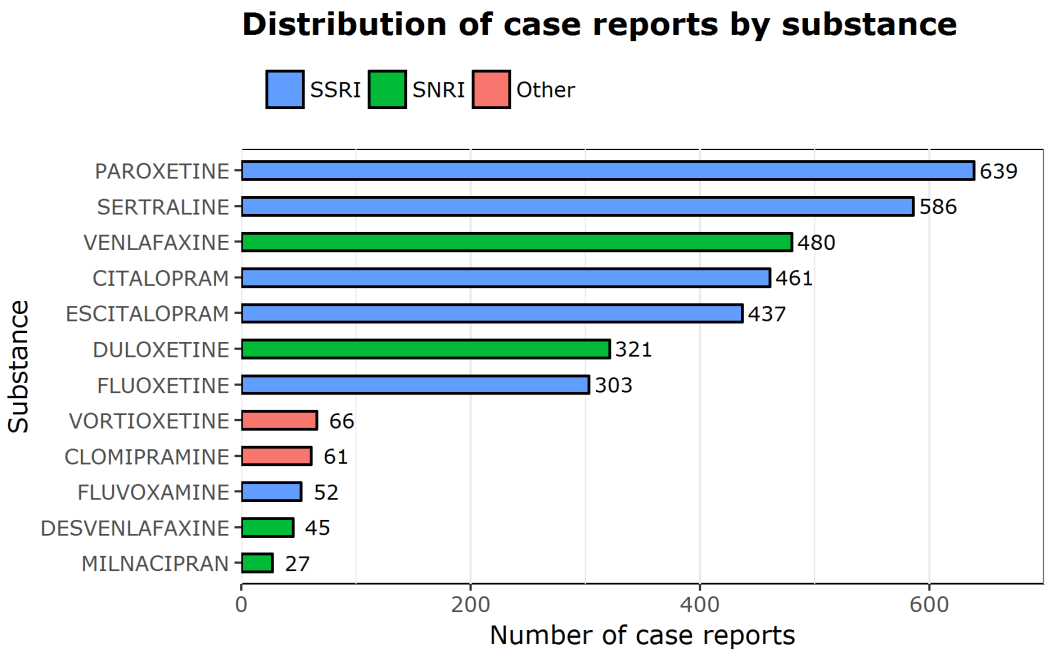


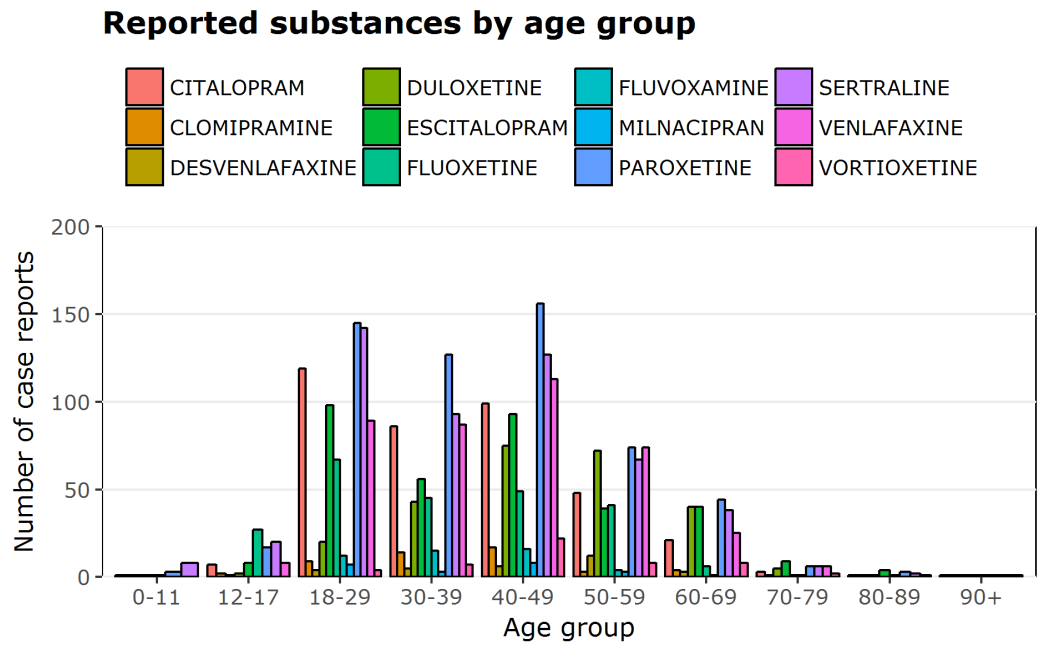
Approximately 23.3% of all reports originate from the United States, while all other non-EEA countries account for 12.6% of all reports. Within the EEA, which accounts for 60.1% of all reports, the three countries with the highest frequency of reports are the United Kingdom (15.3% of all reports), the Netherlands (13.1%) and Germany (9.4%).



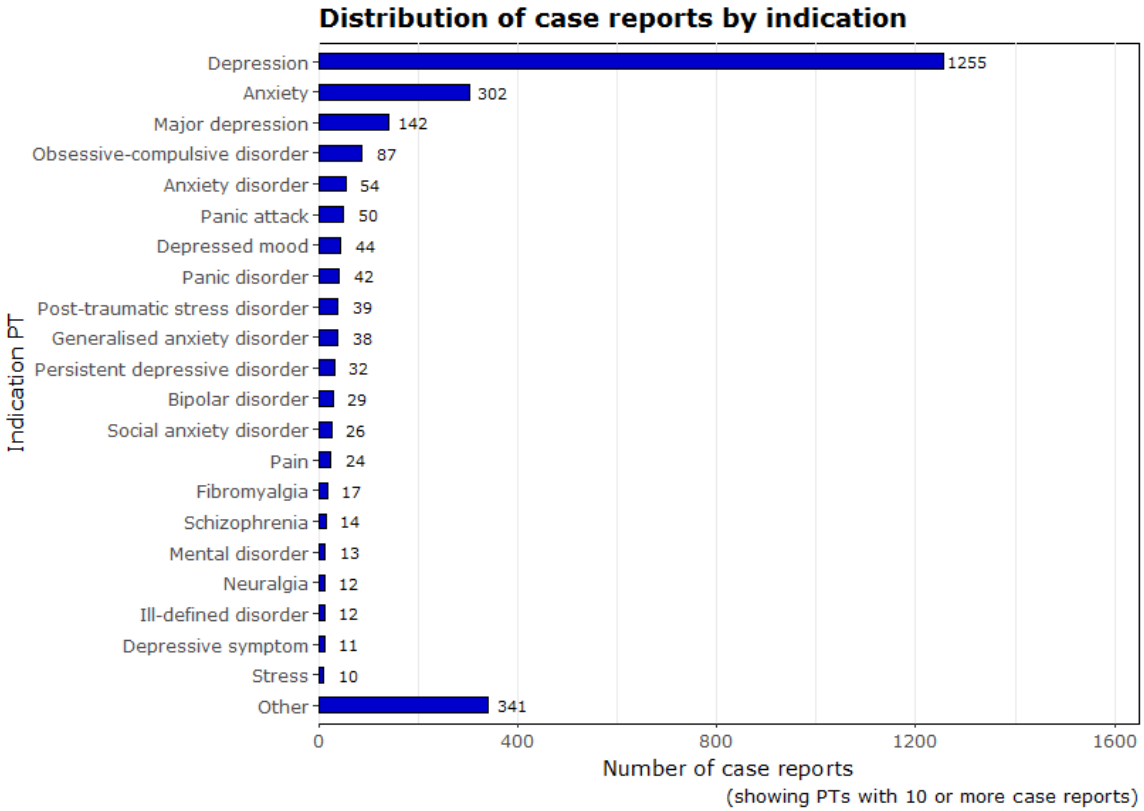
(US and EEA countries with reports are shown, all other non-EEA cases as 'Other')

Overall, selective serotonin reuptake inhibitors were most commonly reported, with paroxetine and sertraline accounting for the highest numbers of cases. Amongst serotonin and norepinephrine reuptake inhibitors, venlafaxine was reported with the highest frequency. This trend was generally consistent across age groups.

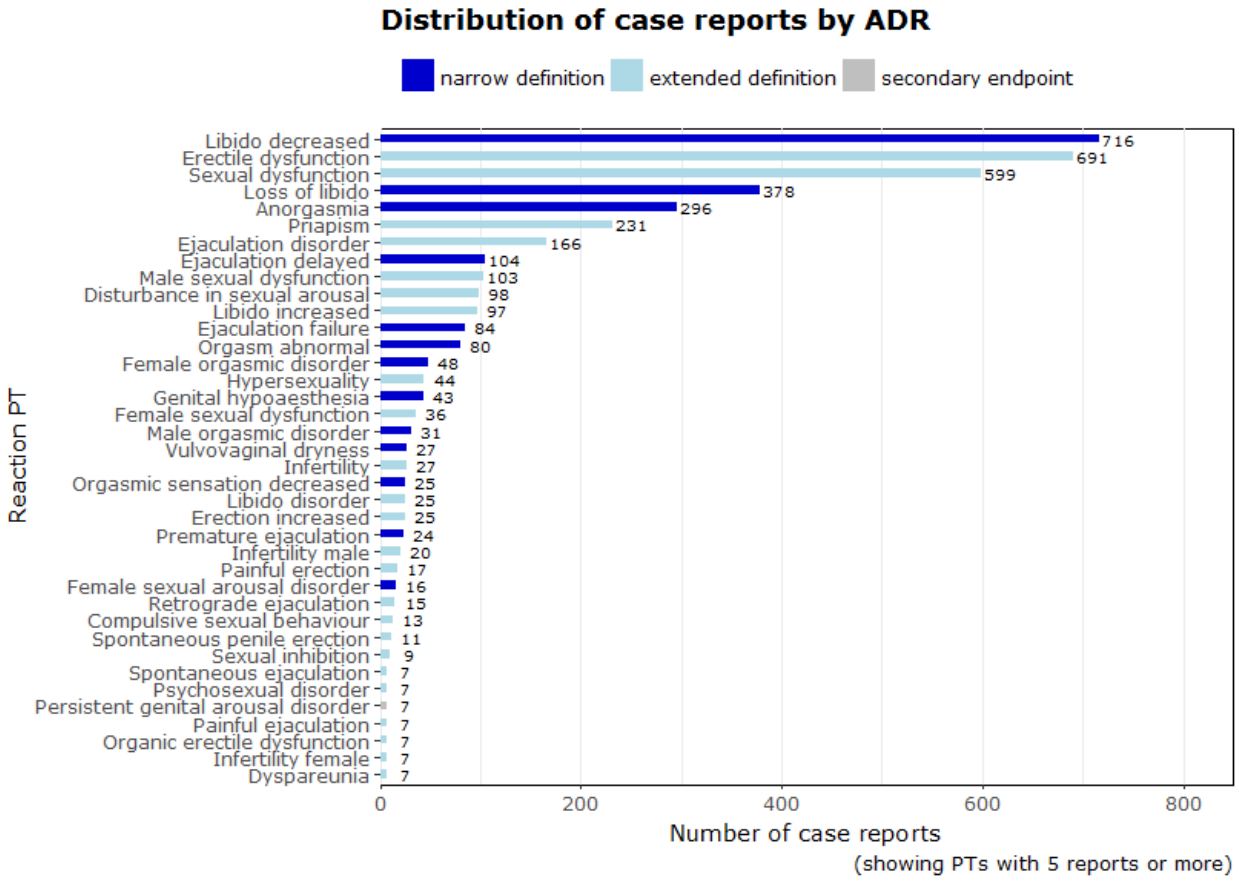




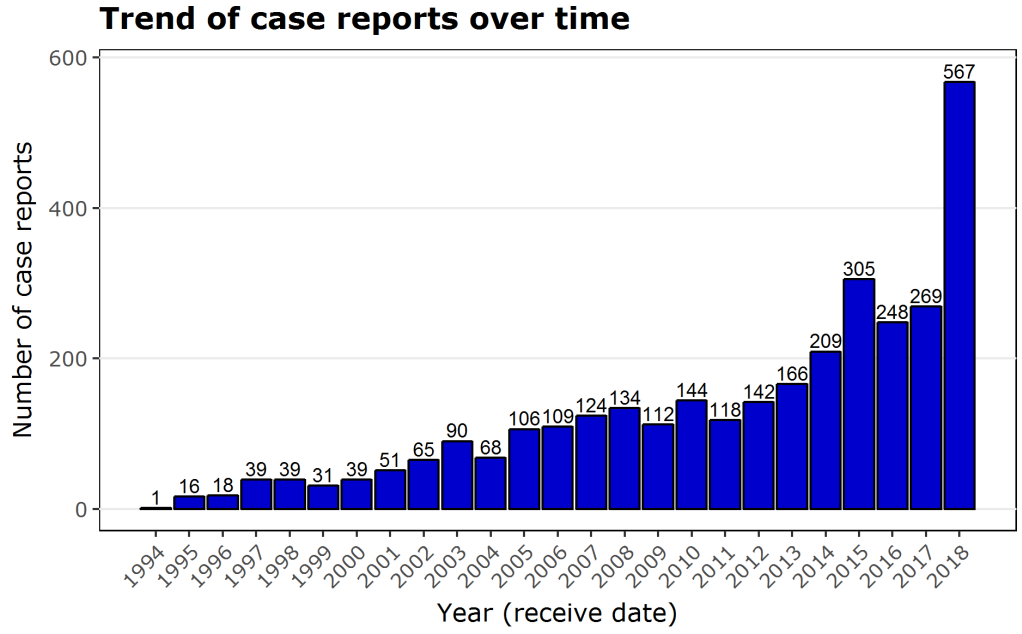
The most frequently reported MedDRA PT for the indication was 'depression' (1,255 cases). Of note, in an equal number of reports (1,255) not displayed in the following graph, the indication was not reported.

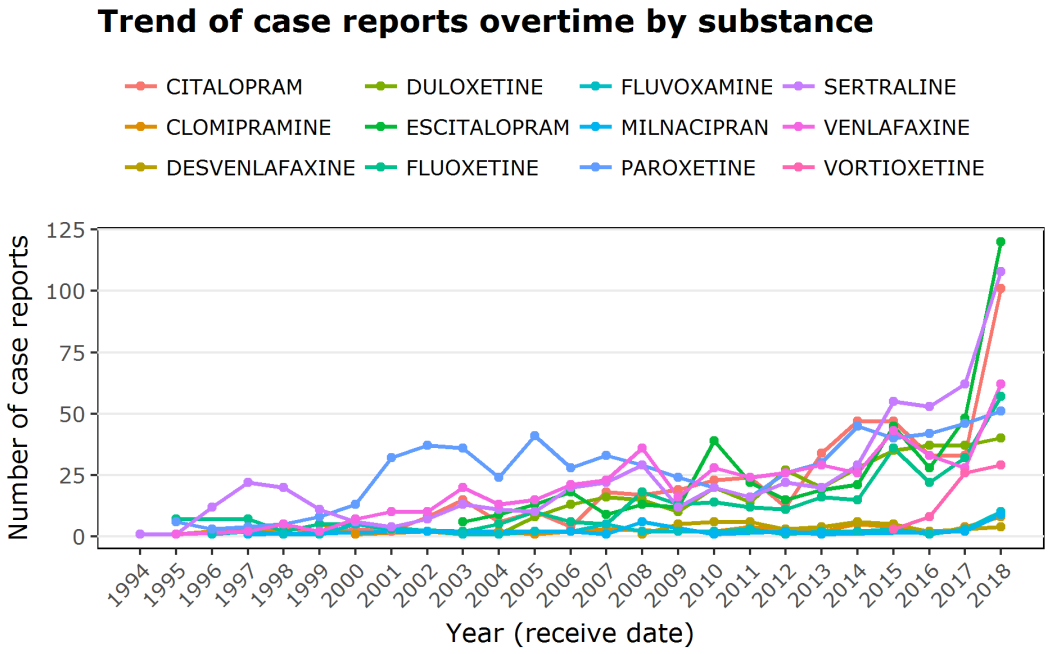

Distribution of case reports by indication
Depression
Anxiety
Major depression
Obsessive-compulsive disorder
Anxiety disorder
Panic attack
Depressed mood
Panic disorder
Post-traumatic stress disorder
Generalised anxiety disorder
Persistent depressive disorder
Bipolar disorder
Social anxiety disorder
Pain
Fibromyalgia
Schizophrenia
Mental disorder
Neuralgia
Ill-defined disorder
Depressive symptom
Stress
Other
1255
302
142
87
54
50
44
42
39
38
32
29
26
24
17
14
13
12
12
11
10
341
Indication PT
0
400
800
1200
1600
Number of case reports
(showing PTs with 10 or more case reports)

Within the narrow definition, the most frequently reported reaction PTs are 'libido decreased' (716), 'loss of libido' (378) and 'anorgasmia' (296). Within the extended definition, 'erectile dysfunction' (691), 'sexual dysfunction' (599) and 'priapism' (231) account for the highest numbers of reports.

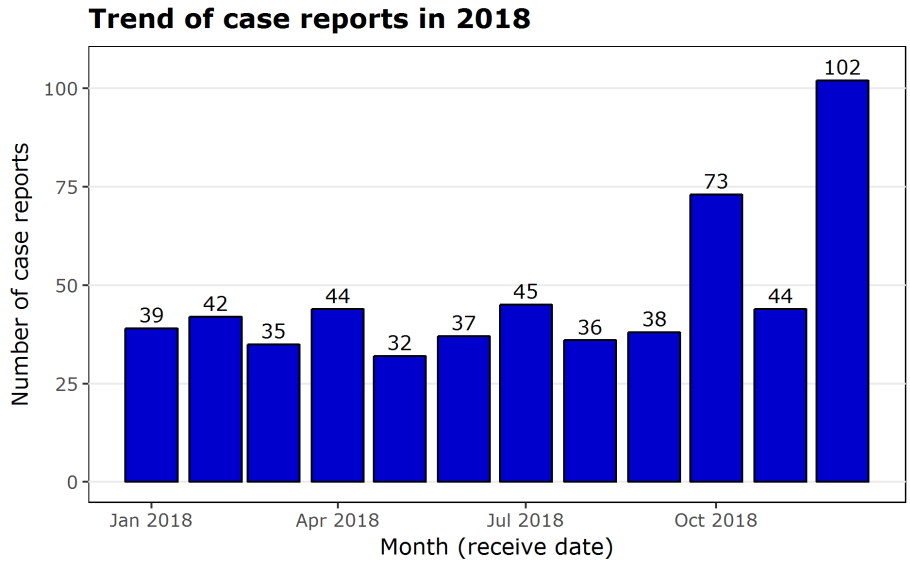


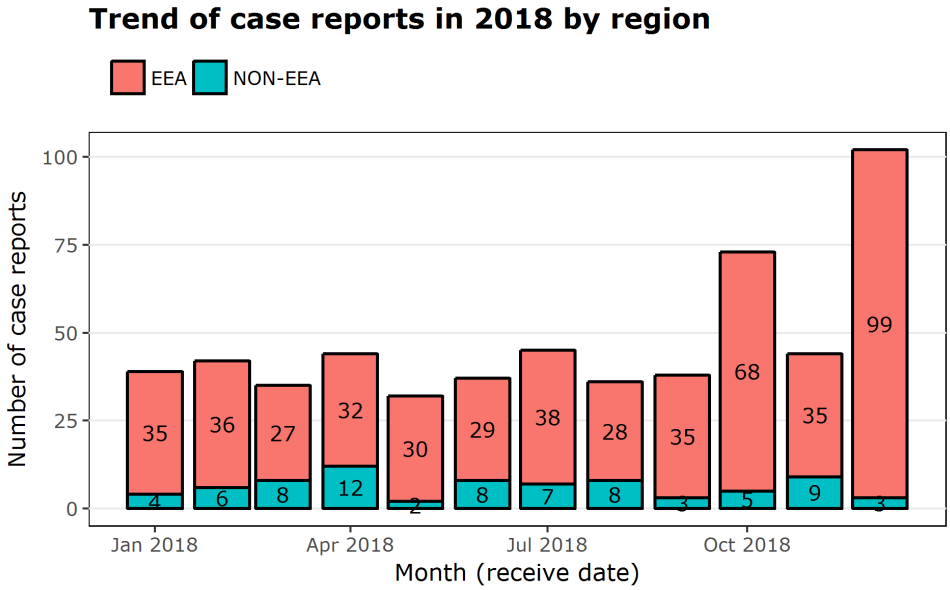
Over time there has been a steady increase in the number of cases reported, but there was a small surge in 2015, and a notable two-fold increase in 2018. The steep increase of reports in 2018 is mainly attributable to escitalopram, sertraline and citalopram.

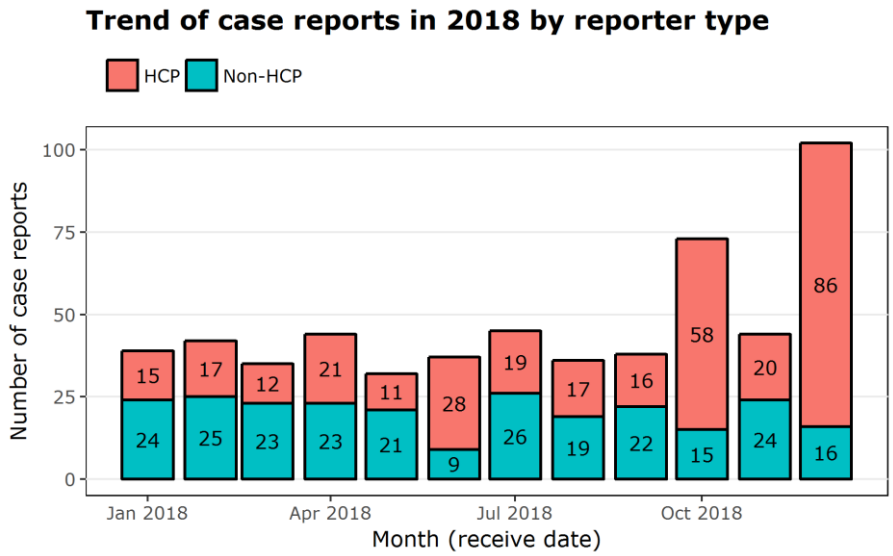


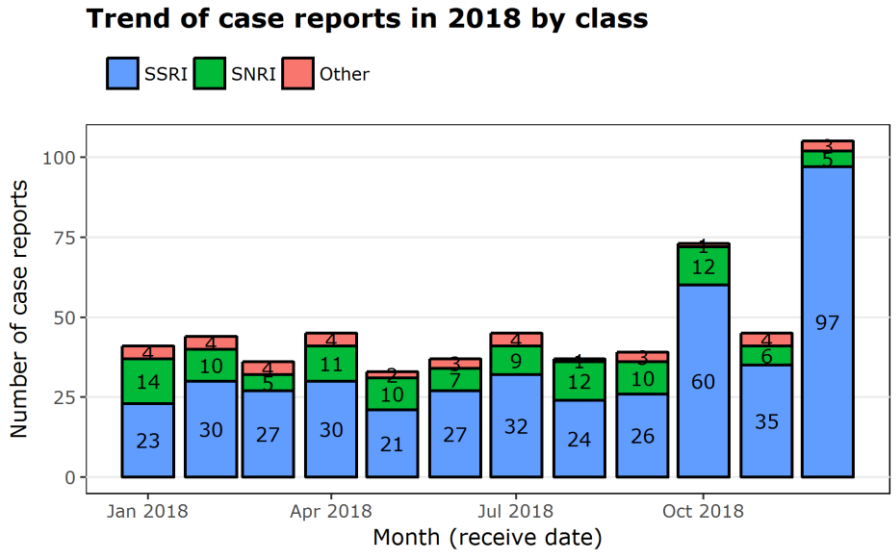


In 2018, there were two reporting peaks in October and December, which were mainly composed of EEA reports from healthcare professionals and for selective serotonin reuptake inhibitors.









5.2. Individual case safety review

5.2.1. Identification of cases of persistent sexual dysfunction

Three methods were used to identify cases of persistent sexual dysfunction. Eight case reports were identified using the **calculation of the time from discontinuation to recovery**. An additional 134 cases were identified using the **calculation of time from discontinuation to receive date, where reaction was ongoing**.

After manual review of the cases identified through **text mining of the narratives in the line listing using natural language processing**, 21 case reports were identified that had persistent sexual dysfunctions. All these 21 case reports, had been identified through the date calculation methods.

5.2.2. Case review appendix

The data-lock point for the inclusion of data in this review was 31 December 2018. From January 2019 to 20 February 2019, 48 additional case reports of sexual dysfunction have been submitted to EV. These are not included in the Summary of the review of cases of persistent sexual dysfunction (5.2.3.) but are discussed in an appendix to this report.

5.2.3. Summary of the review

A total of 142 case reports were analysed. Of these, 18 had no narrative and one was a duplicate.

For the remaining 123 case reports, 27 were considered possibly related. These were mostly considered possibly related based on reasonable temporality and absence of incongruent information.

From the case reports it is difficult to distinguish the risk of sexual dysfunction stemming from the exposure to the drug or from the underlying psychopathological process. This is particularly the case in this series as in no case report is there a mention of recovery from the anxiety or depression. For these reasons, it is difficult to assign a causality category stronger than possible.

Twenty-six case reports were considered unlikely related to the medicinal product. There were multiple reasons for this. In some cases the dose taken seems incompatible with the persistence (e.g. took 11 doses and reaction persisted for two years, took single dose and reaction persisted over 12 months later). Others had inconsistent temporality (e.g. sexual dysfunction initiated 3 years after the stopping the drug, 20 year-old male mentions having sexual dysfunction for seven years, ever since suspending the medicine, and that he had a very active sexual life before starting the medicinal product).

The remaining 54 were considered unevaluable due to poor information in the narratives.

Regarding the duration of the persistence, the reports most often mention vague durations, such as "over 12 months" thus histograms of the actual persistence cannot be plotted.

Overall, the evidence does not seem particularly strong to the reviewers, however 84 of the 123 case reports were from patients, which indicates a significant level of concern from patients that seems to warrant some mitigation.

5.2.4. Relevant case reviews

5.2.4.1. EU-EC-612876, HR-LUNDBECK-DKLU1020152

36M height not reported and weight 86kg, treated with escitalopram 10mg/d po for 111 days from 11/May/2005 to 11/Aug/2005 for Post Traumatic Stress Disorder. The patient had a medical history of heavy smoking (20 cigarettes/day), alcohol abuse and Post Traumatic Stress Disorder. Concomitant medication included atenolol 50mg/d po from uu/uu/2001 and ongoing, zolpidem 10mg/d po from 11/May/2005 and ongoing and simvastatin 20mg/d po from 15/Jan/2004 and ongoing. Indication for all concomitant medication not reported. The patient was treated for PTSD (Post Traumatic Stress Disorder) for many years. On 11/May/2005 therapy was changed and escitalopram was introduced with 5 mg/d for 3 days and the increased to 10 mg/d. Four months after the initiation of escitalopram the patient complained that since he had started with escitalopram his sexual arousal almost disappeared. Escitalopram therapy was discontinued on 30/Aug/2005 and sulpiride 100 mg/d was introduced. About one month later his sexual dysfunction recovered.

5.2.4.2. EU-EC-1440064, NL-LRB-48398

55M experienced affective disorders, abnormal sexual function, insomnia and weight increase following administration of sertraline for indication post-traumatic stress syndrome with a latency period of 3 weeks. Concomitant medication was not reported. The sertraline has been replaced by venlafaxine, 4 months later patient has not recovered yet. NARRATIVEINCLUDECLINICAL: Volledige omschrijving symptomen: affectieve stoornis, agressie, angst, anorgasme, verminderd libido, depressie, nachtmerrie, slaapstoornis, gewichtstoename 15 kilo, suicide-gedachten, lever opgezet Bijwerking behandeld: nee Eerder gehad: niet van toepassing Andere factoren: onbekend Aanvullende gegevens:ik vind het maatschappelijk zeer onegwenst dat: 1. uw instituut niet eerder bekend is geworden bij de bevolking in het algemeen en daardoor belangrijke en levensreddende informatie onbekend is gebleven; 2. uw instituut niet eerder zijn maatschappelijke plicht om de bevolking objectief en volledig van de juiste informatie m.b.t. haar gezondheid heeft ingelicht; en 3. uw directie in een tv-programma haar verantwoordelijkheid m.b.t. de gezondheid van de bevolking ontwijkt door te wijzen nar derden (o.m. artsen en geneesmiddelen-producenten) voor het verkrijgen van informatie. Naar mijn mening hoort u onafhankelijk onderzoek al dan niet in samenwerking met patienten-organisaties in andere landen te doen om tot een objectieve berichtgeving te komen BACKGROUNDINFORMATION: Onderstaande info is verstuurd aan de melder: De door u gemelde symptomen zijn bekende bijwerkingen van zowel Zoloft als Efexor. Sommige effecten zouden echter (mede) verklaard kunnen worden door de onderliggende klachten. REMARKS: 21-02-2005:afdeling verwerking:de melding geeft aan dat de bijwerking 200203 ontstaan is, daarom 15-03-2002 als begindatum bijwerking ingevoerd Reporter Comments- Not available Sender Comments- Not available

5.2.4.3. EU-EC-1827560, NL-LRB-75768

37M experienced impotence following administration of venlafaxine for anxiety disorder with a latency of 2 days after start. The patient has not recovered after cessation of suspect drug at time of reporting. Concomitant medication was not reported. NARRATIVEINCLUDECLINICAL: De volgende extra info is beschikbaar: Behandelingbijwerking : Bijwerking is niet behandeld Klachten eerder : Geen bijwerkingen Andere oorzaken : geen andere oorzaken BACKGROUNDINFORMATION: De volgende informatie is verstuurd aan melder: Impotentie komt als bijwerking van venlafaxine vaak voor. Dat wil zeggen bij 1 tot 10% van de gebruikers. Bij u ontstonden de klachten kort na de start van de venlafaxine. Dat maakt het aannemelijk dat het om een bijwerking gaat en dat andere oorzaken minder waarschijnlijk zijn. Mocht de impotentie niet verdwijnen na staken van de venlafaxine, dan is het raadzaam uw behandelend arts te raadplegen. REMARKS: Reporter Comments- Primary source is: Patient, inhoudelijke terugkoppeling: ja Sender Comments- Due to incompatibility between latency period and data, the latency period was corrected to 2 days (which was reported) by the Netherlands Pharmacovigilance Centre Lareb.

5.2.4.4. EU-EC-3267910, DE-BFARM-09077275

Narrative - Symptomdetails: Das wiederholte Aussetzen der Wahrnehmung folgte immer auf eine schwere ca. 10-30 Sekunden lange Episode der Parästhesie (gefühlt: elektrischer Strom der sich aus den Extremitäten bis zur Wirbelsäule/Kopf vorarbeitet und zu dem Aussetzen der Wahrnehmung führt. Es wird schwarz vor Augen, man hört einen hochfrequenten lauten Ton für einige Sekundenbruchteile.) Am ersten Tag wurden diese Episoden vom akuten Gefühl der Angst begleitet, da die Ursache zunächst unklar war und keine Möglichkeit bestand das Problem zu unterdrücken oder zu beheben. Die Abstände zwischen den Episoden blieben in den ersten zwei-drei Tagen unverändert, wurden danach

aber immer länger und traten schließlich nur noch zusammen mit den bewegungsabhängigen Komponenten der Parästhesie auf. Das gleiche betrifft die Stärke der Parästhesie während der Episoden. Die Parästhesie wurde durch Bewegung ausgelöst/verstärkt, zunächst durch jede abrupte Bewegung, in der zweiten Woche nur noch durch schnelle (vor allem diagonale) Augenbewegung (z.B. aus der Mitte nach oben links) und trat vor allem auf der gegenüber der Blickrichtung liegenden Seite des Körpers. Anfangs betraf das Gefühl die gesamte Körperseite (vor allem Hand, Fuß, Arm und Bein) auf, betraf einige Wochen später schließlich nur noch Hand und Arm. Einnahme-Details: Die Symptome folgten auf das Absetzen der geringsten im Handel verfügbaren Dosis des Medikamentes (30mg, 1x Täglich), nachdem einige Wochen zuvor die Dosis ohne Probleme von 60mg, 1x Täglich, auf 30mg 1x Täglich reduziert wurde. Am 27.04 wurde zur Linderung der noch verbleibenden Entzugserscheinungen auf das Anraten des behandelnden Arztes eine geringe Dosis - einige Granulen aus der Kapsel - oral eingenommen. Dies führte innerhalb von ca. 30-60 min. zu einer vollständigen Rückkehr aller Symptome vom 16.04 die bis zum Folgetag andauerten, wonach keine weiteren Darreichungsversuche erfolgten. Auswirkungen auf das Leben des Patienten: Konzentriertes Arbeiten oder auch intensives Teilnehmen am Privatleben waren während der ersten Wochen praktisch unmöglich, da jede Tätigkeit ständig durch die Parästhesie-Episoden unterbrochen wurde. Die Symptome waren hinreichend schwer um nach wenigen Tagen Suizidgedanken als "Lösung" aufkommen zu lassen, speziell weil keine Besserung eintrat und dementsprechend auch keine in Sicht war. Schnelle Augenbewegung wird auch zur Zeitpunkt der Meldung (16.06.2009, ca. 2 Monate nach letzter Gabe) immer noch von einer "Angst vor dem Stromschlag" begleitet, auch wenn die Symptome selbst scheinbar nicht mehr vorhanden sind. Reporter Comments- Not available Sender Comments- Not available.30M experienced repeated exposure was always followed by a severe episode of paresthesia lasting approximately 10-30 seconds (felt: electric current working from the extremities to the spine / head and exposure It turns black, you hear a high-pitched loud sound for a split second.) On the first day, these episodes were accompanied by the acute feeling of anxiety because the cause was initially unclear and there was no possibility of the problem The gaps between the episodes remained unchanged during the first two-three days, but then became longer and later only appeared together with the movement-dependent components of paresthesia. The same applies to the intensity of paraesthesia during the episodes. Paresthesia was triggered / intensified by movement, first by every abrupt movement, in the second week only by rapid (especially diagonal) eye movement (eg, from the Middle to upper left) and occurred mainly on the opposite side of the body. Initially, the sensation affected the entire body side (especially the hand, foot, arm and leg), affecting only a hand and arm a few weeks later. Ingestion details: Symptoms followed to discontinue the lowest commercially available dose of the drug (30mg, once a day) after a few weeks prior dose reduction from 60mg once daily to 30mg once daily. On 27/04 relief was given of the remaining withdrawal symptoms on the advice of the treating physician a small dose - some granules from the capsule - orally taken. This led within about 30-60 min. To a complete return of all symptoms from 16.04 until the following day, after which no further administration attempts were made. Effects on the patient's life: Concentrated work or even intensive participation in private life were during the first few weeks were practically impossible because every activity was constantly interrupted by the paresthesia episodes. The symptoms were sufficiently severe to give rise to suicidal thoughts as a "solution" after a few days, especially as there was no improvement and, accordingly, none was in sight. Rapid eye movement is also accompanied by a "fear of electrocution" at the time of the announcement (16.06.2009, about 2 months after the last dose), even if the symptoms themselves do not seem to be more are available.

5.2.4.5. EU-EC-4653440, NL-ELI_LILLY_AND_COMPANY-NL201106002354

F had medical history was negative for diabetes. On previous unspecified dates, the patient took pregabalin and experienced events, including abnormal dreams. At the time of the report, the patient was taking unspecified concomitant medications and had been for "years". The patient received duloxetine hydrochloride (Cymbalta) 30 mg, unknown frequency for treatment of unaccountable nerve pain. The start date and lot number were not provided. On an unknown date, the patient experienced abnormal dreams, abnormal orgasms (even whilst driving the car and in most impossible situations), blurry vision (the patient was not able to read a phone number), abnormal muscle contractions (spasms of some kind), itching over the entire body and neuropathy (nervepain). On 29-APR-2011, duloxetine was discontinued. At the time of the report on 08-JUN-2011, the events were still ongoing. Before using duloxetine, the patient did not experience any of the events. The event of blurry vision was considered serious for other medically significant reasons by the company. No treatment measures were indicated and no additional information was provided. Duloxetine remained discontinued. The reporting pharmacist noted it was probable that the events were related to duloxetine use.

5.2.4.6. EU-EC-6088567, NL-LRB-126726

Narrative - SUMMARY: This well documented non-serious spontaneous report from a consumer concerns a male aged 65 years, with polyneuropathy and erectile dysfunction following administration of paroxetine for panic disorder with a latency of 11 years and 6 weeks after start, respectively. The drug paroxetine was withdrawn. The patient has not recovered. Concomitant medication was not reported. The neurologist believes the cause of the neuropathy is idiopathic. The patient has no known medical history. The patient has no known past drug therapy. NARRATIVEINCLUDECLINICAL: De volgende extra info is beschikbaar: paroxetine als oorzaak van de neuropathie is niet bewezen maar staat bovenaan. er is geen diabetes of B12 deficientie (0.19nmol). Was zelf huisarts en heb het middel met veel succes vrij veel voorgeschreven, heb vastgesteld dat het merendeel van de gebruikers de klachten terugkrijgt na stoppen en daardoor chronisch gebruiker is. ik beschouw mijn polyneuropathie als een ernstige zaak. Als dat verband houdt met paroxetine gebruik en met name met de duur van het paroxetine gebruik is de vraag of er meer problemen gaan komen nu de groep langgebruikers groeit. Het lijkt mij dat het hier zenuwschade betreft en dus een irreversibele aandoening. Een polyneuropathie door eigen doen, of dat van de voorschrijver, komt hard aan. Lareb meldt in 2006 150 ssri-gerelateerde gevallen. U begrijpt dat ik zeer geintereseeerd ben in de kennis over de relatie tussen ssri en neuropathie en in de ontwikkeling van het aantal bekende gevallen en dat ik daar bezorgd over ben voor anderen. het is mij duidelijk dat Lareb mij daarin niet verder kan helpen. Behandelingbijwerking : bijwerking is niet behandeld Klachten eerder : n.v.t. Andere oorzaken : geen andere oorzaken Follow-up: 30-08-2011: Ter aanvulling op eerder verstrekte informatie: Uw informatie is voor mij zeer waardevol. Polyneuropayhie bij paroxetinegebruik is zo zelden beschreven dat de vraag sterker wordt of er verband is. Er is in elk geval sprake van langdurig gebruik van paroxetine en tijdens gebruik ontstane klachten, er is geen andere verklaring. Mijn huisarts was direct en stevig overtuigd van het verband tussen paroxetine en de gediagnosticeerde neuropathie. De neuropathie bestaat symmetrisch aan de benen en in zeer lichte mate en niet constant aan de armen. Er is spake van parestesieën van de voetzolen tot onder de knieën, sterk verlaagde fijne tast van de voeten en in mindere mate van de benen en een verlaagde APR en KPR. Follow-up: 6-11-2012: Melder: nalv mijn melding 126726: door de neuroloog is besloten dat mijn door haar vastgestelde en bewezen polyneuropathie idiopathisch is en niet wordt veroorzaakt door paroxetine zoals door mijn gemeld. Beoordelaar: 12-11-2012: Summary aangepast.Causuality polyneuropathy re-assessed. REMARKS: Reporter Comments- Primary source is: Patient, inhoudelijke terugkoppeling:

ja Sender Comments- Not available. 65M experienced polyneuropathy and erectile dysfunction following administration or paroxetine for panic disorder with a latency of 11 years and 6 weeks after start, respectively. The drug paroxetine was withdrawn. The patient has not recovered. Concomitant medication was not reported. The neurologist believes the cause of the neuropathy is idiopathic. The patient has no known medical history. The patient has no known fits drug therapy. Paroxetine as the cause of neuropathy is not proven but is at the top. There is no diabetes or B12 deficiency (0.19nmol). Was a doctor yourself and have prescribed the drug with much success, I have found that the majority of the users get the symptoms back after stopping and therefore are chronic users. I consider my polyneuropathy as a serious matter. If this is related to paroxetine use and in particular with the duration of paroxetine use, the question is whether more problems will arise as the group of long-term users grows. It seems to me that this concerns nerve damage and thus an irreversible condition. A polyneuropathy by doing its own, or that of the prescriber, is coming hard. Lareb reported 150 SSRI-related cases in 2006. You understand that I am very interested in the knowledge about the relationship between SSRI and neuropathy and in the development of the number of known cases and that I am worried about that for others. It is clear to me that Lareb can not help further. Polyneuropayhia in paroxetine use is so rarely described that the question becomes stronger or related. In any case, there is a long-term use of paroxetine and complaints arising during use, there is no other explanation. My doctor was immediately and firmly convinced of the relationship between paroxetine and the diagnosed neuropathy. The neuropathy exists symmetrically on the legs and very slightly and not constantly on the arms. There is spess of paresthesia from the soles of the feet to below the knees, greatly reduced fine touch of the feet and to a lesser extent of the legs and a lowered APR and KPR. Reporter: following my report 126726: the neurologist has decided that my established and proven polyneuropathy is idiopathic and is not caused by paroxetine as reported by me.

5.2.4.7. EU-EC-6605158, CA-ELI_LILLY_AND_COMPANY-CA201302000502

38M on concomitant medication included hydromorphone and esomeprazole magnesium / naproxen. The patient received duloxetine hydrochloride (Cymbalta) 60 mg daily, orally, for the treatment of pain on 23JUL2012. On the same day, 23JUL2012, the patient experienced problematic increased libido like a rage. He also experienced an overproduction of sperm. This was described as sperm coming out without an erection. The event ejaculation disorder was considered serious for medical significance. The patient had not recovered from the events. Duloxetine was discontinued on 30AUG2012. The pharmacist did not report if the events were related to duloxetine treatment.

5.2.4.8. EU-EC-6901847, NL-LRB-156827

18M experienced impotence following administration of fluoxetine for depression with unknown latency after start. The drug fluoxetine was withdrawn. The patient has been treated with medication and has not recovered 4 years after withdrawal. Concomitant medication was not reported. The patient has no known medical history. NARRATIVE CLUDECLINICAL: Has the side effect been treated? Yes, namely with: medication and therapy Has the patient already used the medicine that causes the side effect (s)? Yes Does the patient have a similar side effect? Yes, namely this side effect: impotence Are there any other causes or circumstances that may have caused or worsened the side effect (s)? No Possible interaction with other medicines? No The patient uses other medicines: no REMARKS: Reporter Comments- Reporting PG20130707112429 comes from www.lareb.nl reporting form Sender Comments- Not available.

5.2.4.9. EU-EC-7067638, NL-LRB-158432

22M experienced sexual dysfunction following administration or paroxetine for depression with a latency or 2 days after start. The drug paroxetine was withdrawn. The patient has not recovered. Concomitant medication was not reported. The patient has no known medical history. The patient has no known fits drug therapy. NARRATIVE CLUDECLINICAL: Has the side effect been treated? No Has the patient used the medicine that causes the side effect (s) before? No Are there any other causes or circumstances that may have caused or worsened the adverse reaction (s)? No Other serious abnormalities: Post-SSRI sexual dysfunction Possible interaction with other medicines? No The patient uses other medicines: no REMARKS: Reporter Comments- Reporting PG20130819010321 comes from www.lareb.nl reporting form Sender Comments- Not available.

5.2.4.10. EU-EC-7312557, IE-IMB-2013-017293

20M experienced Erectile dysfunction following treatment with LEXAPRO (escitalopram) & Efexor XL for Anxiety. Concomitant medications: None. Medical history/concurrent conditions: Not reported. The patient commenced therapy with LEXAPRO at a dose of 10mg per oral from the 14/Aug/2006 to the 30/Mar/2007 and Efexor XL at a dose of 75mg per oral from the 01/May/2007 to the 02/Apr/2009. On an unreported date, the patient experienced erectile dysfunction. The patient took 10mg LEXAPRO up to approximately Mar/2007 and then 5mg for a month. The patient indicated that he started using Efexor XL shortly after and took 75mg for approximately 3 months, then up to 150mg for approximately 10 months and then back down to 75mg until the end of 2008. The patient then took 37.5mg for about 4 months and then stopped. The patient reported that he had erectile dysfunction while on both medications. The patient indicated that he thought the reaction would recover after discontinuation of medications but the patient has been off all medication for 4 years, is not on any other medication, leads a healthy lifestyle, has no health problems and at the time of reporting the reaction was persisting. The reporter indicated that the reaction started while on the medications. The reporter confirmed he first experienced the reaction 4 months after starting medication.

5.2.4.11. EU-EC-7725963, NL-LRB-169605

45M experienced libido decreased following administration of fluoxetine for depression with a latency of 1 week after start. The drug fluoxetine was withdrawn. The patient has not recovered (10 years after withdrawal). Concomitant medication was not reported. The patient has no known medical history. The patient has no known past drug therapy. NARRATIVEINCLUDECLINICAL: Is of zijn de bijwerking(en) behandeld? Nee Heeft de patient het geneesmiddel dat de bijwerking(en) veroorzaakt al eerder gebruikt? Nee Zijn er mogelijk andere oorzaken of omstandigheden die de bijwerking(en) kunnen hebben veroorzaakt of verergerd? Nee Extra informatie: ik slikte Prozac. Het eerste bijverschijnsel was verlies van zin in seks, dat weet ik nog zo goed omdat ik er zó verbaasd over was. Elke week daarna volgde nog een bijverschijnsel van de bijsluiter, droge mond etc. Gestopt na een week of 12. Alle bijverschijnselen verdwenen langzamerhand en de seksuele aandrang werd wel ietsje meer, maar haalde bij lange na niet wat het ooit geweest was. Mogelijke wisselwerking met andere geneesmiddelen? Nee Gebruikt de patient nog andere geneesmiddelen: nee REMARKS: Reporter Comments- Melding PG20140311042338 is afkomstig van www.lareb.nl meldformulier Sender Comments- Due to incompatibility between reported latency period and calculated latency from drug start date and start date of reaction, the latency period was corrected to 1 week by the Netherlands Pharmacovigilance Centre Lareb.

5.2.4.12. EU-EC-7796387, CA-HEALTH CANADA-000528936

F administered Cipralex tablets (Generic name: escitalopram) 2.5 mg once daily per oral started on 11/Mar/2013 and discontinued on 24/Mar/2013 for sleep disorder due to possible anxiety issues. On XX/Mar/2013, within 5 days of starting the escitalopram therapy she developed muscles spasms of the pelvic floor, persistent genital arousal feelings, an over active urge to void her bladder, pain and burning in the urethra pain and burning in the bladder, burning pain in the vagina and pins and needles sensations in her legs, which she referred to as restless legs syndrome. The patient was also prescribed escitalopram for sleep disorder which constitutes an off label use. All of this caused the patient to be sad and upset and she could not sleep. At the time of reporting, the status of the escitalopram therapy was "discontinued" and the outcome of these adverse events was "not recovered". The patient started taking gabapentin on 24/Apr/2013 which has helped 50 percent of her symptoms, bladder has calmed down and the burning pain in the vagina. The patient is seeing a therapist and has started on clonazepam 5 mg at bedtime for sleep due to painful spasms of the pelvic floor. Patient's medical history comprised of 2 pregnancies (both healthy), non-smoker, no alcohol use, some anxiety, insomnia and sleep disorder due to possible anxiety issues (onset dates not reported). Concomitant medications were not used. Sender Comments- Confounding factor in this case is the patient's underlying anxiety which may cause an alteration of the perception of the patient's symptoms. A temporal relationship between escitalopram and the events is possible as time from treatment initiation to onset of events was within 5 days. In this case, the patient was prescribed off label a low dose of escitalopram for sleep disorder due to anxiety. There is a negative dechallenge as escitalopram was discontinued and the events didn't resolve. Missing information include the patient's medical history (e.g. neurological disorders), exact event onset dates, laboratory findings and investigations (e.g. neurological examination, infection), final diagnosis. A causal relationship between escitalopram and the events is considered as not related due to negative dechallenge, low dose of 2.5 mg per day and underlying anxiety.

5.2.4.13. EU-EC-8552192, NL-LRB-183464

41M experienced anorgasmia (patient has libido and can get an erection) following administration of paroxetine for anxiety disorder with a latency of few days after start. These symptoms persisted also after the drug was withdrawn (now more than 4 years ago). Concomitant medication was not reported. The patient has no known medical history. The patient has no known past drug therapy. NARRATIVEINCLUDECLINICAL: Is of zijn de bijwerking(en) behandeld? Nee Heeft de patient het geneesmiddel dat de bijwerking(en) veroorzaakt al eerder gebruikt? Nee Zijn er mogelijk andere oorzaken of omstandigheden die de bijwerking(en) kunnen hebben veroorzaakt of verergerd? Nee 9 jaar geleden kreeg ik paroxetine voorgeschreven vanwege een depressie. Na het slikken hiervan verdween in een paar dagen tijd het orgasme-gevoel. En dat is, ook na het stoppen met slikken, nooit meer teruggekomen. Ik heb dus wel een libido, kan een erectie krijgen, ejaculeer, alleen er is geen enkel gevoel meer bij het orgasme. Het ''orgasme-gevoel' is nooit meer teruggekomen. De link met het slikken van paroxetine is voor mij overduidelijk. Mogelijke wisselwerking met andere geneesmiddelen? Nee Gebruikt de patient nog andere geneesmiddelen: nee REMARKS: Reporter Comments- Melding PG20141022121809 is afkomstig van www.lareb.nl meldformulier Sender Comments- Not available 41M experienced anorgasmia (patient has libido and can be an erection) following administration of paroxetine for anxiety disorder with a latency of few days after start. These symptoms persisted after the drug was withdrawn (now more than 4 years ago). Concomitant medication was not reported. The patient has no known medical history. Has the patient used the medicine that causes the side effect (s) before? No. Are there any other causes or circumstances that

may have caused or worsened the adverse reaction (s)? No. 9 years ago I received paroxetine because of depression. After swallowing, the orgasm feeling disappeared in a few days. And that is, even after stopping swallowing, never come back. So I have a libido, can get an erection, ejaculate, only there is no more feeling at the orgasm. The 'orgasm feeling' has never returned. The link with swallowing paroxetine is obvious to me. Possible interaction with other medicines? No. The patient uses other medicines: no

5.2.4.14. EU-EC-8752891, JP-GLAXOSMITHKLINE-JP2014JPN033508

31M received paroxetine for depression and obsessive-compulsive disorder. Co-suspect products included escitalopram oxalate (Lexapro) for depression and obsessive-compulsive disorder. Concurrent medical conditions included depression and obsessive-compulsive disorder. Concomitant products included polycarbophil calcium (Colonel), traditional chinese medicine, valproic acid (Depakene) and trazodone hydrochloride (Desyrel). On 6th December 2012, the patient started Paxil Cr (oral) 12.5 mg once daily (12.5 mg daily). On 18th December 2012, the dose was changed to 25 mg once daily (25 mg daily). On 25th December 2012, the dose was changed to an unknown dose and frequency. On 18th June 2013, the dose was changed to an unknown dose and frequency. On 21st May 2013, the patient started Paxil (oral) 20 mg daily. On 4th June 2013, the dose was changed to an unknown dose and frequency. On 4th June 2013, the patient started Lexapro (oral) 10 mg daily. On 11th June 2013, the dose was changed to an unknown dose and frequency. On 14th January 2014, the dose was changed to an unknown dose and frequency. On an unknown date, unknown after starting Paxil Cr and Paxil, the patient experienced sexual dysfunction (serious criteria disability), erectile disturbance (serious criteria disability), ejaculation delayed (serious criteria disability) and diarrhoea. Paxil Cr was discontinued on 25th June 2013 (Dechallenge was negative). Paxil was discontinued on 11th June 2013 (Dechallenge was negative). Lexapro was discontinued on 4th March 2014 (Dechallenge was negative). On an unknown date, the outcome of the sexual dysfunction, erectile disturbance, ejaculation delayed and diarrhoea were not recovered/not resolved. The reporter considered the sexual dysfunction, erectile disturbance and ejaculation delayed to be related to Paxil Cr. The reporter considered the diarrhoea to be unrelated to Paxil Cr and Paxil. The reporter considered the sexual dysfunction, erectile disturbance and ejaculation delayed to be unrelated to Paxil. 06 December 2012: On initial examination, depression and obsessive-compulsive disorder was diagnosed. 25 December 2012: Although he complained of sexual dysfunction (erectile dysfunction and delayed ejaculation), the priority was put on treatment. Thus, the dose of Paxil CR was increased to 50 mg/day. 21 May 2013: Because of insufficient effect on obsessive-compulsive disorder, Paxil IR 20 mg/day was added to treatment. 04 June 2013: Sexual dysfunction was severe. Thus, treatment shift to Lexapro was initiated: Lexapro 10 mg/day, Paxil CR 50 mg/day, Paxil IR 10 mg/day. 11 June 2013: Lexapro dose was increased to 20 mg/day. Paxil CR was continued at 50 mg/day. Unknown date: Diarrhoea became remarkable, but Lexapro was continued. Unknown date: Obsessive-compulsive disorder completely resolved with Lexapro. As of 10 December 2014: Sexual dysfunction and diarrhoea still persisted. Referral to a specialist on erectile dysfunction at a urology department was under consideration.

5.2.4.15. EU-EC-9745976, LT-SMCA-2560

21M was administered with Cipralex tab. 10 mg daily, Rispolept tab. 3 mg daily and Parkopan tab. 2 mg daily for depression treatment. During this treatment the patient experienced these symptoms: slight gynecomastia, weight increased, late dystonia (painful muscle spasms in the back and the face which almost disappeared within 9 months), peripheral neuropathy (Nervous burning, pain in the left arm and left leg, therefore occurred limp. After medicines withdrawn lasted for about 7 months, almost

disappeared.), sexual dysfunction which caused the patient to disability. He can not live normal sexual life because no longer feel desire in women. All of these symptoms occured approximately on 07-NOV-2014 and continues until now. On the reporting date the patient was not recovered.

5.2.4.16. EU-EC-10409781, NL-LRB-214021

58F experienced loss of libido following administration of duloxetine for neuropathic pain with a latency of 68 days after start. The drug duloxetine was withdrawn. The patient has not recovered 5 months after withdrawal. Concomitant medication was pregabaline. The medical history indicates that the patient had Spinal column stenosis and also had Herniated nucleus pulposus. The patient has no known past drug therapy. NARRATIVEINCLUDECLINICAL: Is of zijn de bijwerking(en) behandeld? Nee Heeft de patient het geneesmiddel dat de bijwerking(en) veroorzaakt al eerder gebruikt? Nee Zijn er mogelijk andere oorzaken of omstandigheden die de bijwerking(en) kunnen hebben veroorzaakt of verergerd? Ja, namelijk: - kanaalstenose L3-L4 en Lyrica gebruik Mogelijke wisselwerking met andere geneesmiddelen? Nee Gebruikt de patient nog andere geneesmiddelen: ja REMARKS: Reporter Comments- Melding ZG20160218081340 is afkomstig van www.lareb.nl meldformulier Sender Comments- Not available

5.2.4.17. EU-EC-10505197, US-009507513-1406USA006221

litigation case - 32M was prescribed and began consuming finasteride (PROPECIA) (dose, duration and indication not reported). While consuming finasteride (PROPECIA), he began to suffer and was diagnosed with erectile dysfunction and related sexual dysfunction. To date, the patient continues to suffer from the adverse side effects noted above. Information has been received from a lawyer and a 36 year old male regarding a case in litigation. On 20FEB07, the patient (pt) was started on finasteride (PROPECIA) 1mg for hair loss (onset 2005/diagnosis 20FEB07.) Therapy with finasteride (PROPECIA) was discontinued on 01SEP12. Pt also underwent hair transplant surgery for hair loss. It was reported the patient experienced erectile dysfunction and loss of sex drive as a result of taking finasteride (PROPECIA). His symptoms began in NOV2011 and he was diagnosed 31JAN12. The patient reported having discussion with his physician regarding whether his injury was related to use of finasteride (PROPECIA). He does not recall what he was told. Medical history included: injury to L knee (with L knee surgery on 21DEC04; granted worker's compensation disability 21DEC04 to 03JAN15). The patient did not smoke or consume alcohol. Before his injury pt was treated with unspecified antidepressants (from APR2011 to present) and with blood pressure (hypertension) lowering medication (dates not provided). The patient also reported depression, anxiety and insomnia as a result of taking finasteride (PROPECIA). Symptoms occurred in FEB2011 and were diagnosed in APR2011. He was treated by a physician and a psychiatrist with bupropion hydrochloride (WELLBUTRIN), alprazolam (XANAX) and escitalopram oxalate (LEXAPRO) from APR2011 to present. He is still experiencing the injury. The patient did not participate in any clinical trials. Information has been received from medical records concerning a 33 year old male (previously reported as 36) who did not smoke with a family history of diabetes mellitus, cerebrovascular accident and hypertension (father). 13FEB07: Pt discussed hair replacement grafts to the front/top, but wanted to wait until after his wedding in MAY07. Finasteride (PROPECIA) was discussed. On 20FEB07 OV pt seen for loss of hair for past several years. There were other family members that have alopecia. On 29MAY07 OV follow-up. The patient was taking finasteride (PROPECIA) 1 mg daily and so far there were no side effects with improved hair growth. He has prominent hair loss from sides and the top of his head. There was obvious hair growth since last visit. Finasteride (PROPECIA) was prescribed 1 mg, one tablet daily. On 16OCT2007 OV the patient was taking finasteride (PROPECIA) daily. So far there were no side effects

and the patient reported improved hair growth. The physician reviewed drug side effects with the patient. The patient was prescribed finasteride (PROPECIA) 1 mg tablets, one per day. Blood work was ordered which included CBC, complete metabolic profile, TSH, urinalysis (no results reported). He was to return to office in 4 months. 10APR09 OV the patient taking finasteride (PROPECIA) and so far there were no side effects. He reported improved hair growth. Labs were ordered which included TSH, lipid panel comprehensive metabolic profile, urinalysis, PSA, 25 OH vitamin D, total free testosterone (no results reported). The patient was to return to office in 3 months. A refill for finasteride (PROPECIA) 1 mg tablets, one per day was given. On 17DEC09 pt had pain in the testicles which started the previous Sunday. It developed abruptly and the pain was constant. He denied penile drainage. He had no prior history of such a problem. There was no evidence of testicular swelling or scrotal swelling. Inguinal areas were unremarkable bilaterally. Diagnosis: orchitis and epididymitis. The patient continued his finasteride (PROPECIA) 1mg tablet daily. He also had an unspecified vitamin deficiency. Labs were ordered: CBC, TSH, lipid panel, Comprehensive metabolic profile, 25 OH vitamin D. Ultrasound of testicles and scrotum was ordered (no results reported). 17FEB10: Pre-op checklist for hair transplantation indicated pt was taking finasteride (PROPECIA). He underwent hair replacement grafting. MR dated 31JAN2012, O.V. The pt reported that escitalopram (LEXAPRO) caused his sex drive to go down. It was noted that the pt. was taking finasteride (PROPECIA), 1 mg tablet, once daily, at the time of this visit. Assessment: decreased libido. Escitalopram (LEXAPRO) was discontinued. The pt's testosterone level on his last blood work was noted to be fine. MR dated 13JUN2012, O.V., It was noted that the pt. was taking finasteride (PROPECIA), 1 mg tablet, once daily, at the time of this visit. The pt. c/o decreased libido. A recheck of his testosterone level was ordered (result not provided). MR dated 13AUG2012, noted the pt. was taking tadalafil (CIALIS) but erectile dysfunction (ED) was still an issue. It was noted that the pt was taking finasteride (PROPECIA) 1mg tablet daily at the time of this visit. He was given a prescription for testosterone gel (TESTIM TRANSDERMAL GEL). The pt. was instructed to discontinue using finasteride (PROPECIA). 14OCT12 the pt was seen by a physician (phy) for a psychotherapy evaluation. The pt presented with symptoms of depression, anxiety, inattentive/impulsivity, difficulties sleeping, difficulties eating, always feeling nervous and/or shaky/sweaty, impulsive decision making, lacking a filter, hyperactivity, difficulties motivating self, and lack of concentration/focus. The pt cries frequently and has been dealing with grief and loss for several years. The pt.'s diagnoses included general anxiety disorder, major depression and attention deficit/hyperactivity disorder. The phy recommended unspecified medication and cognitive therapy every 2 weeks for 6 months duration. MR dated 05MAR2013 a formal Health Record included the pt.'s medication list which noted that on an unspecified date the pt. began treatment with finasteride (PROPECIA), 1 mg tablet, one tablet daily. Finasteride (PROPECIA) was noted to have been inactivated on 03FEB2012 (previously reported in the pt.'s fact sheet as discontinued on 01SEP2012). Pharmacy records received on 31-MAR-2016 indicated that prescriptions for finasteride (PROPECIA-MSD) 1 mg tablets, were dispensed regularly from 20-FEB-2007 to 04-AUG-2012. Information from medical records contained the following adverse experiences: migraine unspecified, osteoarthrosis leg (29-MAY-2007; obesity (16-OCT-2007); diarrhea (29-NOV-2008), acute conjunctivitis (appr 06-MAR-2009), changes in skin texture (10APR09); contact dermatitis, unspecified pruritic disorder (11JUL14); other specified diseases of hair and hair follicles (17DEC09); acute sinusitis, headache (12JAN10); gallbladder removal (NOV2011); contact with or exposure to venereal disease (09JAN2014); carpal tunnel syndrome, pain in joint involving hand (01AUG2014); Lyme disease, plantar fascial fibromatosis (31OCT2014); tachycardia (13JUN2012); essential hypertension (05MAR2013), elevated TG (triglycerides)/pure hyperglyceridemia (13AUG2012); nonspecific abnormal results of function study of liver (31JAN2012); agoraphobia with panic disorder (03OCT2011); palpitations, not feeling well (31AUG2011); rash on back of neck (17DEC2009); hypertension (no date provided, unclear if before

or after initiating finasteride (PROPECIA) therapy). Upon internal review, gallbladder removal was determined to be another important medical event

5.2.4.18. EU-EC-10954142, NL-LRB-222871

38F experienced libido decreased following administration of citalopram for depression with a latency of 2 weeks after start. The drug citalopram was withdrawn after 6 months. The patient has not recovered 2 years after withdrawal. Concomitant medication was sumatriptan. The patient has no known medical history. The patient has no known past drug therapy. NARRATIVEINCLUDECLINICAL: Is of zijn de bijwerking(en) behandeld? Nee Heeft de patient het geneesmiddel dat de bijwerking(en) veroorzaakt al eerder gebruikt? Nee Zijn er mogelijk andere oorzaken of omstandigheden die de bijwerking(en) kunnen hebben veroorzaakt of verergerd? Nee Extra informatie: ik heb 6 maanden Citalopram geslikt vanaf oktober 2013. Ik ben gestopt in maart 2014. Mijn libido is nog steeds niet hersteld. Mogelijke wisselwerking met andere geneesmiddelen? Nee Gebruikt de patient nog andere geneesmiddelen: ja REMARKS: Reporter Comments- Melding PG20160721075359 is afkomstig van www.lareb.nl meldformulier Sender Comments- 27-7-2016 assessor Lareb: Due to incompatibility between latency period and data, the latency period was corrected to 2 weeks by the Netherlands Pharmacovigilance Centre Lareb (based upon reporter's narrative).

5.2.4.19. EU-EC-12483005, GB-MHRA-EYC 00156197

24M was prescribed fluoxetine hydrochloride 9 years ago for anxiety and depression. I remember taking it for exactly 4 days at the standard dose of 20mg per day before stopping the drug. I stopped the drug because I had an extreme reaction to it, which left me with total sexual dysfunction. By sexual dysfunction, I mean total loss of sexual pleasure including total absence of pleasure at ejaculation (anorgasmia), much weakened erection, and a muted response to touch. It also gave me anhedonia, in that I cannot derive pleasure though smell and taste. It also strongly affected my sleep and being able to dream or deep sleep is a near impossibility as a result of this drug. This was 9 years ago and I am still experiencing these same symptoms with no improvement. Over the years I have visited many psychologists and psychiatrists. I was given 2 responses; that my sexual dysfunction and anhedonia is a result of my existing depression, so they decide to prescribe me another antidepressant. Secondly, no side effect from a drug can possibly last that number of years. I have to say I had perfect sexual functioning in all 4 phases of the sexual response when I was diagnosed with depression before I took fluoxetine. It was only until after I took the drug that I experienced sexual dysfunction. The side effect hit me like a truck, it wasn't a gradual response - the side effect came on so strongly it was like day and night. And yes the side effect never went away years after stopping the drug. I still have a muted response to sexual stimuli and anorgasmia. This is an extremely serious condition that I cannot believe the medical community is turning a blind eye to or passing it off as a "symptom of depression". It may not be common because not everyone who takes antidepressants will end up with post selective serotonin reuptake inhibitor (SSRI) sexual dysfunction, but this should not be ignored as it is a very debilitating condition that has and continues to adversely affect my quality of life and many other people too. FU received: I may have already touched upon this in my detailed report to you about Post selective serotonin reuptake inhibitors (SSRI) Sexual Dysfunction, but just in case I have not, ever since taking fluoxetine I have had extreme genital numbness, almost like local anaesthetic grade numbness that have persisted for over 9 years since cessation of the drug. I did not experience this before I took the drug, even at the height of my depression. Within a few days of the taking It is very noticeable. A totally muted response to touch. Please who ever is investigating the sexual side effects of SSRI, treat this with utmost seriousness. This is absolutely NOT a symptom of

depression. Every time I visit a psychiatrist or a psychologist, that is the typical narrow minded response they use. The other reason is the "side effects cant last that long". PSSD must absolutely be brought to awareness and accepted by the mainstream medical community. Being told this is just depression, is like being accused of a crime I did not commit. The amount of injustice and suffering this drug has caused me is indescribable.

5.2.4.20. EU-EC-10000183356, NL-LRB-00251535

33M - experienced libido decreased and erectile dysfunction, following administration of paroxetine tablet 20mg for depression with a latency of 7 days after end, although these adverse effects started to a lesser extent during the use of paroxetin, and aggravated after stop of this drug. The patient did not recover in 29 months after drug withdrawal. The patient has no medical history. The patient has no past drug therapy. Post-SSRI-sexual disfunction was diagnosed by a physician. The patient mentioned that he had no depression anymore, nor thyroid problems, diabetes or hormonal deviations.

5.2.4.21. EU-EC-10000980365, NL-LRB-00272985

25F experienced restless genital syndrome (tingling, paraesthesia) following administration of sertraline for anxiety with a latency of 1 day after start. The drug was withdrawn after 10 days and the patient is not recovered 5 months later. The patient mentions she experiences the reaction continuously and the intensity varies. It starts with tingling and changes to throbbing pain in the afternoon. She experiences the most intense pain in the evening but it does not wake her up at night. The patient is being treated by a urologist, a gynaecologist and a pelvic floor physiotherapist for relaxation of the pelvic floor muscles. She also visited an outpatient pain clinic and is treated with pregabalin. She has been treated with clonazepam which was withdrawn because she did not want to be treated with a benzodiazepine. The patient has tried acupuncture and hypnotherapy, both without effect. The patient does not have restless leg syndrome. She does have an overactive bladder which is treated with mirabegron. However, during treatment with sertraline she did not use other medication. The patient has no medical history. The patient has no past drug therapy.

5.2.4.22. EU-EC-10001089414, GB-MHRA-EYC 00171226

42M experienced sexual dysfunction (impotence) whilst on treatment. Following discontinuation continued difficulty maintaining erections, plus onset of premature ejaculation. Follow up - no previous history of premature ejaculation, symptoms still present (12 months following cessation of SSRI treatment).

5.2.4.23. EU-EC-10001472865, GB-MHRA-EYC 00178088

24F started taking Seroxat (paroxetine) last year and stopped in the same year. In the 6 months since stopping it I still haven't recovered sensation of my clitoris. After reading online it sounds like post selective serotonin reuptake inhibitors (SSRI) sexual dysfunction can last for years or may be permanent.This side effect even after stopping the medicine wasn't made clear on the leaflet in the box. My general practitioner (GP) didn't mention it. If it doesn't get better, I will likely go to my GP. I need to stress firstly that it's been 7 months since I've stopped taking Seroxat and I'm still suffering from the sexual side effects. The last month I've had small improvements, but clitoral sensitivity is nowhere near to what it was before I started taking the medication, and orgasms are muted and pleasureless. I have never suffered from any sexual dysfunction before I started taking Seroxat. Everything physically worked how it should. There was no warning on the Seroxat leaflet, nor was I

told by my general practitioner, that these affects could carry on long after stopping the medication. I had a 'brain zap' the other night when trying to sleep. They are well documented when withdrawing from Seroxat. I believe it is something to do with the way the brain reacts to the change with the medication and I had not had any since the first two weeks I stopped taking it. I am not sure if something is changing again in my brain recently and if it has anything to do with sexual side effects starting to get better but I thought it was worth a mention.

5.2.4.24. EU-EC-10001579371, GB-MHRA-EYC 00166119

46F had medical history included polycystic ovarian syndrome, anxiety, fatigue and panic attack (brutal panic attacks for over 1 year following traumatic event). Past drugs included propolis, amorolfine for fungal infection of nail, diphenhydramine hydrochloride (Nytol) for difficulty sleeping and antihistamines. The patient has stopped her antihistamines after a mild anaphylactic reaction to her propolis throat spray. Concomitant medications included cetirizine hydrochloride and bach rescue remedy night. On 07-Aug-2017, the patient commenced therapy with oral citalopram hydrobromide at a dose of 10 mg as needed (form: not reported) for difficulty sleeping. On 02-Sep-2017, 26 days after starting citalopram hydrobromide, the patient experienced eating disorder. On 04-Sep-2017 (latency 28 days), after un-tapered cessation of medicine citalopram hydrobromide, she had restlessness, nausea, vomiting, shakiness and clenching already sore jaw tighter and tighter. On 05-Sep-2017 (latency 29 days), she had genital numbness, agitation, needed to keep moving and increased urination and slept for 16 hours straight. On 06-Sep-2017 (latency 30 days), she had intense unfocused rage (atypical), conscious smell of testosterone on her arms and hands (digestive biscuit odour), testosterone rushes, gastrointestinal, diahorrea and burning heat from pudendum. On 07-Sep-2017 (latency 31 days), patient had excessive vaginal lubrication, unconnected to any stimuli, or desire, burning numbness on left hand side of genitalia, quivering sensation all over and cramp in calf muscles and hands. On 08-Sep-2017 (latency 32 days), considerable pain from left crus/ leg and dorsalis of clitoris, she had to brace and pull hard with both hands to remove tampon, could not insert another (leg pain and vulvovaginal pain). On 09-Sep-2017 (latency 33 days), panic attack triggered spontaneous ejaculatory orgasm, vomited bile, extreme, painful genital arousal and spontaneous clitoral-vaginal orgasms every 6-10 seconds for 10 hours, until she fall asleep (panic attack and female orgasmic disorder). On 10-Sep-2017 (latency 34 days), the patient woke up mid St. Vitus dance (abnormal involuntary movements), her clothes literally dripping wet from nocturnal genital emissions, white tongue, genital pain spontaneous orgasms, heat lubrication and relentless sexual/genital frustration. On 11-Sep-2017 (latency 35 days), her clitoral glans was numb, dorsalis swollen and spasming (vaginal spasm genital swelling exhaustion), endless orgasming seeming to actively increase urgency of frustration. She was exhausted and tearful. She Felt like CRO (cathode) experiment all over and was scared. On 12-Sep-2017 (latency 36 days), she was mental anguish and self-disgust, had negative thoughts, could not leave house as too out of control, her body was still betraying her (self-hatred). On 13-Sep-2017 (latency 37 days), her thoracic diaphragm cramping painfully, she had tried DT massage and acupressure on dorsalis - inducing dysentery-like cramps up to said diaphragm. On 14-Sep-2017 (latency 38 days), her jaw mishitting hard- bleeding gums, legs dancing, sleepwalking, including eating and bizarre online research (abnormal behaviour). On 15-Sep-2017 (latency 39 days), evidently she had been shouting and screaming at noisy neighbours in choice Italian, whilst sleepwalking. Clitoran glans has joined the party. On 16-Sep-2017, she had break from orgasming, painfully aroused, she was weak and despondent. There was noticeable smell of condensed urea. She was in anger and had vertigo and headache (onset date: 16-Sep-2017 and latency: 40 days). On 17-Sep-2017 (latency: 41 days), the patient had heavy uterine pain and pressure; she had tremors all over and pain in joint cavity of knees. Any slight tension in the diaphragm was setting off painful

waves of orgasm and burning pain in genitals and anus. On 28-Sep-2017 (latency 52 days), she was sweating profusely, forearms smell strongly of vanilla, eyes mildly yellow, labia swollen and red, shaking visibly with chattering teeth and cramp in arms and hands. She suspected that this would not be happening had the medicine been tapered off. The reason for her stopping said treatment was documented in her previous yellow card (tinnitus, bruxism, jaw blenching, tension across upper back, clicking at bas of skull and surrounds) and she felt it would be of benefit to look at these in tandem. Her system was already in shock, before she unwisely took these tablets and she was still experiencing panic attacks. The threat was still there, and her personal circumstance was rapidly deteriorating in front of her eyes. She did not want this medication and stated so three times, giving from her PoV valid reasons. She allowed herself to be steamrollered under a chemical cosh as she was so utterly desperate for sleep. The tablets flattened her out somewhat and did, in all honesty give her some relief as she was more relaxed. She did not however get sleep. On unknown date the patient also had breast pain female (latency: unknown). Reportedly, the patient has been unable to eat since sleep-eating redskin peanuts, notwithstanding. The patient was drinking miso broth with various pre and pro biotic foodstuffs and chia pureed in and drinking lots of Switchel for electrolytes and green and white teas for antioxidants was drinking excessive amounts of water. She was trying to stay sane by meditating (40 year practice) and using breathing techniques (introduced to swimming in infancy and swam daily through to her teenage years, so find calm in shallow upper lung breathing, and actively relax when spending extended periods in a mental simulation of a non-breathing underwater state). The patient was going to receive paracetamol tonight (10-Oct-2017). Action taken: Permanently discontinued on 03-Sep-2017 Corrective treatment: citalopram for panic attack and anguish; lot of ice and cold packs, topical ibuprofen gel for uterine pain, vulvovaginal pain and breast pain female; not reported for others Outcome: Not applicable for 'drug dose titration not performed'; unknown for breast pain female; not recovered for rest of the events. Seriousness criteria: Disability for all the events 'This suspected adverse reaction report is submitted and classified as a medication error solely and exclusively to ensure the marketing authorization holder's compliance with the requirements set out in Directive 2001/83/EC and Module VI of the Good Pharmacovigilance Practices. The classification as a medical error is in no way intended, nor should it be interpreted or construed as an allegation or claim made by the marketing authorization holder that any third party has contributed to or is to be held liable for the occurrence of this medication error.

5.2.4.25. EU-EC-10001821310, ES-GLAXOSMITHKLINE-ES2018GSK121213

60M received paroxetine hydrochloride (Motivan) film-coated tablet 20 mg once daily (20 mg daily) on an unknown date. An unknown time after starting Motivan, the patient experienced impotence, libido decreased, erection inadequate and male genital atrophy. Motivan was continued with no change. On an unknown date, the outcome of the impotence, libido decreased, erection inadequate and male genital atrophy were not recovered/not resolved. It was unknown if the reporter considered the impotence, libido decreased, erection inadequate and male genital atrophy to be related to Motivan. The patient was under treatment with Motivan for one year and took one tablet each morning. 2 or 3 weeks after he had started taking Motivan he felt a reduction in sexual desire and when he achieved it, the resulting erection was insufficient and strange which prevented him from engaging in sexual relations for the entire duration of the treatment. 4 months after finishing treatment with Motivan, the events reappeared. The patient described them as sexual inappetence and penile atrophy, they had not disappeared but had been maintained without any decrease. The patient stated that the adverse events converted into a sequelae and he became impotent. Follow up was received on 10 Jul 2018, This case was reported for paroxetine hydrochloride (Motivan) film-coated tablet for anxiety disorder. Previously administered products included Fluvoxamine. Concurrent medical conditions included

agoraphobia. Concomitant products included olanzapine, amitriptyline hydrochloride + medazepam (Nobritol) and clonazepam (Rivotril). On 12th August 2016, the patient started Motivan 20 mg once daily (20 mg daily). On an unknown date, an unknown time after starting Motivan, the patient experienced impotence, libido decreased, erection inadequate and male genital atrophy. Motivan was continued with no change. On an unknown date, the outcome of the impotence and erection inadequate were not reported and the outcome of the libido decreased and male genital atrophy were not recovered/not resolved. The reporter considered the impotence, libido decreased, erection inadequate and male genital atrophy to be related to Motivan. The patient was taking treatment for anxiety disorder which consisted of 1 capsule of Norbital, 1 Tablet of Olanzapine of 2.5 mg and a quarter tablet of Rivotril before going to bed. 1 tablet of Motivan 20 mg during breakfast. 7 months after finishing the anxiety treatment, the adverse events were still present, permanently without intermittence (lack of sexual desire and penile atrophy), same as during the treatment period. No other medication was taken by the patient during treatment, not even paracetamol. No medicinal plants were taken either except Tilia and chamomile. No dietary supplements were taken either. Alcoholic beverages were not taken either. Before starting the treatment, the patient took 1 daily tablet of Fluvoxamine 100 mg as treatment for agoraphobia, which he had suspended whilst he was under treatment for the anxiety disorder. After finishing the anxiety treatment he had returned to taking Fluvoxamine. The patient stated that he had never noted any sexual dysfunction, no symptoms similar to those presented with paroxetine while under treatment with Fluvoxamine and he stated that he had taken Fluvoxamine for years. The patient believes that Paroxetine is still doing its effect even 7 months after ceasing treatment and the adverse event has become a sequelae maybe a permanent one.

5.2.4.26. EU-EC-10002574731, SE-MPA-2018-007058

32M - 2018-007058 (0.0) Rapport från en konsument angående en 32-årig man. Rapporterat misstänkt läkemedel var Sertraline Accord (sertraline) som gavs för depression sedan mitten av mars. Rapporterad misstänkt biverkning är förlorad sexdrift. Konsumenten märkte fördröjd utlösning ganska tidigt efter påbörjad behandling. Efter några veckor fick han svårare att behålla erektionen och senare blev det svårare att uppnå erektion. Han får inte morgonstånd längre. Sertraline Accord sattes ut i mitten av juni. Förlopp: Ännu ej tillfrisknat. Fallet bedömt som allvarligt, bestående funktionsnedsättning. Reporter Comments- Not available Sender Comments- Not available. 32M received Sertraline Accord (sertraline) given for depression since mid-March. Reported suspected side effect is lost sex drive. The consumer noticed delayed ejaculation quite early after treatment started. After a few weeks he was more difficult to maintain the erection and later it became more difficult to achieve an erection. He doesn't get morning stays anymore. Sertraline Accord was released in mid-June. Procedures: Not yet recovered. The case assessed as serious, permanent disability.

5.2.4.27. EU-EC-10002754976, SE-MPA-2018-007717

36F - 2018-007717 (0.0) Rapport från en konsument angående en 36-årig kvinna. Rapporterat misstänkt läkemedel var escitalopram för nedstämdhet, vilket kvinnan tog under 10 år. Cirka en vecka efter utsättningen av escitalopram drabbades kvinnan av genital upphetsning utan koppling till sexuell lust (PGAD). "Upphetsande känslor i genitalierna, svullna genitalier, smärta i magen (känns som livmodern), överaktiv blåsa." Kvinnan återinsattes på escitalopram. Förlopp: Ännu ej tillfrisknat. Fallet bedömt som allvarligt, viktig medicinsk händelse. Reporter Comments- Not available Sender Comments- Not available. 36F received escitalopram for depression, which the woman took for 10 years. About 1 week after the release of escitalopram, the woman was affected by genital arousal

without a link to sexual desire (PGAD). "Excitatory feelings in the genitals, swollen genitals, pain in the stomach (feels like the uterus), overactive bladder." The woman was re-inserted into escitalopram. Procedures: Not yet recovered. The case assessed as serious, important medical event.

Annex I – List of active substances

- Citalopram
- Citalopram oxalate
- Escitalopram
- Fluoxetine
- Fluoxetine hydrochloride, phentermine hydrochloride
- Fluoxetine, olanzapine
- Fluvoxamine
- Paroxetine
- Paroxetine acetate
- Sertraline
- Desvenlafaxine
- Venlafaxine
- Duloxetine
- Milnacipran
- Clomipramine
- Vortioxetine

Annex II – Endpoints

Endpoint	**MedDRA** codes for the case definition
Primary endpoint	
Post-SSRI sexual dysfunctions (PSSD) (narrow definition)	Preferred terms • Genital hypoaesthesia • Loss of libido • Libido decreased • Female sexual arousal disorder • Anorgasmia • Female orgasmic disorder • Male orgasmic disorder • Orgasm abnormal • Orgasmic sensation decreased • Premature ejaculation • Ejaculation delayed • Ejaculation failure • Vulvovaginal dryness Lowest level terms • Nipple hypoaesthesia • Nipple hypoesthesia
Post-SSRI sexual dysfunction (PSSD) (extended definition)	All terms from PSSD plus: Any remaining terms from preferred terms under HLTs: • Orgasmic disorders and disturbances • Paraphilias and paraphilic disorders • Sexual and gender identity disorders NEC • Sexual arousal disorders • Sexual desire disorders • Erection and ejaculation conditions and disorders • Sexual function and fertility disorders NEC
Secondary endpoints	
Persistent genital arousal disorder (PGAD)	Preferred terms • Persistent genital arousal disorder

Annex III – Text mining of the narratives in the line listing of reports

Table 1: Text mining steps

Preparation of narratives	•	Removed all residual html tags (e.g.) • Transformed multiple whitespace in single space • Changed case to lower case
Patterns to match	•	persis; chroni; ongoin; prolong
Regular expression	•	[^.]*(persis|chroni|ongoin|prolong)\w+[^.]*
Selection of true cases of persistence	•	Manual review of the individual sentences extracted

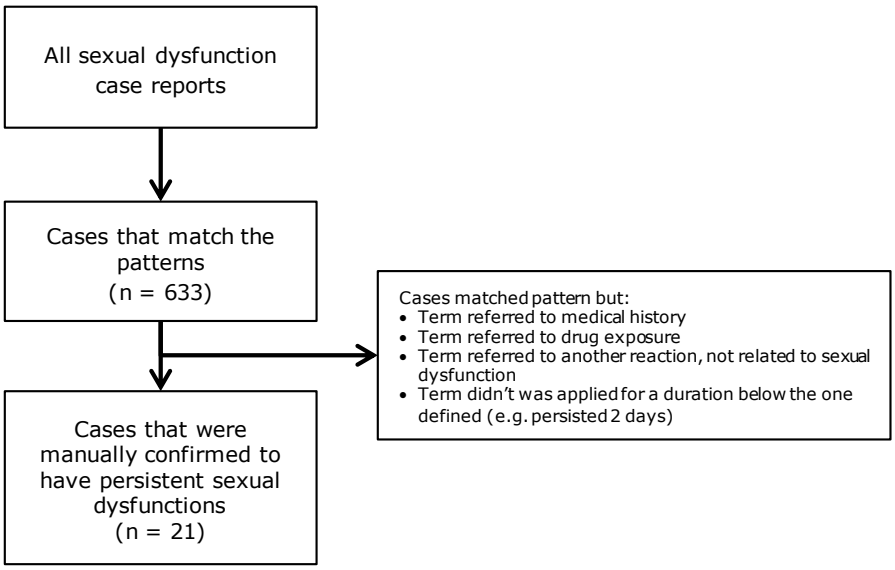


Figure 1: Text mining results

Annex IV - Case reports by medicinal product

Fluoxetine case counts

PT	Counts
Anorgasmia	38
Disturbance in sexual arousal	10
Ejaculation delayed	7
Ejaculation disorder	17
Ejaculation failure	7
Erectile dysfunction	86
Erection increased	2
Excessive masturbation	1
Exhibitionism	2
Female orgasmic disorder	6
Female sexual arousal disorder	4
Female sexual dysfunction	1
Genital hypoaesthesia	10
Hypersexuality	12
Hypoaesthesia	104
Infertility female	1
Libido decreased	75
Libido disorder	2
Libido increased	14
Loss of libido	36
Male orgasmic disorder	2
Male sexual dysfunction	3
Organic erectile dysfunction	1
Orgasm abnormal	8
Orgasmic sensation decreased	5
Painful erection	2
Paraphilia	1
Premature ejaculation	2
Priapism	25
Retrograde ejaculation	2
Sexual dysfunction	100
Spontaneous penile erection	2
Vulvovaginal dryness	3

Citalopram case counts

PT	Counts
Anorgasmia	71
Disturbance in sexual arousal	22
Dyspareunia	1
Ejaculation delayed	13
Ejaculation disorder	31
Ejaculation failure	8
Erectile dysfunction	138
Erection increased	4
Female orgasmic disorder	17
Female sexual arousal disorder	2
Female sexual dysfunction	16
Gender dysphoria	1
Genital hypoaesthesia	11
Hypersexuality	3
Hypoaesthesia	113
Infertility	5
Infertility male	1
Libido decreased	98
Libido disorder	3
Libido increased	8
Loss of libido	67
Male orgasmic disorder	5
Male sexual dysfunction	32
Nocturnal emission	4
Organic erectile dysfunction	1
Orgasm abnormal	15
Orgasmic sensation decreased	9
Painful erection	3
Persistent genital arousal disorder	2
Premature ejaculation	6
Priapism	35
Psychosexual disorder	5
Retrograde ejaculation	1
Sexual dysfunction	99
Sexual inhibition	4
Spontaneous penile erection	4
Vulvovaginal dryness	4

Duloxetine case counts

PT	Counts
Anorgasmia	34

Compulsive sexual behaviour	1
Disturbance in sexual arousal	12
Dyspareunia	2
Ejaculation delayed	9
Ejaculation disorder	15
Ejaculation failure	4
Erectile dysfunction	102
Erection increased	2
Female orgasmic disorder	2
Female sexual arousal disorder	2
Female sexual dysfunction	1
Gender dysphoria	1
Genital hypoaesthesia	2
Hypersexuality	5
Hypoaesthesia	468
Infertility	1
Infertility female	2
Infertility male	3
Libido decreased	126
Libido disorder	9
Libido increased	17
Loss of libido	58
Male orgasmic disorder	2
Male sexual dysfunction	2
Orgasm abnormal	16
Orgasmic sensation decreased	1
Painful ejaculation	2
Painful erection	3
Premature ejaculation	1
Priapism	15
Retrograde ejaculation	5
Sexual dysfunction	104
Spontaneous ejaculation	1
Vulvovaginal dryness	2

Fluovoxamine case counts

PT	Counts
Anorgasmia	4
Disturbance in sexual arousal	2
Ejaculation delayed	2
Ejaculation disorder	4
Ejaculation failure	1
Erectile dysfunction	8
Hypoaesthesia	54
Libido decreased	7

Libido increased	7
Loss of libido	7
Male orgasmic disorder	1
Priapism	15
Sexual dysfunction	9

Sertraline case counts

PT	Counts
Anorgasmia	65
Compulsive sexual behaviour	3
Disturbance in sexual arousal	23
Dyspareunia	3
Ejaculation delayed	28
Ejaculation disorder	26
Ejaculation failure	22
Erectile dysfunction	152
Erection increased	9
Excessive masturbation	1
Excessive sexual fantasies	1
Female orgasmic disorder	12
Female sexual arousal disorder	1
Female sexual dysfunction	11
Gender dysphoria	2
Genital hypoaesthesia	13
Hypersexuality	10
Hypoaesthesia	247
Infertility	8
Infertility female	3
Infertility male	3
Libido decreased	142
Libido disorder	3
Libido increased	15
Loss of libido	88
Male orgasmic disorder	15
Male sexual dysfunction	17
Organic erectile dysfunction	1
Orgasm abnormal	15
Orgasmic sensation decreased	9
Painful erection	5
Persistent genital arousal disorder	3
Premature ejaculation	7
Priapism	74
Retrograde ejaculation	1
Sexual dysfunction	126
Sexual inhibition	2

Spontaneous ejaculation	1
Spontaneous penile erection	4
Vulvovaginal dryness	11

Clomipramine case counts

PT	Counts
Anorgasmia	9
Disturbance in sexual arousal	2
Ejaculation delayed	2
Ejaculation disorder	13
Ejaculation failure	1
Erectile dysfunction	28
Female sexual arousal disorder	1
Hypoaesthesia	33
Infertility male	1
Libido decreased	9
Libido disorder	1
Libido increased	1
Loss of libido	6
Male orgasmic disorder	1
Orgasm abnormal	2
Premature ejaculation	2
Priapism	2
Sexual dysfunction	15

Escitalopram case counts

PT	Counts
Anorgasmia	29
Compulsive sexual behaviour	2
Disturbance in sexual arousal	23
Ejaculation delayed	19
Ejaculation disorder	28
Ejaculation failure	13
Erectile dysfunction	129
Erection increased	7
Female orgasmic disorder	15
Female sexual arousal disorder	6
Female sexual dysfunction	3
Genital hypoaesthesia	6
Hypersexuality	6
Hypoaesthesia	160
Infertility	3
Infertility female	1

Infertility male	3
Libido decreased	110
Libido disorder	4
Libido increased	10
Loss of libido	66
Male orgasmic disorder	5
Male sexual dysfunction	40
Organic erectile dysfunction	1
Orgasm abnormal	14
Orgasmic sensation decreased	2
Painful ejaculation	1
Painful erection	10
Persistent genital arousal disorder	1
Premature ejaculation	6
Priapism	35
Psychosexual disorder	2
Retrograde ejaculation	1
Sexual dysfunction	137
Sexual inhibition	1
Spontaneous penile erection	9

Venlafaxine case counts

PT	Counts
Anorgasmia	78
Compulsive sexual behaviour	3
Disturbance in sexual arousal	13
Dyspareunia	4
Ejaculation delayed	10
Ejaculation disorder	50
Ejaculation failure	6
Erectile dysfunction	166
Erection increased	2
Exhibitionism	1
Female orgasmic disorder	5
Female sexual arousal disorder	1
Female sexual dysfunction	3
Gender dysphoria	1
Genital hypoaesthesia	8
Hypersexuality	6
Hypoaesthesia	277
Infertility	4
Infertility female	4
Infertility male	4
Libido decreased	148
Libido disorder	4

Libido increased	18
Loss of libido	102
Male orgasmic disorder	17
Male sexual dysfunction	13
Organic erectile dysfunction	1
Orgasm abnormal	15
Orgasmic sensation decreased	5
Paedophilia	1
Painful ejaculation	6
Painful erection	1
Paraphilia	2
Premature ejaculation	6
Priapism	25
Psychogenic erectile dysfunction	1
Psychosexual disorder	2
Retrograde ejaculation	2
Sexual dysfunction	125
Sexual inhibition	3
Spontaneous ejaculation	6
Vulvovaginal dryness	4

Desvenlafaxine case counts

PT	Counts
Anorgasmia	3
Disturbance in sexual arousal	2
Ejaculation delayed	2
Ejaculation disorder	1
Erectile dysfunction	8
Excessive sexual fantasies	1
Hypoaesthesia	54
Infertility	2
Libido decreased	20
Libido increased	4
Loss of libido	2
Male sexual dysfunction	5
Orgasm abnormal	5
Painful ejaculation	1
Paraphilia	1
Priapism	2
Sexual dysfunction	11
Vulvovaginal dryness	3

Paroxetine case counts

PT	Counts
Anorgasmia	50
Compulsive sexual behaviour	5
Disturbance in sexual arousal	31
Dyspareunia	2
Ejaculation delayed	41
Ejaculation disorder	45
Ejaculation failure	40
Erectile dysfunction	158
Erection increased	5
Excessive masturbation	1
Excessive sexual fantasies	1
Exhibitionism	1
Female orgasmic disorder	6
Female sexual arousal disorder	3
Female sexual dysfunction	10
Genital hypoaesthesia	4
Hypersexuality	4
Hypoaesthesia	286
Infertility	7
Infertility male	9
Libido decreased	227
Libido disorder	7
Libido increased	30
Loss of libido	108
Male orgasmic disorder	3
Male sexual dysfunction	6
Organic erectile dysfunction	3
Orgasm abnormal	12
Orgasmic sensation decreased	4
Painful erection	2
Premature ejaculation	2
Priapism	48
Psychosexual disorder	1
Retrograde ejaculation	3
Sexual dysfunction	141
Sexual inhibition	4
Transvestism	1
Vulvovaginal dryness	2

Vortioxetine case counts

PT	Counts
Anorgasmia	8
Disturbance in sexual arousal	2
Ejaculation delayed	1
Ejaculation disorder	1
Erectile dysfunction	11
Female orgasmic disorder	2
Hypoaesthesia	19
Libido decreased	26
Libido disorder	1
Loss of libido	9
Male sexual dysfunction	2
Orgasm abnormal	6
Priapism	2
Sexual dysfunction	23
Vulvovaginal dryness	1

Appendix – Description of cases received between data-lock point and 20 February 2019

Forty-eight additional case reports have been submitted to EV. Of these, 43 have missing information and one seems to be a duplicate and thus these are unevaluable.

In one case report, the sexual dysfunction occurred concurrently with aggravation of depression whereas another case seems related to withdrawal symptoms. Both these cases suggest a psychopathological cause for the sexual dysfunction.

One is a report of a study and not a case review. Finally, there is one case, minimally described where PSSD was said to be present after more than 3 or 4 years, however the nature of PSSD was not detailed and the MedDRA code selected was merely "sexual dysfunction".