Sexual adverse drug reactions: patient impact and potential for pharmaceutical care

Gordijn, C.M.

Chapter 5

Patient reporting of sexual adverse events on an online platform for medication experiences

R. Gordijn, W. Wessels, E. Kriek, M.P.J. Nicolai, H.W. Elzevier, L. Visser, H.J. Guchelaar, M. Teichert

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Abstract

Aims

For >300 drugs, sexual side effects are included in the drug information leaflet. As sexual adverse events (sAEs) may be more easily shared at online medication platforms, patient-reported drug experiences may add to the current knowledge on sAE experiences. This study evaluated patient reports from the online platform mijnmedicijn.nl for the frequency of sAE reporting, gender differences concerning sAEs and to assess drugs with disproportional sAE reporting.

Methods

On the online platform, terms for sAE as used by patients were collected with a poll. Subsequently, drug reports posted between 2008 and 2020 were searched for sAE with the identified terms. From the retrieved reports, the sAE frequencies and complaints and Reporting Odds Ratios (ROR) were calculated, stratified for gender and drug (class). sAE reporting was considered disproportional frequent if the lower 95% confidence interval bound of the ROR >2.0.

Results

For 189 drugs, sAE were identified in 2408 reports (3.9%). Women posted 1383 reports (3.5% of all female reports) and men 1025 (4.7%). Almost half of the sAE reports addressed antidepressants: 586 reports of women (ROR 4.2; 95% CI 3.8–4.7) and 510 reports of men (ROR 7.5; 95% CI 6.6–8.5). Disproportional high numbers of sAE reports were found for 27 drugs, mostly antidepressants, hormonal contraceptives and drugs used in benign prostatic hyperplasia. Of these drugs with frequent sAEs, 7 had low sAE risks in their professional drug information.

Conclusion

One in 25 drug reports on mijnmedicijn.nl included sAEs. The sAEs were reported frequently for antidepressants, contraceptives and drugs used in benign prostatic hyperplasia.

Introduction

Sexuality is a central aspect of being human. An abundance of research has shown that sexual function can be impaired by common diseases such as depression, diabetes and hypertension [1]. Additionally, drug treatments may also impact sexual function. In previous research we have shown that sexual adverse drug reactions (sADRs) are registered for 346 drugs in their Summary of Product Characteristics (SmPC) [2]. Presumably, these sADRs were spontaneously reported by participants of registration trials. Consequently, the sADRs in the registration files may not reflect the real-world incidence of sexual complaints during drug treatment [3, 4]. Indeed, in the case of selective serotonin receptor inhibitors (SSRIs), the difference in frequencies of sADRs mentioned in the drug label (6-26%) and reported in post-marketing studies (30–60%) was so noticeable that the US Food and Drug Authority (FDA) recently published an advice on how to systematically collect sADRs information for registration files [3].

To understand the impact of drugs on sexuality, it is important to realize that sexuality is a complex trait, influenced by biological, psychological, relational and socio-cultural factors [5]. These influences also interact, e.g. a physical condition may alter a person's psychological well-being. Since both chronic diseases and their drug treatments can influence sexuality, identifying the single impact of one drug on sexuality becomes challenging.

As sexual physiology is mainly based on vasocongestion and myotonia, any drug that affects arteries, nerves, and musculoskeletal function may theoretically impact sexual function [5]. Indeed, most drugs registered with sADRs target the nervous system (105 drugs (30%)) and the cardiovascular system (89 drugs (26%)) [2]. Similarly, research about medication-induced sexual dysfunction generally focused on antidepressant, antipsychotic, anxiolytic, mood-stabilizing and cardiovascular drugs, with an additional interest for drugs targeting the genitourinary organs or hormonal balances [6-11]. Although these studies have given valuable insight in the prevalence of sADRs for certain drugs, little is known about sADRs outside their scope of research. Moreover, the sADRs were often studied as single entities for one gender, e.g. erectile dysfunction during treatment with cardiovascular drugs. Contrarily, the SmPC texts of the drugs often listed several sADRs for one drug, without gender-specificity [2]. This impedes a more specific prediction of sADR risks for individual patients.

In the field of pharmacovigilance, underreporting remains a well-known limitation and this may be more pronounced for sexual complaints [12]. Patients were shown reluctant to report sexual complaints to their healthcare providers [13]. Presumably, they are more comfortable with sharing this sensitive information anonymously online. Indeed, respondents to an European pharmacovigilance survey indicated that one of the benefits

of patient-reporting was that they could report embarrassing symptoms directly to their national agency [14]. To supplement the current collection of adverse events (AE), data extraction from social media such as Twitter or health forums is increasingly investigated [15]. The first studies with these new AE sources showed their ability to capture the less-frequently reported AEs [15].

The present study aimed to add to the current knowledge on sexual adverse events (sAEs) by evaluating patient reports shared on an online platform for drug experiences (mijnmedicijn.nl). We defined patient-reported sexual complaints as sAEs because the complaints were not evaluated by healthcare professionals for causality with the drug in use. The primary objective was to identify the number of drugs with at least one sAE report and the types of sAE reported, stratified for gender. For a better understanding of causal inference, the sAE reports were assessed with information on de- or rechallenge, changes in sAE experiences after the first period of treatment and patients' doubts about the association with the drug. The secondary objective was to identify drugs with disproportional numbers of sAE reports with the reporting odds ratio (ROR).

Methods

Design

This observational study explored patients' online reporting of a change in sexual function that occurred during drug treatment (sAE) at a platform for medication experiences.

Data source

Patient reports of sAE were searched on an online platform for drug experiences, mijnmedicijn.nl. Users of the platform can share their experiences in a drug report, together with additional information such as their age, gender, drug and drug brand. These data are summarized and can be commented in publicly available drug overviews on the platform. The platform aims to support drug users by collecting and sharing their experiences with drugs. It is a product of an independent private business (Insight Pharma Services BV, Apeldoorn, The Netherlands) that currently is available in 11 countries. Editors of mijnmedicijn.nl validated each drug report to only include drug experiences, cutting out commerce and unrelated opinions (e.g. about healthcare professionals). Moreover, although platform users can share experiences with more than one drug, editors deleted accounts with suspiciously high numbers of posts. The online platform 'mijnmedicijn.nl', was launched in 2008 for drug users in the Netherlands and contains information and

drug reports written in Dutch. Information posted on the platform is collected in the related database and was available for this research. The majority of data collected has been published at the platform between 2014 and 2020. To the best of our knowledge, information from this platform has not been used before in published scientific research.

Collection of sAE terms

Medical terms for sexual symptoms generally differ from the language patients use to describe their complaints. To be able to thoroughly search for patient-reported sexual complaints, users of mijnmedicijn.nl were asked to describe sAE in their own terms in an online poll that was initiated for this study. The poll was visible to all platform users between April and June 2019. The poll asked what came to mind when the reader thought of sexual side effects. Initially, most responders filled in one sAE for each gender. To stimulate the responders to provide more terms, multiple free text spaces were added as additional options for both genders.

After three months, the sAE terms from the poll were collected and cleaned from unrelated responses (e.g. advertisement) or responses that were unspecific for the symptom (e.g. 'vagina'). Terms that concerned the sexual reproduction organs but did not necessarily change sexual function were excluded, for example genital irritation. Terms that by themselves were not associated with sexual function were specified for their effects on sexuality (e.g. 'low desire' was listed as 'low desire in sex') and otherwise excluded. From the remaining terms, the shortest terms were used (e.g. libido for 'zero libido'). This resulted in a list of 125 sAE terms (see supplement A). Notably, although the term would also be found when it was part of a larger word or word group (e.g. 'sex' within 'sexual activity'), both the short and longer terms were included in the list of sAE terms to be able to identify which words would be used most in the reports. Lastly, the list also included spelling errors detected during the collection of the sAE terms, since those spelling errors could also occur in drug reports.

Data collection

Drug reports published on mijnmedicijn.nl between April, 2008 and March, 2020, were searched with the 125 selected sAE terms. Each detected drug report was extracted from the Dutch division of the multilingual database, together with information on the drug (name and Anatomical Therapeutic Chemical (ATC) code [16]), the age and gender of the reporter[17]. The total number of posted reports on the platform were extracted for the same time period and the same information components for drug, age and gender. Subsequent comments on original drug reports were excluded from the data collection.

Data preparation

Each extracted drug report was read by at least one researcher (R.G., E.K.) to check if indeed a sAE was reported and if the information in the report matched with the additional characteristics that were filled in (age, gender, drug name). Discrepancies between the drug report and the additional characteristics were corrected based on the information from the drug report. Duplications of reports were deleted. In addition, reports were tagged for mentioning certain events, notably discontinuation or decrease in dose, which could result in a positive dechallenge (sAE disappeared), negative dechallenge (sAE remained) or rechallenge (reappearance sAE when drug (dose) restarted). Other tags concerned positive effects on sexual function, the sAE disappearing after the starting phase of the treatment and a suspicion that other drugs or diseases (also) caused the change in sexual function. Whether a sAE was considered positive or negative was based on the patient's evaluation, e.g. if someone reported to be satisfied with the unintended side effect of less desire for sex, this was tagged as a positive sAE. Reports that were difficult to tag or could be interpreted in multiple ways were discussed and agreed upon in a consensus meeting (R.G., E.K.).

Outcomes

The sAE frequencies for the primary objective were calculated for each drug and stratified for gender and age groups. In addition, the types of sAE (e.g. vaginal dryness, libido) experienced with each drug were summarized based on the sAE terms that were identified in the reports. Additional outcomes for the first objective were the number of reports with information on de- or rechallenges, doubts about the association of the sAE with the drug, the sAE that were considered a positive change for the drug user or sAE that had decreased or disappeared in the first weeks of the drug treatment. For the secondary objective, the reporting odds ratio (ROR) was calculated as proposed by Bate and Evans [18].

Data analysis

The number of reports with sAE were calculated for each of the outcomes with descriptive statistics. Drug reports with sAE were stratified for gender, the total numbers also for age groups. For drug classes on ATC level 2 and for drugs with three or more reports with a sAE, the ROR was calculated as the sAE proportion for the individual drug, divided by the sAE proportion for all drugs on the platform. The signal for disproportionally was considered strong if the lower bound of the 95% confidence interval (CI) of the ROR was >2.0. Lastly, the user numbers of the drugs in the Netherlands in 2019 were retrieved from the publicly available GIP databank from the National Health Care Institute in the

Netherlands (https://www.gipdatabank.nl/) to assess whether low numbers of reports on the platform might be explained by low user numbers.

Results

A total of 61 623 drug reports were posted between 2008 and 2020 on mijnmedicijn.nl (Figure 5.1). The sAE search terms were detected in 5.3% of these reports. After cleaning the data, 2408 reports with sAE remained (3.9%), with 65 sAE terms for 189 drugs. The sAE were reported for a broad range of drugs, that covered 11 of the 14 ATC classes on level 1. However, most sAE reports belonged to two of these classes: drugs targeting the nervous system (ATC class N; n=1341) and genito-urinary system and sex hormones (ATC class G; n=761). Treatment cessation or dose reduction was mentioned in 666 reports with sAE, which was a positive dechallenge in 208 reports and negative in 9 reports. Rechallenge was mentioned in 24 reports, which were all positive. Infrequently, the sAE was experienced as positive (n=83; 3.4% of reports with sAE). The number of reports with sAE for individual drugs can be found in Supplement B, the frequency of labels (e.g. dechallenge, positive sAE) in Supplement C.

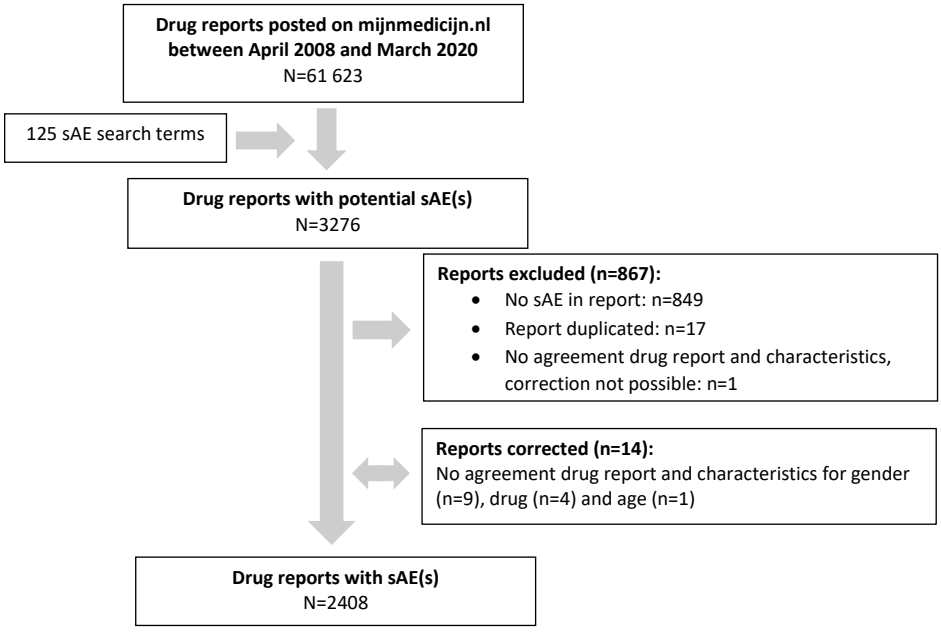

Figure 5.1: Description of the collection of drug reports with sexual adverse events on mijnmedicijn.nl.
sAE = sexual adverse event.

Table 5.1: Overview of reports with sexual adverse events posted on mijnmedicijn.nl (2008–2020)

		Reports of women			Reports of men		
ATC groups (level 1 and level 2)		All	with sAE	ROR (95% CI)[a]	All	with sAE	ROR (95% CI)[a]
A	***A02*** *Drugs for acid related disorders*	936	-		786	5	0.1 (0.1–0.3)
	A08 *Antiobesity preparations, excl. diet products*	112	-		18	1	
	A10 *Drugs used in diabetes*	656	-		539	10	0.4 (0.2–0.7)
C	***C01*** *Cardiac therapy*	150	-		210	1	
	C02 *Antihypertensives*	86	-		29	1	
	C03 *Diuretics*	245	2		199	12	1.3 (0.7–2.3)
	C05 *Vasoprotectives*	67	-		38	1	
	C07 *Beta blocking agents*	983	14	0.4 (0.2–0.7)	683	39	1.2 (0.9–1.7)
	C08 *Calcium channel blockers*	359	3	0.2 (0.1–0.7)	341	22	1.4 (0.9–2.2)
	C09 *Agents acting on the renin-angiotensin system*	808	5	0.2 (0.1–0.4)	872	39	0.9 (0.7–1.3)
	C10 *Lipid modifying agents*	1267	1		1577	37	0.5 (0.3–0.7)
D	***D05*** *Antipsoriatics*	135	1		111	-	
	D10 *Anti-acne preparations*	559	3	0.1 (0.0–0.5)	240	3	0.3 (0.1–0.8)
	D11 *Other dermatological preparations*	89	1		58	-	
G	***G01*** *Gynecological antiinfectives and antiseptics*	356	1		3	-	
	G02 *Other gynecologicals*	2819	227	**2.7 (2.3–3.2)**	43	3	1.5 (0.5–4.9)
	G03 *Sex hormones and modulators of the genital system*	3283	384	**4.7 (4.2–5.3)**	123	6	1.0 (0.5–2.4)
	G04 *Urologicals*	147	-		680	122	**4.9 (4.0–6.0)**
H	***H02*** *Corticoids for systemic use*	208	-		137	1	
	H03 *Thyroid therapy*	1339	3	0.1 (0.0–0.2)	233	1	
J	***J01*** *Antibacterials for systemic use*	2629	3	0.0 (0.0–0.1)	987	2	
	J05 *Antivirals for systemic use*	40	-		167	1	
L	***L01*** *Antineoplastic agents*	162	-		129	2	
	L02 *Endocrine therapy*	624	55	**2.8 (2.1–3.7)**	99	20	**5.2 (3.2–8.5)**
	L04 *Immunosuppressants*	751	1		454	2	
M	***M01*** *Antiinflammatory and antirheumatic products*	904	-		528	2	
	M03 *Muscle relaxants*	51	-		51	1	
	M04 *Antigout preparations*	23	-		122	1	
	M09 *Other drugs for disorders of the musculo-skeletal system*	28	-		14	1	
N	***N02*** *Analgesics*	2157	2		1263	19	0.3 (0.2–0.5)
	N03 *Antiepileptics*	1475	10	0.2 (0.1–0.3)	881	27	0.6 (0.4–0.9)
	N04 *Anti-parkinson drugs*	143	-		129	2	
	N05 *Psycholeptics*	2354	43	0.5 (0.4–0.7)	1939	80	0.9 (0.7–1.1)
	N06 *Psychoanaleptics*	7393	598	**3.6 (3.2–4.0)**	3948	538	**5.6 (4.9–6.4)**
	N07 *Other nervous system drugs*	920	4	0.1 (0.0–0.3)	677	18	0.5 (0.3–0.9)
R	***R03*** *Drugs for obstructive airway diseases*	815	3	0.1 (0.0–0.3)	489	3	0.1 (0.0–0.4)
	R06 *Antihistamines for systemic use*	671	1		318	-	
S	***S01*** *Ophthalmologicals*	221	1		183	2	
	TOTAL	39 873	1383		21 750	1025	

ATC=Anatomical Therapeutic Chemical; sAE=sexual adverse event; 95%CI=95% confidence interval; ROR=Reporting Odds Ratio, calculated as the proportion of sAE for the specific drug class divided by the proportion of sAE for all drug classes.
[a] If the lower bound of the 95% confidence interval of the ROR is above 2, the ROR is shown in **bold** in this table.

Gender-stratified numbers of sAE reports

Men posted 1025 drug reports with sAE (4.7% of all drug reports posted by men) and women 1383 drug reports (3.5% of all drug reports posted by women), see Table 5.1. Women reporting sAE were mostly 20–29 years (n=506), whereas men who reported sAE were most often 40–49 years old (n=244), see Figure 5.2. Uncertainty about the association with the specific drugs was mentioned by fewer women (n=32; 2.3% of reports with sAEs) than men (n=45; 4.4% of reports with sAEs).

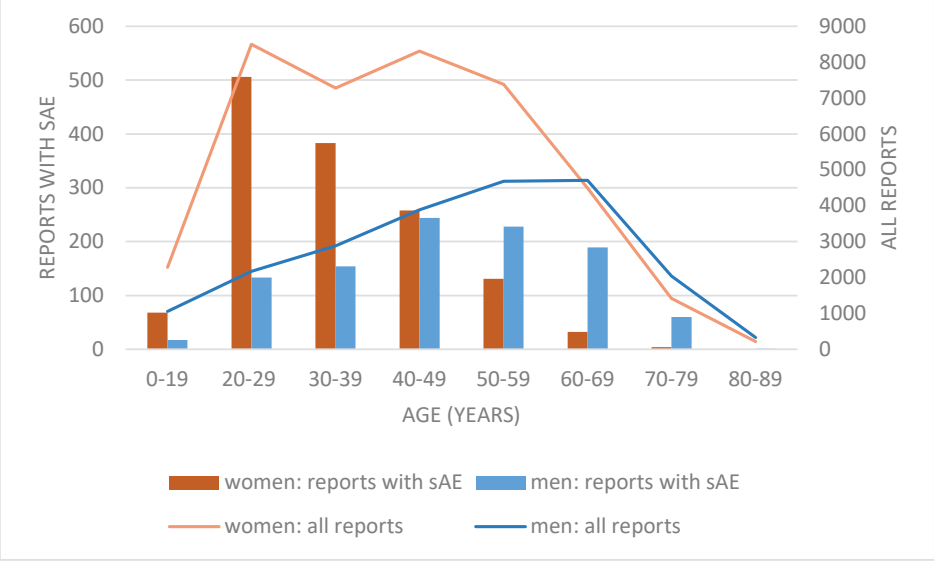

Figure 5.2: Number of reports with sexual adverse events posted by women and men for each age category in comparison to all reports on mijnmedicijn.nl (2008–2020).
sAE = sexual adverse event.

Almost half of the sAE reports on mijnmedicijn.nl addressed antidepressants. For these drugs, men mentioned sAE relatively more often than women. For example, sAE were found for venlafaxine in 22% of the reports of men (n=102) and in 10% of the reports of women (n=101). The most notable gender difference was found for cardiovascular drugs, with 152 reports with sAE posted by men and 26 reports by women. For drugs targeting the genito-urinary system, the reports with sAE showed inherent gender differences, e.g. 604 women posted reports with sAE for contraceptives and 118 men for drugs used for benign prostate hypertrophy (BPH).

The most common reported sAE type concerned a change in desire, which was mentioned in 427 reports of men (41.7%) and 1059 reports of women (76.6%), see supplement D. Most commonly, desire-related changes were described with 'libido', a term used in 325

reports of men (31.7%) and in 806 reports of women (58.3%). Besides changes in desire, men also reported changes in erectile function (n=346; 33.8%), orgasm (n=150; 14.6%), ejaculation (n=108; 10.5%) and arousal (n=21; 2.0%). For women, other reported sAE types were changes in orgasm (n=140; 10.1%), vaginal dryness (n=48; 3.5%), arousal (n=24; 1.7%) and pain during sex (n=24; 1.7%). In addition, the sAEs were unspecified (e.g. 'sexual problem') in 161 reports of men (15.7%) and 183 reports of women (13.2%).

Disproportional high numbers of sAE reports

The ROR indicated disproportional high numbers of sAE reports for 22 drugs for one of the genders and for another 5 drugs for both genders. Most of these drugs belonged to five drug classes on ATC level 2: Other gynecologicals (G02), Sex hormones and modulators of the genital system (G03), Urologicals (G04), Endocrine therapy (L02) and Psychoanaleptics (N06). Table 5.1 shows that the RORs for these drug classes also indicated disproportional high numbers of sAE reports on ATC level 2. Within drug classes G02 and G03, most sAE were attributed to hormonal contraceptives (ATC classes G02B and G03A), for which women reported sAE 5.6 times more often than for other drugs (95% CI 5.0–6.3). Within drug class L02, the disproportional signal was attributed to the aromatase inhibitors (ATC class L02BG) and the gonadotropin releasing hormone (GnRH) analogues (ATC class L02AE). The highest proportion of sAE was found for drugs used in BPH, with thirty percent of the reports including at least one sAE (ROR 9.6; 95% CI 7.7–12.0).

As most sAE within drug class N06 concerned antidepressants (ATC class N06A), these are presented in more detail in Table 5.2. Women reported sAE for antidepressants 4.2 times more often than for other drugs (95% CI 3.8–4.7) and men 7.5 times more often (95% CI 6.6–8.5). The selective serotonin reuptake inhibitors (SSRIs, ATC class N06AB), amitriptyline, venlafaxine and mirtazapine received most drug reports and most reports with sAE. Disproportional high numbers of sAE reports were found for sertraline, paroxetine, citalopram, escitalopram, venlafaxine and for men also for clomipramine and duloxetine.

Besides drugs within the drug classes G02, G03, G04, L02 and N06, three other drugs had received disproportional high numbers of reports with sAE from men: lisinopril and diuretics (ROR 6.2 (95% CI 2.0–19.2)), gemfibrozil (ROR 10.1 (95% CI 2.5–40.5)) and risperidone (ROR 3.4 (95% CI 2.1–5.5)). For women, the disproportional high numbers of reports concerned only drugs within the beforementioned drug classes.

Of the 27 drugs with disproportional high numbers of reports with sAE, 20 were registered with >1% risk for sADRs in their SmPC text. Seven drugs had lower risks registered: four hormonal contraceptives (0.1–1% risk), two cardiovascular drugs (0.1–1% risk) and

anastrozole (not registered with sADRs). In addition, for 58 drugs for which sAE were reported on mijnmedicijn.nl, no sADRs were found in their SmPC text.

Table 5.2: Gender-stratified numbers and proportions of sexual adverse events for antidepressants (ATC group N06A)

				Reports by women			Reports by men		
ATC group	Drug	Users in NL[a]	sADR risk in SmPC[b]	All	With sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
N06AA	Clomipramine	26 046	>10%	128	12	2.9 (1.6–5.3)	81	14	**4.3 (2.4–7.6)**
	Amitriptyline	201 720	1–10%	407	10	0.7 (0.4–1.3)	153	7	1.0 (0.5–2.1)
	Nortriptyline	64 796	1–10%	103	3[d]	0.8 (0.3–2.6)	74	4	1.2 (0.4–3.2)
N06AB	Fluoxetine	57 408	1–10%	365	22	1.8 (1.2–2.8)	131	18	3.3 (2.0–5.4)
	Citalopram	181 260	1–10%	815	100	**4.1 (3.3–5.1)**	278	63[d]	**6.2 (4.7–8.3)**
	Paroxetine	145 860	>10%	907	122	**4.6 (3.8–5.7)**	442	98[d]	**6.3 (5.0–7.9)**
	Sertraline	93 386	>10%	662	84[d]	**4.2 (3.4–5.4)**	255	72[d]	**8.5 (6.4–11.2)**
	Fluvoxamine	16 660	0.1–1%	171	15	2.7 (1.6–4.6)	83	8	2.2 (1.0–4.5)
	Escitalopram	75 179	1–10%	560	73[d]	**4.3 (3.4–5.6)**	263	64[d]	**6.9 (5.1–9.2)**
N06AF	Fenelzine	184	-	10	2[d]	-	7	0	-
	Tranylcypromine	1918	0.001–0.01%	62	1[d]	-	27	0	-
N06AG	Moclobemide	951	'unknown'	12	0	-	16	1[d]	-
N06AX	Trazodon	12 191	'unknown'	43	1	-	29	4	3.2 (1.1–9.3)
	Mirtazepine	125 480	-	340	4	0.3 (0.1–0.9)	249	8	0.7 (0.3–1.4)
	Bupropion	27 466	-	319	14[d]	1.3 (0.7–2.2)	184	16[d]	1.9 (1.2–3.2)
	Venlafaxine	103 080	1–10%	962	101[d]	**3.4 (2.8–4.3)**	461	102[d]	**6.3 (5.0–7.9)**
	Duloxetine	30 631	1–10%	268	18[d]	2.0 (1.2–3.3)	102	27[d]	**7.4 (4.8–11.6)**
	Agomelatine	2075	-	71	2	-	37	1[d]	-
	Hypericum	-	-	41	1	-	41	2[d]	-
	Vortioxetine	5403	'unknown'	39	1	-	10	1	-
			TOTAL	6285	586	**4.2 (3.8–4.7)**	2923	510	**7.5 (6.6–8.5)**

ATC=Anatomical Therapeutic Chemical; NL=Netherlands; ROR=Reporting Odds Ratio; 95% CI=95% confidence interval; sADR=sexual adverse reaction; sAE=sexual adverse event; SmPC=Summary of Product Characteristics.

[a] Data from GIP databank, 2019. '-' should be interpreted as no users.

[b] Risk for sADRs as percentage of users. '-' should be interpreted as no risk registered, 'unknown' should be interpreted as too little cases of sADRs to estimate a risk.

[c] If the lower bound of the 95% confidence interval of the ROR is above 2 (unrounded numbers), the ROR is shown in **bold** in this table.

[d] Also reports with a positive effect: for women the positive sAE were mostly desire-related (two cases additionally reported a positive effect on orgasms): one report for sertraline, escitalopram, fenelzine, tranylcypromine and duloxetine, two reports for nortriptyline, three reports for venlafaxine and five reports for bupropion. For men the positive sAE mostly concerned orgasms and desire: one report for citalopram, escitalopram, moclobemide, agomelatine and hypericum, two reports for paroxetine, sertraline and duloxetine and three reports for bupropion and venlafaxine.

Discussion

Unintended effects on sexual function were found in 4% of the patient-reported drug experiences posted for 189 drugs on mijnmedicijn.nl. Men and women differed in their

age and frequency for reporting sAE, the drugs for which they reported sAE and the type of sexual complaint experienced. Twenty-seven drugs showed disproportionally frequent sAE reporting, which mostly concerned antidepressants, hormonal contraceptives, drugs used in BPH, aromatase inhibitors and GnRH analogues. Of these drugs, seven were registered with a low risk for sADRs in their SmPC text, thus showing a potential sAE underestimation in the registration trials. The high frequencies of sAE reporting found for several drugs implies that the influence on sexual function is an important aspect of those drug treatments.

To our best knowledge, this is the first study that evaluated patient-reported sAE from social media. The chosen online platform exclusively focused on medication experiences, with the benefit of a simple data extraction in comparison to the AE extraction methods needed for platforms such as medical forums and Twitter [15, 19]. Other advantages of the data source were the patient and drug characteristics in the platform database and the qualitative rich information in the drug experiences. Moreover, sAE experiences were posted for a broad range of drugs, which enabled an exploration of differences between drugs and between men and women. Another advantage was the use of patient-reported sAE terms, as patients can have difficulty understanding sexual function terms [20]. In comparison, previous studies that collected AE from online drug reviews either annotated AEs to medical terms [21-25] or extracted side effect expressions from the drug reports [26]. Those studies had different aims, as they primarily investigated the process of AE collection [21, 22, 26] or the utility of social media data in comparison other AE sources such as pharmacovigilance systems [23-25]. Such comparisons with pharmacovigilance systems were difficult for this study, as pharmacovigilance studies about sAE only investigated sAE in relation to SSRIs or only presented drugs with the highest RORs for sAE [27-29]. The latter study with the highest RORs was published by the Dutch national pharmacovigilance center Lareb and investigated a similar total number of sAE, also most frequently for antidepressants [29]. In contrast to our study, the majority of sAE reported at Lareb were reported by men (72% vs 43%) and statins were among the drug groups with most sAE reports. Presumably, embarrassment around sAE caused low sAE reporting rates at pharmacovigilance centers, as demonstrated for the French Pharmacovigilance System (FPS) [27]. Indeed, at mijnmedicijn.nl sAE were 18 times more often reported than at FPS (3.9% vs 0.2% of reports in the databases). Moreover, the sAE reported at FPS and Lareb could often be considered more objectively noticed (e.g. anorgasmia, impotence) than the mostly desire-related sAE reported at mijnmedicijn.nl [27]. The high proportion of desire-related sAE at mijnmedicijn.nl suggests that this sAE influenced the reporters' quality of life. In addition, it highlights the importance for drug users to share their sAE experiences and their reservation to share these with healthcare providers or pharmacovigilance centers.

Therefore, this study of an online medication platform probably reflects the real-world frequency of sAE better than pharmacovigilance systems.

This study showed differences for women and men in their online reporting of sAE. For women, a higher total number of sAE reports was found. This higher number likely derived from the twice higher total number of drug reports in comparison to men. It is well-known that women report more side effects [30, 31]. A multitude of potential reasons exist for this difference, for example a higher polypharmacy rate, reaching a higher age, different baseline characteristics and risks (e.g. longer QT interval, higher prevalence of depression), physiological differences that can lead to higher average drug exposures, receiving different care, a different perception of healthcare professionals and a different attitude towards drugs in women [30]. By contrast, when comparing the proportions of reporting sAE in drug experiences, women in this study reported sAE less frequently than men. Importantly, the lower sAE proportion in women was observed for drugs that both genders used frequently, e.g. antidepressants and cardiovascular drugs. Concordantly, in Lareb, statin-associated decreased libido and SSRI-associated loss of libido and sexual dysfunction showed to have higher odds rates for men than for women [32]. In a meta-analysis about SSRI-associated sAE, men also showed significant higher incidences of desire and orgasm dysfunction, although women reported more arousal dysfunction [6]. Since SSRIs are expected to induce some degree of genital numbness in all users [33], it is unclear why men reported higher percentages of SSRI-associated sexual complaints. Besides biological differences, the gender differences in sAE reporting may be underpinned by different expectations and expressions of female and male sexuality. For example, the concordance between genital response and subjective arousal is more relevant for men than for women [34]. Accordingly, drug influences on genital response might be more noticeable and have more impact for men. Moreover, women are known to report their sexual complaints less frequently to their doctor [35]. This may reflect a societal expectation of women, which possibly also deters women from reporting sexual complaints online. Therefore, future research should explore whether women can identify drug-induced differences in sexual function to the same extent as men (but deter from reporting this) and in which manner the impact of sAE on male and female sexuality may differ.

For this new AE source, limitations inherent to both social media and pharmacovigilance studies applied. Firstly, the platform depends on spontaneous reporting. Therefore, selection bias may have influenced the results. Specifically for sAEs, notoriety bias, underreporting and Weber's effect (increase in reported AE for new drugs within first years of approval) have been found before [27, 36]. However, at mijnmedicijn.nl, potential notoriety bias, exhibited as extremely high numbers of reports, was only found for levothyroxine sodium (n=1229) and plastic IUD with progestogen (n=2302). For the latter drug, media coverage

in France changed the reporting of sAE to the FPS from 6.9% to 47.3% of the reports [36]. Concerning the reporting rates of sAE, general under- or overreporting may have altered the sAE frequencies for individual drugs, but not the ROR values, because both the numerator and denominator would be affected [27]. Importantly, the ROR has an arbitrary cut-off value for disproportionality, for this study a lower CI bound >2.0. This high cut-off value was chosen to increase the specificity of our findings [18]. Additionally, it cannot be excluded that one drug user might have posted multiple sAE reports for different drug experiences. However, due to the checks within the database it is unlikely that this happened often nor that this would fully explain our findings. Lastly, a comparison of sAE frequencies of our study to sADR frequencies from SmPC information requires caution as the denominators of the proportions differed for the related populations.

Sexual side effects were part of at least one drug experience for a broad range of drugs, similar to the wide scope of drug labels that included sADRs [2]. As hypothesized, the drugs associated with sAE in this study mostly targeted arteries, nerves and musculoskeletal function [5]. Hormonal contraceptives and drugs used in BPH were also often associated with sAEs. The association of hormonal contraceptives with sAE remains unexplained [8]. Different possible explanations exist for drugs used in BPH, for which we refer to La Vignera *et al.* [37]. For the remaining drugs with sAE in our study, only few sAE were reported, which were sometimes confirmed in case studies (for omeprazole, isotretinoin, methotrexate and timolol [38-41]) and sometimes explained within the drug reports by indirect effects or presented with uncertainty about the association. For drugs used in diabetes and hypo- or hyperthyroidism, the rare sAE reported in this study may indicate inadequate or excessive treatment effects, as these drugs are known to reduce sexual complaints caused by the diseases [42, 43]. Drugs used for substance dependencies presented substantially higher sAE frequencies in literature than on mijnmedicijn.nl (varenicline 4.3% vs. 0.7%; methadone 14–81% vs. 4.0%; naltrexone 90% vs. 10.3%), possibly due to already existing sexual complaints caused by the substances in those studies [44, 45].

The findings of this study add to our understanding of sAEs. Firstly, sAEs were experienced in about 1 in 25 online drug reports, varied between women and men and mostly concerned desire-related problems. Secondly, it showed that sAE descriptions in drug labels may not always reflect the real-world experiences, as several antidepressants and contraceptives received many more sAE reports in our study than expected from the SmpC text. Therefore, healthcare providers should be alert for patient-reported sAEs, also when the sAE is not described in the drug label. Lastly, this study showed that for sensitive AEs such as sAEs, an online medication platform can contribute to knowledge from pharmacovigilance databases with real-world patient experiences.

Conclusion

One in 25 patient-reported drug experiences on mijnmedicijn.nl included a sexual side effect. For many antidepressants and hormonal contraceptives, the frequency of reporting sAE in the drug experiences on mijnmedicijn.nl was >10%. In addition, gender differences in reporting sAE were revealed. These findings should stimulate healthcare providers to be sensitive to patient-reported sAE and to be mindful of possible under- and overreporting of sAE in the drug labels.

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Supplementary materials

Supplement A: Search terms for sexual adverse events

	Search terms found in reports	Search terms not found in reports
Search terms concerning erection	erectie erektie impotentie potentie impotent inpotent "slappe pik"	"niet hard" "niet stijf" "geen stijve" "verslapping van het lid" "snel slap" "slappe penis" "slappe lul" "stijve lul" "stijve pik"
Search terms concerning vaginal dryness	droogheid "droge vagina" "vaginale droogheid" "vaginale droogte" "niet nat kunnen worden"	lubricatie "droge vagijn" "droogte vagina" "moeite met nat worden" "niet nat worden" "minder nat worden" "niet nat raken" "niet nat zijn" "minder vochtig" "niet vochtig worden" "glijmiddel nodig" "erg vochtig zijn" "droge doos"
Search terms concerning desire or arousal	libido libidi lustgevoelens lustvermindering sekslust sexlust sexdrive sex-drive seksdrive seks-drive "sex drive" geil frigiditeit "zin in seks" "zin in sex" "vermindering van zin" "zin in vrijen" "minder zin hebben" "geen zin hebben"	lustprobleem lustproblemen lustvermeerding frigide nymfomanie hitsig "verhoging van zin" "zin in sexy" "minder zin houden" "zin in erotiek" "zin om seks" "zin om sex" "verandering in behoefte" "geen behoeftes meer" "opgewonden kunnen raken" "lust verliezen" "meer lust" "seks drive" "verminderde drive"

Supplement A continues on next page.

Supplement A: *Continued*

	Search terms found in reports	Search terms not found in reports
	"geen zin meer hebben" "zin om te vrijen" "ik heb geen zin meer" "ik had geen zin meer" "seksuele behoefte" "behoefte aan seks" "behoefte aan sex" "opgewonden raken" "opgewonden worden" "verminderde lust" "weinig lust" "geen lust" "minder lust" "lust verloren"	"versterkte drive" "te weinig verlangen" "te veel verlangen" "psychisch opgewonden" "lichamelijk opgewonden"
Search terms concerning orgasm or ejaculation	orgasme klaarkomen klaargekomen ejaculatie ejaculeren zaadlozing "klaar te komen" "klaar kunnen komen" "hoogtepunt bereiken"	ejaculaat "klaar gekomen" "hoogtepunt niet bereiken"
Search terms concerning pain during sex	vaginisme "pijn bij vrijen" "pijn bij seks" "pijn bij het vrijen" "pijn bij sex"	"pijnlijke coïtus" "pijnlijke coitus"
Non-specific search terms	seks seksueel seksuele sex penetratie "lichamelijk contact"	neuken priapisme oversext oversexd penitratie "gevoel in pik" "gevoel in lul" "gevoel in vagina" "gevoel in penis"

Phrases between quotation marks (") were phrases that could mean something else if only one word of the phrase was found in a drug report.

Supplement B: Drugs with reports with sexual adverse events posted on mijnmedicijn.nl between 2008–2020

			Reports of women			Reports of men		
	Users in NL[a]	sADR risk in SmPC[b]	All	with sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
A02 DRUGS FOR ACID RELATED DISORDERS			936	0	-	786	*5*	0.1 (0.1–0.3)
Omeprazole	1 044 000	-	440	0	-	374	*5*	0.*3* (0.1–0.7)
A08 ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS			112	0	-	18	1	-
Sibutramine	?	-	102	0	-	16	1	-
A10 DRUGS USED IN DIABETES			656	0	-	539	10	0.4 (0.2–0.7)
Metformin	655 050	-	273	0	-	274	5	0.4 (0.2–0.9)
Gliclazide	231 890	-	28	0	-	31	1	-
Glimepiride	46 148	-	32	0	-	21	1	-
Rosiglitazone	?	-	7	0	-	4	1	-
Liraglutide	11 718	-	88	0	-	56	1	-
Empagliflozin	8353	-	13	0	-	25	1	-
C01 CARDIAC THERAPY			150	0	-	210	1	-
Flecainide	42 066	0.001–0.01%	55	0	-	71	1	-
C02 ANTIHYPERTENSIVES			86	0	-	29	1	-
Doxazosin	43 398	0.1–1%	8	0	-	15	1	-
C03 DIURETICS			245	2	-	199	12	1.3 (0.7–2.3)
Hydrochlorothiazide	666 470	0.1–1%	149	2	-	105	7	1.4 (0.7–3.1)
Chlortalidone	64 867	0.1–1%	15	0	-	11	1	-
Indapamide	9664	-	0	-	-	6	2	-
Eplerenone	21 729	-	3	0	-	8	1	-
Hydrochlorothiazide and potassium-sparing agents	33 366	'unknown'	17	0	-	9	1	-
C05 VASOPROTECTIVES			67	0	-	38	1	-
Isosorbide dinitrate (topical)	13 639	-	43	0	-	20	1	-
C07 BETA BLOCKING AGENTS			983	14	0.4 (0.2–0.7)	683	39	1.2 (0.9–1.7)
Propanol	108 760	'unknown'	185	2	-	56	0	-
Sotalol	94 688	1-10%	106	5	1.4 (0.6–3.4)	148	9	1.3 (0.7–2.6)
Metoprolol	1 012 000	0.01–0.1%	424	3	0.2 (0.1–0.6)	305	20	1.4 (0.9–2.3)
Atenolol	81 108	0.01–0.1%	70	3	1.2 (0.4–4.0)	38	2	-
Acebutolol	1151	'unknown'	2	0	-	2	1	-
Bisoprolol	222 840	0.01–0.1%	99	1	-	65	2	-
Nebivolol	42 424	0.1–1%	32	0	-	32	2	-
Labetalol	11 485	1–10%	29	0	-	12	2	-
Carvedilol	21 151	0.1–1%	7	0	-	10	1	-
C08 CALCIUM CHANNEL BLOCKERS			359	3	0.2 (0.1–0.7)	341	22	1.4 (0.9–2.2)
Amlodipine	644 800	0.1–1%	155	2	-	169	18	2.4 (1.5–4.0)
Nifedipine	165 950	0.1–1%	74	1	-	59	4	1.5 (0.5–4.1)
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM			808	5	0.2 (0.1–0.4)	872	39	0.9 (0.7–1.3)
Enalapril	292 170	0.1–1%	85	0	-	81	2	-
Lisinopril	326 390	0.1–1%	80	0	-	96	5	1.1 (0.5–2.7)
Perindopril	342 230	0.1–1%	74	0	-	115	1	-
Ramipril	54 410	0.1–1%	12	0	-	28	3	2.4 (0.7–8.1)
Quinapril	17 576	0.1–1%	3	0	-	5	1	-
Fosinopril	54 429	1–10% [d]	10	0	-	13	1	-
Lisinopril and diuretics	28 256	0.1–1%	10	0	-	17	4	**6.2 (2.0–19.2)**
Perindopril and diuretics	33 720	0.1–1%	8	0	-	15	1	-
Ramipril and diuretics	2992	0.1–1%	5	1	-	6	1	-
Enalapril and lercanidipine	664	0.1–1% [d]	1	0	-	5	1	-
Losartan	360 230	'unknown'	81	1	-	78	2	-
Valsartan	54 245	-	79	2	-	93	5	1.1 (0.5–2.8)
Irbesartan	156 650	0.1–1%	94	2	-	65	3	1.0 (0.3–3.1)
Candesartan	125 550	-	60	0	-	34	1	-
Telmisartan	54 542	-	35	0	-	30	1	-
Valsartan and diuretics	22 066	1–10% [d]	26	0	-	31	2	-
Irbesartan and diuretics	66 722	0.1–1%	25	0	-	29	4	3.2 (1.1–9.3)
Olmesartan medoxomil and amlodipine	3524	0.1–1%	8	0	-	5	1	-

Supplement B continues on next page.

Supplement B: *Continued*

			Reports of women			Reports of men		
	Users in NL[a]	sADR risk in SmPC[b]	All	with sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
C10 LIPID MODIFYING AGENTS			1267	1	-	1577	37	0.5 (0.3–0.6)
Simvastatin	989 130	'unknown'[d]	562	1	-	615	20	0.7 (0.4–1.1)
Pravastatin	129 770	0.1–1%	66	0	-	84	1	-
Atorvastatin	600 520	'unknown'[d]	252	0	-	373	6	0.3 (0.1–0.7)
Rosuvastatin	335 340	'unknown'[d]	187	0	-	270	6	0.5 (0.2–1.0)
Gemfibrozil	11 490	0.01–0.1%	4	0	-	9	3	**10.1 (2.5–40.5)**
Evolocumab	9746	-	24	0	-	40	1	-
D10 ANTI-ACNE PREPARATIONS			559	3	0.1 (0.0–0.5)	240	3	0.3 (0.1–0.8)
Isotretinoin	28 828	'unknown'	389	3	0.2 (0.1–0.7)	199	3	0.3 (0.1–1.0)
D11 OTHER DERMATOLOGICAL PREPARATIONS			89	1	-	58	0	-
Alitretinoin	2789	-	17	1	-	9	0	-
G01 GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS			356	1	-	3	-	-
Clotrimazole	16 610	-	101	1	-	0	-	-
G02 OTHER GYNECOLOGICALS[e]			2819	227	**2.7 (2.3–3.2)**	43	3	1.5 (0.5–4.9)
Plastic IUD with copper	-	-	206	8	1.1 (0.6–2.3)	6	0	-
Plastic IUD with progestogen	12 140	1–10%	2302	175	**2.5 (2.1–2.9)**	18	0	-
Vaginal ring with progestogen and estrogen	1761	1–10%	259	62	**9.1 (6.8–12.2)**	2	0	-
Cabergoline	6236	0.1–1%	22	3	4.4 (1.3–14.9)	12	3	6.7 (1.8–25.0)
G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM[e]			3283[a]	384	**4.7 (4.2–5.3)**	123	6	1.0 (0.5–2.4)
Ethinylestradiol and norethisterone	-	-	10	1	-	0	-	-
Ethinylestradiol and levonogestrel	313 540	0.1–1%	885	118	**4.6 (3.7–5.6)**	11	0	-
Ethinylestradiol and desogestrel	11 573	0.1 –1%	72	17	**8.7 (5.0–15.0)**	0	-	-
Ethinylestradiol and gestodene	2081	0.1–1%	25	3	3.8 (1.1–12.7)	0	-	-
Ethinylestradiol and drospirenone	19 475	0.1–1%	322	65	**7.3 (5.6–9.7)**	5	0	-
Ethinylestradiol and norelgestromin	739	0.1–1%	40	2	-	0	-	-
Estradiol and nomegestrol	958	1–10%	36	6	**5.6 (2.3–13.4)**	0	-	-
Estradiol and dienogest	484	0.1–1%	22	7	**13.0 (5.3–32.1)**	0	-	-
Medroxyprogesterone	13 766	1–10%	171	27	**5.3 (3.5–8.0)**	2	0	-
Etonogestrel	4295	1–10%	427	54	**4.2 (3.1–5.6)**	5	0	-
Desogestrel	2495	1–10%	162	40	**9.4 (6.5–13.4)**	1	0	-
Levonorgestrel	449	-	50	1	-	3	0	-
Testosterone	20 045	0.1–1%	2	1	-	71	6	1.9 (0.8–4.3)
Estriol	82 990	-	65	1	-	1	0	-
Tibolon	8423	-	73	3	1.2 (0.4–3.8)	1	0	-
Medroxyprogesterone	14 272	-	42	4	2.9 (1.0–8.2)	2	-	-
Norethisterone	43 304	-	104	1	-	3	0	-
Lynestrenol	24 777	>10%	96	8	2.5 (1.2–5.2)	4	0	-
Estrogen and dydrogesterone	15 600	-	190	3	0.4 (0.1–1.4)	2	0	-
Norethisterone and estrogen	2689	'unknown'	9	1	-	0	-	-
Cyproterone	5032	>10%	5	1	-	4	0	-
Cyproterone and ethinylestradiol	-	0.1–1%	212	18	2.6 (1.6–4.2)	2	0	-
G04 UROLOGICALS			147	0	-	680	122	**4.9 (4.0–6.0)**
Oxybutynine	25 918	0.001–0.01%[d]	22	0	-	12	1	-
Mirabegron	36 612	-	23	0	-	22	1	-
Vardenafil	?	0.1–1%	0	-	-	13	1	-
Combinations (phentolamine and papaverine)	?	1–10%	0	-	-	45	1	-
Alfuzosin	34 253	'unknown'[d]	1	-	-	49	2	-
Tamsulosin	220 190	1–10%	5	0	-	177	55	**9.6 (6.9–13.2)**
Silodosin	11 710	>10%	0	-	-	20	9	**16.7 (6.9–40.3)**
Tamsulosin and dutasteride	39 248	1–10%	0	-	-	55	18	**10.0 (5.7–17.6)**
Finasteride	29 817	1–10%	3	0	-	45	17	**12.5 (6.8–22.8)**
Dutasteride	27 494	1–10%	0	-	-	42	17	**13.9 (7.5–25.9)**

Supplement B continues on next page.

Supplement B: *Continued*

	Users in NL[a]	sADR risk in SmPC[b]	Reports of women			Reports of men		
			All	with sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
H02 CORTICOSTEROIDS FOR SYSTEMIC USE			208	0	-	137	1	-
Prednisone	13 453	'unknown'	83	0	-	42	1	-
H03 THYROID THERAPY			1339	3	0.1 (0.0–0.2)	233	1	-
Levothyroxine sodium	510 230	-	1229	3	0.1 (0.0–0.2)	223	0	-
Thiamazole	20 473	-	63	0	–	6	1	-
J01 ANTIBACTERIALS FOR SYSTEMIC USE			2629	3	0.0 (0.0–0.1)	987	2	-
Sulfamethoxazole and trimethoprim	94 495	-	65	1	-	41	1	-
Clindamycin	85 439	-	78	0	-	37	1	-
Ciprofloxacin	274 600	-	143	1	-	110	0	-
Nitrofurantoin	661 770	-	726	1	-	55	0	-
J05 ANTIVIRALS FOR SYSTEMIC USE			40	0	-	167	1	-
Emtricitabine, tenofovir disproxil and efavirenz	1717	0.1–1%	1	0	-	38	1	-
L01 ANTINEOPLASTIC AGENTS			162	0	-	129	2	-
Imatinib	?	0.1–1%	18	0	-	10	1	-
Hydroxycarbamide	?	-	6	0	-	2	1	-
L02 ENDOCRINE THERAPY			624	55	**2.8 (2.1–3.7)**	99	20	**5.2 (3.2–8.5)**
Medroxyprogesterone	364	0.1–1%	4	1	-	0	-	-
Leuprorelin	14 841	>10%	66	8	3.9 (1.8–8.1)	15	2	-
Goserelin	13 637	>10%	37	3	2.5 (0.8–8.0)	30	14	**17.9 (8.7–36.8)**
Tamoxifen	29 458	-	247	16	1.9 (1.2–3.2)	12	1	1.8 (0.2–14.2)
Bicalutamide	11 609	1–10%	0	-	-	13	1	1.7 (0.2–13.0)
Anastrozole	16 002	-	126	14	**3.5 (2.0–6.1)**	10	0	-
Letrozole	14 855	0.1–1%	106	11	3.2 (1.7–6.1)	2	0	-
Exemestane	3149	-	27	2	-	0	-	-
Degarelix	707	0.1–1%	0	-	-	11	2	-
L04 IMMUNOSUPPRESSANTS			751	1	-	454	2	-
Adalimumab	?	0.1–1%	127	0	-	99	1	-
Methotrexate	93 521	0.001–0.01%	165	1	-	90	1	-
M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS			904	0	-	528	2	-
Ibuprofen	443 140	-	112	0	-	80	1	-
Etoricoxib	112 450	-	96	0	-	56	1	-
M03 MUSCLE RELAXANTS			51	0	-	51	1	-
Baclofen	18 891	1–10%	31	0	-	39	1	-
M04 ANTIGOUT PREPARATIONS			23	0	-	122	1	-
Febuxostat	2396	0.1–1%	0	-	-	3	1	-
M09 OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM			28	0	-	14	1	-
Hydroquinine	?	-	28	0	-	14	1	-
N02 ANALGESICS			2157	2	-	1263	19	0.3 (0.2–0.5)
Oxycodon	418 840	0.1–1%	351	0	-	278	5	0.4 (0.2–0.9)
Fentanyl	102 500	0.1–1%	91	0	-	90	1	-
Buprenorphine	36 348	0.1–1%	59	0	-	27	1	-
Tramadol and paracetamol	151 290	-	183	0	-	72	1	-
Tramadol	417 690	-	513	2	-	318	10	0.7 (0.3–1.2)
Tapentadol	5595	0.1–1%	13	0	-	8	1	-
N03 ANTIEPILEPTICS			1475	10	0.2 (0.1–0.3)	881	27	0.6 (0.4–0.9)
Clonazepam	27 863	0.01–0.1%	111	1	-	63	5	1.7 (0.7–4.4)
Carbamazepine	34 870	0.001–0.01%	96	2	-	76	1	-
Valproic acid	50 484	0.1–1%	151	1	-	130	0	-
Topiramate	20 286	0.1–1%	218	1	-	35	1	-
Gabapentin	49 908	1–10%	91	0	-	58	3	1.1 (0.3–3.5)
Levetiracetam	41 681	-	148	0	-	112	1	-
Pregabalin	138 320	1–10%	472	5	0.3 (0.1–0.7)	286	16	1.2 (0.7–2.0)
N04 ANTI-PARKINSON DRUGS			143	0	-	129	2	-
Biperiden	9018	-	8	0	-	11	1	-
Pramipexole	35,153	0.1–1%[d]	63	0	-	38	1	-

Supplement B continues on next page.

Supplement B: *Continued*

	Users in NL[a]	sADR risk in SmPC[b]	Reports of women			Reports of men		
			All	with sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
N05 PSYCHOLEPTICS			2354	43	0.5 (0.4–0.7)	1939	80	0.9 (0.7–1.1)
Haloperidol	54 358	1–10%	80	3	1.1 (0.3–3.4)	62	5	1.8 (0.7–4.4)
Flupentixol	3710	1–10%	13	1	-	11	1	-
Chlorprothixene	2027	1–10%	15	1	-	5	0	-
Zuclopenthixol	5403	1–10%	21	2	-	29	4	3.2 (1.1–9.3)
Pimozide	4456	1–10%	24	0	-	28	1	-
Clozapine	14 630	0.001–0.01%	11	0	-	23	1	-
Olanzapine	53 262	>10%	117	4	1.0 (0.4–2.7)	150	13	1.9 (1.1–3.4)
Quetiapine	139 990	1–10%	410	9	0.6 (0.3–1.2)	285	13	1.0 (0.6–1.7)
Sulpiride	1971	1–10%	26	2	-	16	3	4.7 (1.3–16.4)
Amisulpride	350	-	8	1	-	6	0	-
Lithium	29 818	-	119	4	1.0 (0.4–2.6)	87	2	0.5 (0.1–1.9)
Risperidone	47 232	1–10%	115	7	1.8 (0.8–3.9)	134	19	**3.4 (2.1–5.5)**
Aripiprazole	28 860	1–10%	145	3	0.6 (0.2–1.8)	110	5	1.0 (0.4–2.4)
Paliperidone	4014	1–10%	23	*2*	-	36	5	3.3 (1.3–8.4)
Diazepam	64 618	0.001–0.01%	88	1	-	99	0	-
Potassium clorazepate	6930	'unknown'	6	0	-	38	1	-
Prazepam	614	0.001–0.01%	3	0	-	3	1	-
Alprazolam	28 732	1–10%	172	0	-	125	1	-
Buspirone	2145	-	6	0	-	7	1	-
Lormetazepam	11 963	1–10%	22	0	-	17	1	-
Temazepam	102 130	-	109	1	-	75	2	-
Zolpidem	29 925	0.001–0.01%	101	2	-	53	1	-
N06 PSYCHOANALEPTICS			7393	598	**3.6 (3.2–4.0)**	3948	538	**5.6 (4.9–6.4)**
Clomipramine	26 046	>10%	128	12	2.9 (1.6–5.3)	81	14	**4.3 (2.4–7.6)**
Amitriptyline	201 720	1–10%	407	10	0.7 (0.4–1.3)	153	7	1.0 (0.5–2.1)
Nortriptyline	64 796	1–10%	130	3	0.7 (0.2–2.1)	74	4	1.2 (0.4–3.2)
Fluoxetine	57 408	1–10%	365	22	1.8 (1.2–2.8)	131	18	3.3 (2.0–5.4)
Citalopram	181 260	1–10%	815	100	**4.1 (3.3–5.1)**	278	63	**6.2 (4.7–8.3)**
Paroxetine	145 860	>10%	907	122	**4.6 (3.8–5.7)**	442	98	**6.3 (5.0–7.9)**
Sertraline	93 386	>10%	662	84	**4.2 (3.4–5.6)**	255	72	**8.5 (6.4–11.2)**
Fluvoxamine	16 660	0.1–1%	171	15	2.7 (1.6–4.6)	83	8	2.2 (1.0–4.5)
Escitalopram	75 179	1–10%	560	73	**4.3 (3.4–5.6)**	263	64	**6.9 (5.1–9.2)**
Fenelzine	184	-	10	2	-	7	0	-
Tranylcypromine	1918	0.001–0.01%	62	1	-	27	0	-
Moclobemide	951	'unknown'	12	0	-	16	1	-
Trazodon	12 191	'unknown'	43	1	-	29	4	3.2 (1.1–9.3)
Mirtazepine	125 480	-	340	4	0.4 (0.2–1.1)	249	8	0.7 (0.3–1.4)
Bupropion	27 466	-	319	14	1.7 (1.0–2.8)	184	16	1.9 (1.2–3.2)
Venlafaxine	103 080	1–10%	962	101	**4.5 (3.7–5.6)**	461	102	**6.3 (5.0–7.9)**
Duloxetine	30 631	1–10%	268	18	2.6 (1.6–4.2)	102	27	**7.4 (4.8–11.6)**
Agomelatine	2075	-	71	2	-	37	1	-
Hypericum	?	-	41	1	-	41	2	-
Vortioxetine	5403	'unknown'	39	1	-	10	1	-
Dexamfetamine	39 118	'unknown'	275	4	0.5 (0.2–1.4)	247	10	0.9 (0.5–1.6)
Methylphenidate	191 230	0.001–0.01%	659	7	0.4 (0.2–0.8)	642	11	0.3 (0.2–0.6)
Modafinil	2606	0.1–1%	11	0	-	18	1	-
Atomoxetine	4232	1–10%	50	1	-	64	5	1.7 (0.7–4.3)
N07 OTHER NERVOUS SYSTEM DRUGS			920	4	0.2 (0.1–0.5)	677	18	0.5 (0.3–0.9)
Nicotine	?	-	42	0	-	26	2	-
Varenicline	?	0.1–1%	643	3	0.2 (0.1–0.5)	424	4	0.2 (0.1–0.5)
Disulfiram	9067	-	10	0	-	25	3	2.8 (0.8–9.2)
Acamprosate	2906	1–10%	9	0	-	11	2	-
Naltrexone	4449	1–10%	19	1	2.0 (0.3–14.9)	20	3	3.6 (1.0–12.2)
Methadone	14 483	1–10%	38	0	-	61	4	1.4 (0.5–3.9)
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES			815	3	0.1 (0.0–0.4)	489	3	0.1 (0.0–0.4)
Indacaterol	5031	-	4	0	-	7	1	-
Salmeterol and fluticasone	215 080	-	137	2	-	69	1	-
Formoterol and budesonide	161 310	-	106	0	-	60	1	-
Budesonide	62 503	-	25	1	-	10	0	-

Supplement B continues on next page.

Supplement B: *Continued*

	Users in NL[a]	sADR risk in SmPC[b]	Reports of women			Reports of men		
			All	with sAE	ROR (95% CI)[c]	All	With sAE	ROR (95% CI)[c]
R06 ANTIHISTAMINES FOR SYSTEMIC USE			671	1	-	318	0	-
Cetirizine	64 094	'unknown'	108	1	-	62	0	-
S01 OPHTHALMOLOGICALS			221	1	-	183	2	-
Timolol, combinations	110 030	'unknown[d]	13	1	-	19	2	-

NL=Netherlands; 95%CI=95% confidence interval; ROR=Reporting Odds Ratio, calculated as the proportion of sAE for the specific drug (class), divided by the proportion of sAE for all drug(s)(classes); sADR=sexual adverse drug reaction; sAE=sexual adverse event; SmPC=Summary of Product Characteristics.

[a] Data from GIP databank, 2019. '-' should be interpreted as no users, '?' as no information available on number of users.

[b] Risk for sADRs as percentage of users. '-' should be interpreted as no risk registered, 'unknown' should be interpreted as too little cases of sADRs to estimate a risk.

[c] If the lower bound of the 95% confidence interval of the ROR is above 2, the ROR is shown in **bold** in this table.

[d] The SmPC indicates that the ADR was observed for the drug class or is seen in related drugs and thus called a pharmacological class effect.

[e] The sex of the male users of contraceptives is likely female, considering the indication of contraceptives.

Supplement C: Causality events mentioned in drug reports with sexual adverse events and number of positive sexual adverse events

	Number of women (%)	Number of men (%)
Dechallenge (drug dose decreased or treatment stopped)	416 (30.1)	250 (24.4)
• Because of sexual adverse event	36 (2.6)	53 (5.2)
• Positive (sexual adverse event disappeared)	121 (8.7)	87 (8.5)
• Negative (sexual adverse event remained)	6 (0.4)	13 (1.3)
Rechallenge (drug dose or treatment restarted)	13 (0.9)	11 (1.1)
Uncertainty about sexual adverse events because of potential other causes (e.g. disease, comedication)	32 (2.3)	45 (4.4)
Positive sexual adverse events	50 (3.6)	33 (3.2)
• Related to desire or arousal	47	14
• Related to orgasm	2	9[a]
• Related to pain during sex	1	-
• Related to erectile function	-	12
• Related to ejaculation	-	3
• Unspecific	2	1

[a] In 8 of 9 cases of men reporting positive orgasm-related sexual adverse events, this concerned elongation of the time to orgasm.

Supplement D: Types of sexual adverse events in drug reports posted on mijnmedicijn.nl between 2008–2020

	Women reporting sAE							Men reporting sAE						
		Type of sAE[a]							Type of sAE[a]					
	Drug reports (n)	Desire	Arousal	Vaginal dryness	Pain	Orgasm	Unspecific	Drug reports (n)	Desire	Arousal	Erectile function	Ejaculation	Orgasm	Unspecific
A02 DRUGS FOR ACID RELATED DISORDERS	0							5			5			
Omeprazole	0							5			5			
A08 ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS	0							1			1			
Sibutramine	0							1			1			
A10 DRUGS USED IN DIABETES	0							10	4		4			2
Metformin	0							5	3		1			1
Gliclazide	0							1	1					
Glimepiride	0							1						1
Rosiglitazone	0							1			1			
Liraglutide	0							1			1			
Empagliflozin	0							1			1			
C01 CARDIAC THERAPY	0							1			1			
Flecainide	0							1			1			
C02 ANTIHYPERTENSIVES	0							1			1			
Doxazosin	0							1			1[b]			
C03 DIURETICS	2	2						12	4		6		1	2
Hydrochlorothiazide	2	2						7	3		2			1
Chlortalidone	0							1	1		1			
Indapamide	0							2			2			
Eplerenone	0							1						1
Hydrochlorothiazide and potassium-sparing agents	0							1			1			
C05 VASOPROTECTIVES	0							1			1			
Isosorbide dinitrate (topical)	0							1			1[b]			
C07 BETA BLOCKING AGENTS	14	11	1			2		39	12		26			4
Propanol	2	2						0						
Sotalol	5	3				2		9	1		6			2
Metoprolol	3	3						20	8		14[b]			1
Atenolol	3	2	1					2	1		1[b]			
Acebutolol	0							1			1			
Bisoprolol	1	1						2	1		1			
Nebivolol	0							2	1					1
Labetalol	0							2			2			
Carvedilol	0							1			1			
C08 CALCIUM CHANNEL BLOCKERS	3	3						22	2		17			3
Amlodipine	2	2						18	2		13			3
Nifedipine	1	1						4			4			
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	5	4					1	39	10		29	1		3
Enalapril	0							2	1		1			
Lisinopril	0							5			5			
Perindopril	0							1			1			
Ramipril	0							3	2		2			
Quinapril	0							1			1			
Fosinopril	0							1			1			
Lisinopril and diuretics	0							4			4			
Perindopril and diuretics	0							1			1			

Supplement D continues on next page.

Supplement D: *Continued*

	Women reporting sAE							Men reporting sAE						
		Type of sAE[a]							Type of sAE[a]					
	Drug reports (n)	Desire	Arousal	Vaginal dryness	Pain	Orgasm	Unspecific	Drug reports (n)	Desire	Arousal	Erectile function	Ejaculation	Orgasm	Unspecific
Enalapril and lercanidipine	0							1			1			
Losartan	1						1	2			2	1		
Valsartan	2	1						5	3		4			
Irbesartan	2	2						3	1		1			1
Candesartan	0							1						1
Telmisartan	0							1			1			
Valsartan and diuretics	0							2			2			
Irbesartan and diuretics	0							4	1		2			1
Olmesartan medoxomil and amlodipine	0							1	1					
C10 LIPID MODIFYING AGENTS	1	1				1		37	18		18			5
Simvastatin	1	1				1		20	8		11			3
Pravastatin	0							1						1
Atorvastatin	0							6	4		1			1
Rosuvastatin	0							6	4		3			
Gemfibrozil	0							3	2		2			
Evolocumab	0							1			1			
D10 ANTI-ACNE PREPARATIONS	3	1		1			1	3	3					
Isotretinoin	3	1		1			1	3	3					
D11 OTHER DERMATOLOGICAL PREPARATIONS	1	1						0						
Alitretinoin	1	1						0						
G01 GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	1			1				0						
Clotrimazole	1			1				0						
G02 OTHER GYNECOLOGICALS	227	193	1	6	10	6	41	3	3					
Plastic IUD with copper	8	2		1	1	1	3	0						
Plastic IUD with progestogen	175	128[b]		4	5	5	37	0						
Vaginal ring with progestogen and estrogen	62	60[b]	1	1	4		1	0						
Cabergoline	3	3[b]						3	3[b]					
G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	384	333	9	23	11	2	25	6	2	2	4	1	1	1
Ethinylestradiol and norethisterone	1	1						0						
Ethinylestradiol and levonogestrel	118	96[b]	4	6	2		13	0						
Ethinylestradiol and desogestrel	17	16	2					0						
Ethinylestradiol and gestodene	3	3						0						
Ethinylestradiol and drospirenone	65	59[b]	1	5	6		1	0						
Ethinylestradiol and norelgestromin	2	2						0						
Estradiol and nomegestrol	6	6[b]		1		1		0						
Estradiol and dienogest	7	6[b]		1				0						
Medroxyprogesterone	27	26		1	1		1	0						
Etonogestrel	54	47[b]	2	6	1	1	3	0						
Desogestrel	40	39[b]		1			1	0						
Levonorgestrel	1						1	0						
Testosterone	1	1						6	2[b]	2	4[b]	1[b]	1	1
Estriol	1	1		1				0						
Tibolone	3	2[b]					1	0						
Medroxyprogesterone	4	2		1			1	0						

Supplement D continues on next page.

Supplement D: ***Continued***

	Women reporting sAE							Men reporting sAE						
		Type of sAE[a]							Type of sAE[a]					
	Drug reports (n)	Desire	Arousal	Vaginal dryness	Pain	Orgasm	Unspecific	Drug reports (n)	Desire	Arousal	Erectile function	Ejaculation	Orgasm	Unspecific
Lynestrenol	8	7					1	0						
Estrogen and dydrogesterone	3	3[b]						0						
Norethisterone and estrogen	1						1[b]	0						
Cyproterone	1							0						
Cyproterone and ethinylestradiol	18	15			1		1	0						
G04 UROLOGICALS	0							122	31	2	47	65	19	4
Oxybutynine	0							1			1			
Mirabegron	0							1			1[b]			
Vardenafil	0							1			1		1	
Combinations (phentolamine and papaverine)	0							1			1			
Alfuzosin	0							2			1[b]	1[b]	1	
Tamsulosin	0							55	5		14[b]	43	11	1
Silodosin	0							9	1		4	5	2	
Tamsulosin and dutasteride	0							18	4		8	9	1	2
Finasteride	0							17	11	1	8	3	1	
Dutasteride	0							17	10	1	8	4	2	1
H02 CORTICOSTEROIDS FOR SYSTEMIC USE	0							1						1
Prednisone	0							1						1
H03 THYROID THERAPY	3	3						1			1			
Levothyroxine sodium	3	3						0						
Thiamazole	0							1			1			
J01 ANTIBACTERIALS FOR SYSTEMIC USE	3	3						2	1		1			
Sulfamethoxazole and trimethoprim	1	1						1	1					
Clindamycin	0							1			1			
Ciprofloxacin	1	1						0						
Nitrofurantoin	1	1						0						
J05 ANTIVIRALS FOR SYSTEMIC USE	0							1						1
Emtricitabine, tenofovir disproxil and efavirenz	0							1						1
L01 ANTINEOPLASTIC AGENTS	0							2	1		1			
Imatinib	0							1	1					
Hydroxycarbamide	0							1			1[b]			
L02 ENDOCRINE THERAPY	55	36		14		1	8	20	10		6			5
Medroxyprogesterone	1	1						0						
Leuprorelin	8	6[b]		2		1	1	2	1		1			
Goserelin	3	1		1			1[b]	14	7		3			5
Tamoxifen	16	11		4			2	1	1					
Bicalutamide	0							1	1[b]					
Anastrozole	14	7		6			2	0						
Letrozole	11	8		1			2	0						
Exemestane	2	2						0						
Degarelix	0							2			2			
L04 IMMUNOSUPPRESSANTS	1	1						2	1					1
Adalimumab	0							1	1					
Methotrexate	1	1						1						1

Supplement D continues on next page.

Supplement D: ***Continued***

	Women reporting sAE							Men reporting sAE						
		Type of sAE[a]							Type of sAE[a]					
	Drug reports (n)	Desire	Arousal	Vaginal dryness	Pain	Orgasm	Unspecific	Drug reports (n)	Desire	Arousal	Erectile function	Ejaculation	Orgasm	Unspecific
Ibuprofen	0							1	1					
Etoricoxib	0							1					1	
M03 MUSCLE RELAXANTS	0							1	1					
Baclofen	0							1	1					
M04 ANTIGOUT PREPARATIONS	0							1	1					
Febuxostat	0							1	1					
M09 OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	0							1			1			
Hydroquinine	0							1			1			
N02 ANALGESICS	2	1	1					19	5	1	8	1	3	4
Oxycodon	0							5	3		1			1
Fentanyl	0							1						1
Buprenorphine	0							1			1			
Tramadol and paracetamol	0							1			1			
Tramadol	2	1	1[b]					10	1	1	5	1	3	2
Tapentadol	0							1	1					
N03 ANTIEPILEPTICS	10	6					4	27	13		15		3	2
Clonazepam	1	1						5	1		4		2	1
Carbamazepine	2						2	1	1					
Valproic acid	1	1						0						
Topiramate	1	1						1			1			
Gabapentin	0							3	2		2		1	
Levetiracetam	0							1	1					
Pregabalin	5	3					2	16	8		8			1
N04 ANTI-PARKINSON DRUGS	0							2						2
Biperiden	0							1						1
Pramipexole	0							1						1
N05 PSYCHOLEPTICS	43	23	2	1		7	12	80	38	1	23	3	7	19
Haloperidol	3	3						5	2		2		1	1
Flupentixol	1	1						1	1					
Chlorprothixene	1						1	0						
Zuclopenthixol	2			1		2		4	2		2			
Pimozide	0							1			1			
Clozapine	0							1						1
Olanzapine	4	1				1	2	13	9		2		1	3
Quetiapine	9	6				1	2	13	7	1	2		1	3
Sulpiride	2	2						3	1		1			1
Amisulpride	1		1			1		0						
Lithium	4	3	1					2	1		1			
Risperidone	7	4				1	2	19	6		6	2	2	6[b]
Aripiprazole	3					1	2[b]	5	2		1		1	2
Paliperidone	2	1					1	5	2		2	1	1	1
Diazepam	1						1	0						
Potassium clorazepate	0							1	1		1			
Prazepam	0							1			1			
Alprazolam	0							1			1			
Buspirone	0							1	1					

Supplement D continues on next page.

Supplement D: *Continued*

	Women reporting sAE							Men reporting sAE						
		Type of sAE[a]							Type of sAE[a]					
	Drug reports (n)	Desire	Arousal	Vaginal dryness	Pain	Orgasm	Unspecific	Drug reports (n)	Desire	Arousal	Erectile function	Ejaculation	Orgasm	Unspecific
Temazepam	1	1[b]						2	2					
Zolpidem	2	1					1	1	1					
N06 PSYCHOANALEPTICS	598	427	10	2	3	121	92	538	256	14	121	37	115	97
Clomipramine	12	6				5	2	14	1		4	3	4	3
Amitriptyline	10	8				2		7	2		4			1
Nortriptyline	3	1[b]					2[b]	4	1		2		1	1
Fluoxetine	22	8	4			6	6	18	6	2	3		5	5
Citalopram	100	78	2	1	1	21	8	63	30	1	10	6	16[b]	10
Paroxetine	122	81	1			27	19	98	43	2	20	9	23[b]	20
Sertraline	84	58[b]	1		1	13	20	72	32		8	8	8[b]	23
Fluvoxamine	15	12				2	2	8	1		3		4	2
Escitalopram	73	53[b]				18	10	64	40	1	7	4	18[b]	9
Fenelzine	2	1[b]	1			1		0						
Tranylcypromine	1	1[b]						0						
Moclobemide	0							1			1[b]			
Trazodon	1	1						4		1	3			1
Mirtazepine	4	1					3	8	5				3	1
Bupropion	14	12[b]				2[b]	2[b]	16	13[b]	2	5		1	1
Venlafaxine	101	81[b]	1			18[b]	13	102	57[b]	2	33	4	18[b]	13
Duloxetine	18	12[b]			1	5	2	27	10[b]		6	3	10[b]	6
Agomelatine	2	2						1	1[b]					
Hypericum	1	1						2	2[b]				1	
Vortioxetine	1	1				1		1	1					
Dexamfetamine	4	3[b]					1	10	7[b]	1	4		1	
Methylphenidate	7	5		1			2	11	2	2	5		1	1
Modafinil	0							1	1					
Atomoxetine	1	1						5	1		3		1	
N07 OTHER NERVOUS SYSTEM DRUGS	4	4						18	7	1	7			4
Nicotine	0							2	1		1			
Varenicline	3	3						4	3[b]		2[b]			
Disulfiram	0							3			2			1
Acamprosate	0							2	1					1
Naltrexone	1	1						3	2					1
Methadone	0							4		1	2			1
R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3	3						3	2		2			
Indacaterol	0							1	1		1			
Salmeterol and fluticasone	2	2						1	1					
Formoterol and budesonide	0							1			1			
Budesonide	1	1						0						
R06 ANTIHISTAMINES FOR SYSTEMIC USE	1							0						
Cetirizine	1	1						0						
S01 OPHTHALMOLOGICALS	1	1						2	1		1			
Timolol, combinations	1	1						2	1		1			
TOTAL	1383	1059	24	48	24	140	183	1025	427	21	346	108	150	161

sAE=sexual adverse event; aDrug reports with sAE were identified with one or more sAE terms. In this table all sAE terms are shown that were found for each drug report. The number of drug reports with 'unspecific' sAE terms are calculated only when no specific sAE terms were found in the drug report. bAlso one or more reports with a positive effect.