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

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Chapter 2

Adverse drug reactions on sexual functioning: a systematic overview

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Abstract

Adverse drug reactions (ADRs) that diminish sexual functioning can seriously affect a person's quality of life and can also affect drug adherence. However, no comprehensive overview on the subject is available and a lack of knowledge among healthcare professionals may be present. This systematic review of Summary of Products Characteristics identified 346 drugs registered with at least one sexual ADR. The drug class 'nervous system' (N) was represented most frequently with 105 drugs, followed by 'cardiovascular system' (C) with 89 drugs. For 16 drugs an incidence rate for sexual ADR of >10% was reported and for 98 drugs there was an incidence rate >1%. Because sexual ADRs occur in frequently used drugs, they should be considered in clinical practice to optimize drug treatment.

Introduction

Drugs can affect sexual functioning in various ways with important consequences concerning treatment adherence and quality of life. Adverse drug reactions (ADRs) can reduce sexual function as shown in different reviews for antidepressants [1-4], antipsychotics [5, 6], mood stabilizers and anxiolytic drugs [7], cardiovascular drugs [8, 9], hormonal contraceptives [10-12], cancer treatments [13-15] and alpha-blockers and 5-alpha-reductase inhibitors (5-ARIs) [16-18] used in treatment of benign prostatic hypertrophy (BPH). Some medical conditions are associated with reduced sexual function, such as heart disease, depression and BPH [1, 3, 17-21]. On its own, sexual dysfunction can also cause depression [1]. Treatment of the underlying disease (e.g. with antidepressants, angiotensin II receptor blockers) can improve sexual dysfunction, however drugs used in treatment can also negatively affect sexual function (e.g. betablockers, diuretics, selective serotonin reuptake inhibitors (SSRIs)) [1, 4, 8, 9, 20].

Sexual function is an important factor in the quality of life of a person [22], and this also applies for not-healthy individuals [6, 23]. To them the subjective burden of sexual dysfunction can be as high as the burden of the disease itself, as shown for schizophrenia [6]. Sexual ADRs can lead to a lower treatment adherence, negatively effecting treatment results [24, 25]. This might be fatal with drugs that require strict adherence to be effective, such as anti-HIV medication. In antidepressant treatment, which requires treatment for at least six months, sexual ADRs are one of the most common reasons for early antidepressant treatment cessation [24].

Among healthcare professionals, knowledge and awareness of sexually related ADRs and their consequences for patients might not always be sufficient. Focusing on the desired main treatment effect, potential alternative drugs with the same effect and fewer sexually related ADRs might not get enough attention. Although the majority of cardiologists in the Netherlands reported to inform patients on sexual ADRs of their drug treatment, their knowledge of these effects were evaluated as insufficient [26]. Awareness of sexual problems after cancer treatment is more common [27-29], yet sexual morbidity remains undertreated and not adequately discussed [27, 29-31]. When patients report sexual complaints during clinical medication reviews, 86% suspected their medication as a cause. Yet only for 20% of responders was a sexual ADR listed in the product information of their medication [32]. Owing to this striking difference, Reichenpfader *et al*. concluded in their meta-analysis that most of the efficacy trials during the registration process were not likely to detect sexual ADRs. Study procedures on data collection were not specified and sexual ADRs were not usually primary outcomes [33]. Yet the study procedure influences the incidence of sexual ADRs greatly, as seen for the difference in directly questioning and spontaneously reporting

[6, 21]. In 2015 the U.S. Food and Drug Administration (FDA) stated that antidepressant-related sexual dysfunction should be adequately assessed during clinical trials and described in product labels [34]. Three years later, a citizen petition to the FDA asked revision of all SSRI and SNRI product labels to warn for sexual ADRs [35]. As a first step in the awareness of sexual ADRs an overview is needed to inform clinicians on drugs with reported sexual ADRs, as registered in their regulatory product information, and their incidence rates.

Methods

Design

This study is a systematic review of drugs with sexual ADRs registered in the Summary of Products Characteristics (SmPCs).

Selection of sources to detect drugs with registered sexual ADRs

To obtain a marketing authorisation for a new drug in Europe, the SmPC is a mandatory document to provide regulatory product information. This SmPC must include the basic information about the product as relevant for healthcare professionals. This information must be provided by a specific template including section 4.8 'undesirable effects' in which ADRs are listed. An ADR is harm directly caused by a drug at normal doses [36]. Drug developers and safety authorities evaluate adverse drug events on causality before naming it an ADR and before it is reported in section 4.8 in the SmPC. These ADRs can be collected from clinical trials, post-authorisation safety studies, observational studies and case reports from spontaneous reporting of healthcare providers and patients [37].

Selection of databases listing registered adverse drug reactions for medicinal products

PROTECT adverse drug reaction database

PROTECT was setup by the research consortium Protect as the structured ADR database of the European Medicines Agency (EMA). Its purpose is to improve the efficiency of signal detection processes and to allow updating of the SmPC [38]. The PROTECT database is publicly available and shows all ADRs as registered in section 4.8 of the SmPC. It can be searched on product, drug or ADR. For each ADR a number is added that codes for the incidence rates of a potential occurrence in qualitative terms (i.e. very rare). The version accessed was last updated 30th June 2016.

National registration authority of the Netherlands (CBG)

Since the PROTECT database only includes centrally authorised products [38], the website of the Dutch national registration authority (CBG) was searched as well, for nationally authorised products and products specifically authorised in the Netherlands. This website includes a database of the SmPCs for all drugs that are registered in the Netherlands. The database can be searched with any term, drug or product, showing all SmPCs of those drugs or products or that include that term in their content. For a first set of search terms, section 4.8 of the SmPCs in the CBG database was consulted on 27th and 28th July 2018. The database of the CBG is updated every week, the last update of the version accessed in this search was 25th July 2018. On 17th and 18th August 2018 a second search was performed with an expansion of search terms and a last update on 15th August 2018.

Selection of a dictionary for adverse drug reaction terminology

The PROTECT database and CBG database use the terminology from the Medical Dictionary for Regulatory Activities, MedDRA [39]. MedDRA is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The MedDRA dictionary is organized by the System Organ Class (SOC), divided into High-Level Group Terms (HLGT), which are divided in several High-Level Terms (HLTs) based upon anatomy, pathology, physiology, ethology or function. A HLT covers a group of preferred terms (PTs), one distinct term per symptom, diagnosis or in this case ADR. Synonyms and lexical variants of the PT, named Lower Level Terms (LLTs), are also used in the SmPC writing and are mentioned as the linked PTs in Tables 2.1 and 2.2. The MedDRA version in Dutch was used for the search in the national database of SmPCs in the Netherlands.

Selection of search terms for sexual adverse reactions

Search terms were selected by urologist-sexologists (HE, MN; Figure 2.1). Relevant terms for sexual ADRs related to declined sexual functioning were included and physiological disorders concerning reproduction or disorders concerning gender identity were excluded. Subsequently, SmPC texts were reviewed and synonyms of MedDRA terms detected and not listed in the MedDRA database were added to the list of search terms. The list was supplemented with ADRs that show a change in blood concentration of testosterone or prolactin. Furthermore, Peyronie's disease and vulvovaginal dryness were added.

Detection of drugs with search terms listed in their SmPC information

PROTECT Adverse Drug Reaction Database

The PROTECT database was searched with each MedDRA number of the selected terms (PT and LLT level, because both levels are used in the SmPCs). Drugs matching the search terms were listed together with specific information on age and gender related to the ADR, and ADR incidences rates.

Frequencies of ADRs are described in the SmPC as a percentage or a qualitative term: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000). If an incidence rate was not named, the ADR was listed as 'frequency not known'. Numerical figures in SmPCs were not interpreted in the PROTECT database and consequently listed as 'unknown'. ADRs were listed on substance level. This implied that the information for different brands and combination products were aggregated. If different incidence rates were reported within SmPCs for the same substance, the highest frequency reported was listed. Possible reasons for a difference in frequency rates were use of different clinical trials or different incidence rates in fixed drug combinations.

National registration authority of the Netherlands (CBG)

A search function on the CBG website was used to search for the selected terms in Dutch within the complete SmPC text of each registered product. The resulting list of SmPCs containing one of the search terms was scanned only on substance and Anatomical Therapeutic Chemical (ATC) classification [40]. For all search terms the related substances were listed together with their ATC codes. To obtain information on the incidence rate and possible specifications for gender, age or a pharmacological class effect, the complete SmPC of drugs concerned was downloaded and section 4.8 was scanned. This process started with the SmPC of the highest registration number and, if the product with the highest registration number did not show all the MedDRA search terms for sexual ADRs detected for a substance, additional SmPC texts were screened. Search terms mentioned in a different section than section 4.8 were not included.

Data processing

ADRs are shown as the MedDRA preferred terms. Consequently, if a LLT was detected in the SmPC, the corresponding PT is shown (e.g. impotence (LLT) is listed as erectile dysfunction (PT)). This method is chosen to not exclude drugs that were listed with either LLT or PT in their SmPC and not both terms. Thus, drugs registered with both LLT and

PT are mentioned only once in the table, together with the PT to only show the same hierarchical level of terms in the tables.

The incidence rates are shown in qualitative terms (e.g. uncommon). In case of different incidence rates from the PROTECT database and CBG database for the same ADR and the same drug, the highest incidence rate is registered. For validation, this procedure was repeated for a selection of 10 drugs by a second researcher (MT). Analyses were performed with Microsoft Excel 2016 (Microsoft Corp., Redmond, WA).

Results

With 194 MedDRA search terms (Figure 2.1) a total of 346 drugs were detected with at least one sexual ADR registered in the SmPC (See Table S2.3 in the supplementary material). A total of 249 (72%) drugs were detected only in the national database (CBG), 64 (18%) were detected only in the PROTECT database and 33 (9%) in both databases (Figure 2.2). These drugs belonged to 13 of the 14 drug classes of the ATC classification level 1. Drug class nervous system (N) was represented most with 105 drugs, followed by drug class cardiovascular system (C) with 89 drugs.

Sexual ADRs occurred commonly (in >1% of the users) in 98 drugs. For 16 drugs the sexual ADRs were likely to occur in >10% of the users (See Table S2.1 in supplementary material). An example of this is the aldosterone antagonist spironolactone, which can lead to erectile dysfunction and a decrease in libido in >10% of men.

Table 2.1 lists sexual ADRs discovered for the drugs most frequently used in the Netherlands in 2017. For the most frequently used drugs, diclofenac and simvastatin, no incidence rates were reported in the SmPC. Seven out of the ten most frequently used drugs with sexual ADRs belonged to the anatomical group of the cardiovascular system. Sexual ADRs occurred uncommon or rare. Of the 20 most frequently used drugs, tamsulosin and amitriptyline showed the highest incidence rate (>1%).

For 20 drugs, differences in sexual ADRs for females and males were explicitly stated in the SmPC (Table 2.2). For example, on treatment with goserelin >10% of the females noticed vulvovaginal dryness whereas >10% of men developed erectile dysfunction.

For 13 drug classes, ADRs for sexual functioning were mentioned as an effect for the entire drug class in the corresponding SmPCs (See Table S2.2 in supplementary material). However, the consistency of mentioning this pharmacological class effect in the individual SmPCs varied as seen for the statins: the pharmacological class effect as mentioned for the

ATC groups C10AA, C10BA and C10BX addressed in total 13 statin drugs or combinations but was only mentioned in the SmPC of ten statins. One reason to mention ADRs as pharmacological class effect was that the ADR was not detected in studies for each particular drug but reported for other drugs in the same drug class. Additionally, class effects were stated if incidence rates per drug were not known: In 120 drugs (35%) one or more sexual ADRs were listed with an unknown incidence rate. For 42 drugs with an unknown frequency for one or more ADR, a pharmacological class effect was mentioned.

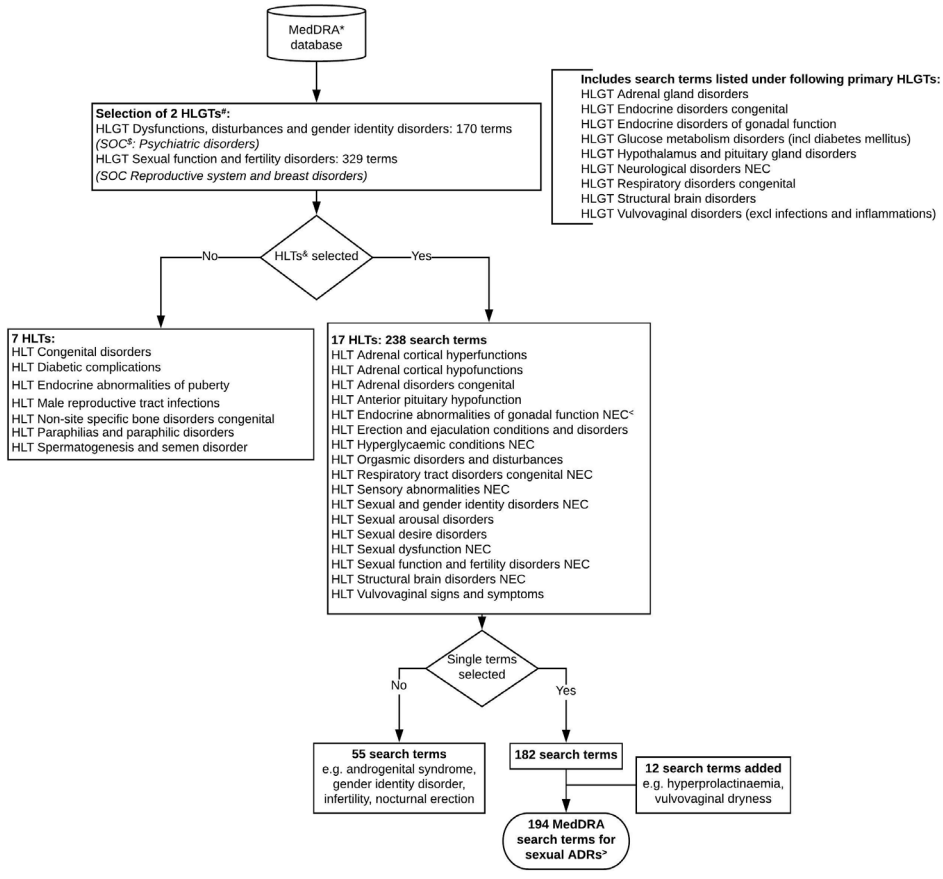

Figure 2.1: Selection of MedDRA search terms for sexual adverse drug reactions.
This figure shows the selection of 194 search terms used to search Summary of Products of Characteristics for registered sexual adverse drug reactions (ADRs). From the MedDRA database the two relevant high-level group terms (HLGTs) were selected. These HLGTs include search terms that belong to other HLGTs but are also relevant for the two selected HLGTs. Of the 24 high-level terms (HLTs) that belong to the selected HLGTs, 17 were found relevant to a decreased sexual functioning. On the lowest hierarchical levels, the single terms, 55 terms were excluded because they were not found relevant to a decreased sexual functioning. Twelve more search terms were added after a first search. There terms were found relevant but are not listed under the two HGLTs. *MedDRA: Medical Dictionary for Regulatory Activities; #HLGTs: High-Level Group Terms; &HLTs: High-Level Terms; <NEC: not elsewhere classified; >ADRs: Adverse Drug Reactions.

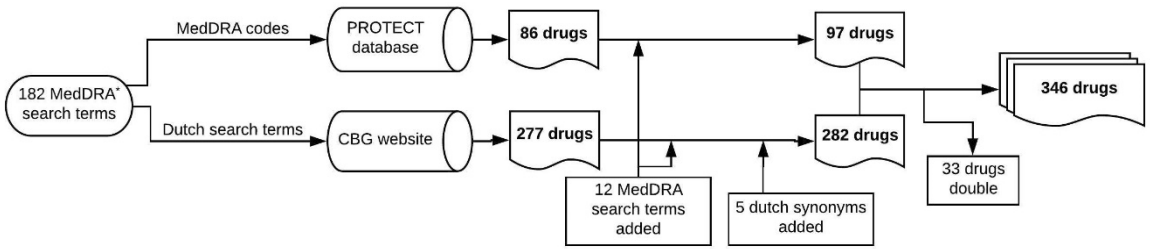

Figure 2.2: Search of drugs with registered sexual adverse drug reactions.
This figure shows how 346 drugs were found with a total of 194 Medical Dictionary for Regulatory Activities (MedDRA) search terms and five Dutch synonyms in two databases. During a first search, the codes of 182 MedDRA terms were used to find 86 drugs in the PROTECT database. With the Dutch synonyms of the same MedDRA terms 277 drugs were found in the database on the website of the registration authority of The Netherlands(CBG). After the first search, 12 MedDRA search terms were added and five Dutch synonyms(not MedDRA terms) were added, to find 16 more drugs. Some drugs were found in both databases, therefore a total of 346 different drugs were found using the search terms in two databases. *MedDRA: Medical Dictionary for Regulatory Activities.

Table 2.1: Most frequently used drugs with sexual adverse drug reactions in the Netherlands

	ATC	Drug	Common	Uncommon	Rare	Unknown, not mentioned or no standard category	Usernumbers in The Netherlands[a]
1	M01AB05	Diclofenac				Erectile dysfunction[c]	1 097 000
2	C10AA01	Simvastatin				Erectile dysfunction, sexual dysfunction[b]	1 075 000
3	C07AB02	Metoprolol			Libido disorder, erectile dysfunction, peyronie's disease, sexual dysfunction		1 021 000
4	C03AA03	Hydrochlorothia-zide	Erectile dysfunction				650 050
5	C08CA01	Amlodipine		Erectile dysfunction			558 710
6	C10AA05	Atorvastatin[b]				Sexual dysfunction	544 150
7	N02AA05	Oxycodone		Libido decreased, erectile dysfunction, hypogonadism			438 460
8	C09AA04	Perindopril		Erectile dysfunction			318 070
9	G03AA07	Levonorgestrel and ethinylestradiol		Libido decreased, dyspareunia, vulvovaginal dryness	Libido increased		311 310
10	C09AA02	Enalapril		Erectile dysfunction			286 710

[a] Based on national health insurance data, the Netherlands, 2017 [Source: Zorginstituut Nederland, GIP (2017)];
[b] 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 (thus the ADR was reported for the drug or for drugs in the same pharmacological class);
[c] The SmPC indicates that the adverse reaction has a doubtful relationship with the drug. ATC: Anatomical Therapeutic Chemical; uncommon: incidence >0.1% and <1%; rare: incidence >0.01% and <0.1%.

Table 2.2: Drugs with sexual adverse drug reactions registered specifically for men or women

ATC	Substance	Very common	Common	Uncommon	Rare	Unknown, not mentioned or no standard category
C03DA01	*Spironalactone*	Libido decreased, erectile dysfunction	Libido decreased			
G03HA01	*Cyproterone*	Libido decreased, erectile dysfunction	Libido decreased			
G04BE03	*Sildenafil*					Spontaneous penile erections
G04BX14	*Dapoxetine*			Male orgasmic disorder		
J05AP01	*Ribavirin*[a]		Sexual dysfunction, erectile dysfunction			
L01XX23	*Mitotane*					Blood testosterone free decreased, blood testosterone decreased
L02AE03	*Goserelin*	Erectile dysfunction, vulvovaginal dryness				
L02AE04	*Triptorelin*	Erectile dysfunction, vulvovaginal dryness, dyspareunia				
L04AA18	*Everolimus*			Hypogonadism		
N05AB02	*Fluphenazine*					Erectile dysfunction, libido disorder

Table 2.2 continues on next page.

Table 2.2: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Unknown, not mentioned or no standard category
N05AF05	*Zuclopenthixol*			Female orgasmic disorder		
N05AH03	*Olanzapine*		Erectile dysfunction			
N06AA10	*Nortriptyline*					Orgasmic disorder
N06AA12	*Doxepin*				Orgasm abnormal, erectile dysfunction	
N06AA16	*Dosulepin*					Orgasm abnormal
N06AB04	*Citalopram*		Anorgasmia			Priapism
N06AB06	*Sertraline*			Sexual dysfunction		
N06AB10	*Escitalopram*		Anorgasmia, ejaculation disorder, erectile dysfunction			Priapism
N06AX16	*Venlafaxine*		Ejaculation disorder, orgasmic disorder	Orgasmic disorder		
R06AD01	*Alimemazine*					Erectile dysfunction

[a] ADR occurs in adults only. Very common: Incidence >10%; Common: incidence >1% and <10%;
Uncommon: incidence >0.1% and <1%; Rare: incidence > 0.01% and < 0.1%; Gray = reported specifically for females; Black = reported specifically for men.

Reports of permanent sexual ADRs after treatment cessation were rare. The SmPCs of finasteride and dutasteride mention that treatment with these drugs could lead to permanent sexual ADRs after the treatment cessation. After treatment with baclofen, priapism could occur as a withdrawal phenomenon. Priapism could lead to secondary loss of erection.

Concluding remarks and discussion

This is the first systematic overview of drugs with registered sexual ADRs. It showed that sexual ADRs are common, being listed for nearly all drug classes. Of the several hundred drugs with registered sexual ADRs, most affect the nervous system and cardiovascular system. Many sexual ADRs occur commonly in users, but only a few very commonly. Most often, the incidence is unknown.

Sexual ADRs are a complex mixture of biological and psychological, primary as well as secondary effects in both brain and body. Additionally, their perception is influenced by the disease state and other risk factors. Some pharmacological mechanisms, especially for the drugs affecting the nervous system and cardiovascular system, can explain the effect on sexual functioning. Drugs affecting the nervous system are known to influence the availability of neurotransmitters such as dopamine, norepinephrine and acetylcholine, which positively influence one or more stages of the human sexual response. Serotonin however decreases desire and arousal [1]. This can be understood as only stimulation of 5HT-2A negatively affecting sexual function, whereas stimulation of 5HT-2C and 5HT-1A facilitate erection and ejaculation, respectively [1]. Other drugs affect the levels of sex hormones or their receptors which explains sexual ADRs for contraceptives, statins (by reducing available cholesterol as a precursor of testosterone), spironolactone (binding to progesterone and androgen receptors), 5-ARI (5-AR catalyses a key rate limiting step in steroidogenesis) and older anticonvulsants (inducing a higher level of sex hormone binding globulin) [7, 9, 11, 16, 17, 41]. Dopamine antagonists appear to increase prolactin levels by blocking D2 receptors in the hypothalamic infundibular system [5]. The sympathetic nervous system is involved in the integration of erection, emission and ejaculation. Inhibiting this system (betablockers) might also induce sexual dysfunction [9]. Indirectly, sedation, extrapyramidal effects, mood changes, weight gain or the nocebo effect can also affect sexual function [5, 8, 16, 42].

The overview of sexual ADRs presented here shows some discrepancies with the current literature. Other overviews were formed by searching databases such as PubMed, MEDLINE and EMBASE, displaying the scope of articles written about this subject which is more prone to publication bias [4]. In most reviews published so far, little information is available

on the incidences and mechanisms for some drug groups such as alimentary tract and metabolism (ATC group A), blood and blood forming organs (B), dermatologicals (D), antiinfectives for systemic use (J), musculo-skeletal system (M), respiratory system (R), sensory organs (S) and various (V). Although in clinical reviews SSRIs are among the drugs rating the highest frequency for sexual ADRs (from 15 to 80%) [1, 2], only paroxetine and sertraline were registered with >10% for sexual ADRs. The reviews generally reported decreased sexual desire in all antipsychotics (N05A) [5, 43]. However, only for eight of the 25 antipsychotics a decrease or loss of libido was registered in the SmPC.

In some reviews gender differences for sexual ADRs were mentioned [2, 5], for example more elevated prolactin levels in women compared to men during long term treatment with typical antipsychotics [44, 45]. In 1997, a study in depressed patients on treatment with sertraline or paroxetine concluded that SSRIs could worsen sexual functioning in men, but increase desire and arousal in women [46]. Yet of the SSRIs, gender differences were only specified in the SmPC for citalopram and sertraline.

Several options have been suggested to decrease the occurrence of sexual ADRs: before starting treatment, clinical evaluation should take place to modify risk factors that influence sexual function such as medical comorbidities, substance abuse, hormonal changes and psychological issues [1, 4, 5].

The diagnosis of treatment-emergent sexual dysfunction could be complicated by the same risk factors (e.g. cofounding by indication) and co-medication. If sexual ADRs occur, options are to wait for a spontaneous reduction of side effects over time, to reduce doses or, if possible, take drug holidays. Suppletion with other drugs (e.g. sildenafil, bupropion) or to switch within the same drug class to drugs with fewer sexual ADRs were also suggested [47].

Recent findings suggest that treatment-emergent sexual dysfunction can persist in some individuals after discontinuation of the medication. More specifically, this has been described for SSRIs as post-SSRI sexual dysfunction (PSSD) and for 5-ARIs as post-finasteride syndrome (PFS) [48-51]. In a study including >10 000 patients, after stopping 5-ARIs, 1.4% developed persistent erectile dysfunction (persistent defined as >90 days after stopping) and, of the patients that developed erectile dysfunction during treatment, 31.5% developed persistent erectile dysfunction [51]. The prevalence of PSSD is less known and, although different theories exist to explain the pathophysiology and to come up with treatment strategies, treatment of PSSD remains challenging [48].

Information for this overview was collected from the database of the official European registration authority, EMA, for centrally authorized drugs and additionally for drugs authorised in the Netherlands. By combining two databases, the overview presented is as

complete as possible for drugs registered in the Netherlands. We expect that this is also valid for other European countries. Because it was not possible to search within all SmPCs on the EMA website, the overview was created with the PROTECT database, with the disadvantage that it was only updated up to June 2016. However, updates from the national database were more recent, up to August 2018. We used MedDRA terms for our search for sexual ADRs. This might not cover synonyms or additional sexual problems. To this end, more search terms were added to the search, defined from additional terms in SmPC texts and by the clinical sexologists. This identified sexual ADRs in 16 additional drugs. Although some drugs might still have been missed, we assume that our search strategy was as complete as possible.

The information and incidence rates as mentioned in the SmPC texts might be up for discussion because the reviews about sexual ADRS discuss that only some of the studies they found used a validated sexual function rating scale, some lacked a baseline or placebo control and the prevalence of sexual dysfunction was often not a primary or even secondary goal of research [2, 4, 5, 7, 8, 51, 52]. Moreover, culture and time may influence incidence rates as well, since sexual ADRs are perceived in other ways in different cultural backgrounds and in different times, e.g. the occurrence of sexual ADR was reported significantly less before the year 2000 [53]. This lack of sensitivity might also be true for the sexual ADRs reported in trials and, consequently, the registered sexual ADRs as shown here might underestimate the problem. Uncertainty from research is likely as pharmacological class effects and gender differences were only mentioned in the SmPCs of some drugs, and not in similar drugs with a comparable working mechanism to cause sexual ADRs. In addition, SmPCs for the same drug should name the same sexual ADRs with the same frequencies because of the same information in the literature. However, during this search, differences were found for the ADRs mentioned as well as the corresponding incidence rates.

Recently, there is more attention in research on the importance of sexual ADRs for the quality of life of a patient and treatment adherence. However, the awareness of sexual ADRs is still low under healthcare professionals and underreported during clinical trials [51, 53]. There are different mediums possible to inform patients about the sexual ADRs before starting treatment, such as more information in product labels, folders or videos in healthcare practices and education for healthcare professionals to address these issues. No studies on patients' preferences have been found so far, yet to offer a tailor-made medical treatment, the preference of the patient should be the priority.

During clinical trials more attention should be paid to evaluate changes in sexual functioning. Additionally, little is known about effects from concomitant therapy with

several drugs that impair sexual function. The influence of sexual ADRs on poor adherence should be studied in chronic treatments for life threatening conditions and for drugs with a narrow therapeutic range.

In conclusion, this paper provides a comprehensive overview of sexual ADRs including an estimate of their frequencies for a substantial number of frequently used drugs. Information about sexual ADRs is considered essential for improving treatment adherence and patient quality of life.

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Supplementary data

Table S2.1: (Combinations of) drugs reported with sexual adverse drug reactions

ATC	(Combination of) drugs	Very common	Common	Source[#]
A Alimentary tract and metabolism				
A03AX12	**phloroglucinol**		erectile dysfunction	CBG
A07EA06	**budesonide**		erectile dysfunction	CBG
A08AA62	**bupropion and naltrexone**		ejaculation delayed^*(naltexone)*	EMA
A10BD05	**metformin and pioglitazone**		erectile dysfunction	EMA
A10BG03	**pioglitazone**		erectile dysfunction	both
A16AX06	**miglustat**		libido decreased	EMA
C Cardiovascular system				
C02AC01	**clonidine**		erectile dysfunction	CBG
C03DA01	**spironalactone**	libido decreased[#], erectile dysfunction[#]	libido decreased*	CBG
C07AA07	**sotalol**		sexual dysfunction	CBG
C07AG01	**labetalol**		erectile dysfunction	CBG
C07FX05	**metoprolol and ivabradine**		libido disorder^*(metoprolol)*	CBG
C09AA09	**fosinopril**[-]		sexual dysfunction	CBG
C09BA07	**benazepril and diuretics**		erectile dysfunction^*(thiazide diuretics)*	CBG
C09DA03	**valsartan and diuretics**		erectile dysfunction^*(hydrochlorothiazide)*	CBG
C09DX01	**valsartan, amlodipine and hydrochlorothiazide**		erectile dysfunction	EMA
C09XA52	**aliskiren and hydrochlorothiazide**		erectile dysfunction^ *(hydrochlorothiazide)*	EMA
G Genito-urinary system and sex hormones				
G02BA03	**plastic IUD with progestogen**		libido decreased	CBG
G02BB01	**vaginal ring with progestogen and estrogen**		libido decreased	CBG
G03AA14	**nomegestrol and estradiol**		libido decreased	EMA
G03AC02	**lynestrenol**		libido decreased	CBG
G03AC06	**medroxyprogesterone**		libido decreased	CBG
G03AC08	**etonogestrel**		libido decreased	CBG
G03AC09	**desogestrel**		libido decreased	CBG
G03DB08	**dienogest**		loss of libido	CBG
G03DC03	**lynestrenol**	libido decreased	libido increased	CBG
G03HA01	**cyproterone**	libido decreased[#], erectile dysfunction[#]	libido decreased*	CBG
G04BE01	**alprostadil**		spontaneous penile erection, erection increased, peyronie's disease	CBG
G04BE30	**combinations (of drugs used in erectile dysfunction)**		erection increased	CBG
G04BX14	**dapoxetine**		erectile dysfunction, libido decreased	CBG

Table S2.1 continues on next page.

Table S2.1: ***Continued***

ATC	(Combination of) drugs	Very common	Common	Source[#]
G04CA02	**tamsulosin**		ejaculation disorder, retrograde ejaculation, ejaculation failure, ejaculation delayed	CBG
G04CA03	**terazosin**	erectile dysfunction	libido increased, priapism	CBG
G04CA04	**silodosin**	ejaculation failure, retrograde ejaculation		EMA
G04CA52	**tamsulosin and dutasteride**		erectile dysfunction, libido decreased, ejaculation disorder	CBG
G04CA53	**tamsulosin and solifenacin**		ejaculation disorder, retrograde ejaculation, ejaculation failure	CBG
G04CB01	**finasteride**		libido decreased, erectile dysfunction	CBG
G04CB02	**dutasteride**		ejaculation disorder, erectile dysfunction, libido decreased	CBG
H Systemic hormonal preparations, excluding sex hormones and insulins				
H05BX01	**cinacalcet**		blood testosterone decreased	both
J Antiinfectives for systemic use				
J05AE01	**saquinavir**		libido decreased	EMA
J05AP01	**ribavirin[&]**		libido decreased, sexual dysfunction[#], erectile dysfunction[#]	both
J05AP03	**boceprevir**		libido disorder, erectile dysfunction	EMA
J05AR10	**lopinavir and ritonavir**		erectile dysfunction	both
L Antineoplastic and immunomodulating agents				
L01AC01	**thiotepa[$]**	hypogonadism		EMA
L01DB11	**pixantrone**		spontaneous penile erection	EMA
L01XE04	**sunitinib**		ejaculation disorder	EMA
L01XE05	**sorafenib**		erectile dysfunction	EMA
L01XE16	**crizotinib**		blood testosterone decreased	EMA
L02AE01	**buserelin**		erectile dysfunction, loss of libido	CBG
L02AE02	**leuprorelin**	erectile dysfunction	dyspareunia	CBG
L02AE03	**goserelin**	libido decreased, erectile dysfunction[#], vulvovaginal dryness*		CBG
L02AE04	**triptorelin**	libido decreased, erectile dysfunction[#], vulvovaginal dryness*, dyspareunia*, ejaculation failure, ejaculation disorder	loss of libido	CBG
L02BB01	**flutamide**	libido decreased, erectile dysfunction		CBG
L02BB02	**nilutamide**	libido decreased, erectile dysfunction		CBG
L02BB03	**bicalutamide**		erectile dysfunction, libido decreased	CBG
L03AB10	**peginterferon alfa-2b**		libido decreased[&], sexual dysfunction, erectile dysfunction	EMA

Table S2.1 continues on next page.

Table S2.1: ***Continued***

ATC	(Combination of) drugs	Very common	Common	Source#
L03AB11	**peginterferon alfa-2a**		libido decreased,erectile dysfunction	EMA
L04AA18	**everolimus**		erectile dysfunction	CBG
L04AX04	**lenalidomide**		erectile dysfunction	EMA
M Musculo-skeletal system				
M03BX01	**baclofen**		sexual dysfunction	CBG
M09AB02	**collagenase**		dyspareunia, painful erection, erectile dysfunction	EMA
N Nervous system				
N01BB20	**combinations (lidocaine, prilocaine)**		erectile dysfunction	EMA
N02CX02	**clonidine**		erectile dysfunction	CBG
N03AX12	**gabapentin**		erectile dysfunction	CBG
N03AX16	**pregabalin**		libido decreased, erectile dysfunction	both
N04BC09	**rotigotine**		libido increased~, libido disorder, hypersexuality~	EMA
N05AD01	**haloperidol**		sexual dysfunction	CBG
N05AD06	**bromperidol**	hyperprolactinaemia		CBG
N05AE03	**sertindole**		ejaculation disorder, erectile dysfunction	CBG
N05AF01	**flupentixol~**		libido decreased	CBG
N05AF03	**chlorprothixene**		libido decreased	CBG
N05AF05	**zuclopenthixol**		libido decreased, ejaculation failure, erectile dysfunction	CBG
N05AG02	**pimozide**		erectile dysfunction	CBG
N05AH03	**olanzapine**	blood prolactin increased	libido decreased, erectile dysfunction#	both
N05AH04	**quetiapine**		hyperprolactinaemia	CBG
N05AL01	**sulpiride**		hyperprolactinaemia	CBG
N05AL03	**tiapride**		hyperprolactinaemia	CBG
N05AX08	**risperidone**		hyperprolactinaemia, libido decreased, erectile dysfunction	CBG
N05AX12	**aripiprazole**		erectile dysfunction	both
N05AX13	**paliperidone**		hyperprolactinaemia	both
N05BA08	**bromazepam**		erectile dysfunction, libido decreased, hyperprolactinaemia	CBG
N05BA12	**alprazolam**		libido decreased, libido increased, sexual disfunction	CBG
N05CD06	**lormetazepam**		libido decreased	CBG
N06AA04	**clomipramine**	libido disorder, erectile dysfunction		CBG
N06AA09	**amytriptyline**		libido decreased, erectile dysfunction	CBG
N06AA10	**nortriptyline**		libido decreased, erectile dysfunction	CBG
N06AA21	**maprotiline**		libido disorder, erectile dysfunction	CBG

Table S2.1 continues on next page.

Table S2.1: *Continued*

ATC	(Combination of) drugs	Very common	Common	Source[#]
N06AB03	**fluoxetine**		ejaculation disorder, ejaculation delayed, libido decreased, loss of libido, erectile dysfunction, retrograde ejaculation, premature ejaculation	CBG
N06AB04	**citalopram**		ejaculation disorder, ejaculation failure, female orgasmic disorder, anorgasmia* erectile dysfunction, libido decreased, loss of libido	CBG
N06AB05	**paroxetine**	sexual dysfunction		CBG
N06AB06	**sertraline**	ejaculation disorder	erectile dysfunction	CBG
N06AB10	**escitalopram**		anorgasmia*, ejaculation disorder[#], erectile dysfunction[#], libido decreased	CBG
N06AX16	**venlafaxine**		erectile dysfunction, ejaculation disorder[#], anorgasmia, libido decreased, orgasmic disorder[#]	CBG
N06AX21	**duloxetine**		ejaculation delayed, ejaculation disorder, libido decreased, erectile dysfunction, orgasm abnormal	both
N06BA09	**atomoxetine[&]**		ejaculation disorder, erectile dysfunction, decreased libido	CBG
N07BB03	**acamprosate**		female sexual arousal disorder, erectile dysfunction, libido increased	CBG
N07BB04	**naltrexone**		ejaculation delayed, erectile dysfunction	CBG
N07BB05	**nalmefene**		libido decreased, loss of libido	EMA
N07BC02	**methadone**		libido decreased, erectile dysfunction	CBG
N07BC51	**buprenorphine, combinations**		libido decreased, erectile dysfunction	both

ATC: Anatomical Therapeutic Chemical; EMA: Substance found in PROTECT database, which lists the centrally authorised products at EMA; Both: The product is registered in both sources; Very common: Incidence > 10%; Common: incidence >1% and < 10%; & ADR occurs in adults only; $ ADR occurs in children only; # ADR occurs in men only; *ADR occurs in women only; ~ 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 (thus the ADR was reported for the drug or for drugs in the same pharmacological class); ^ Reported for one of the substances in a combination product, for (substance).

Table S2.2: Drug class effects reported in the SmPC

ATC of report[$]	Drug class reported	ADR reported as drug class effect
C02CA04, G04CA01, N06AX05	**alpha 1-blocker**	*priapism*
C08DA51, C09BB10	**phenylalkylamine calcium channel blockers**	blood prolactin increased, *erectile dysfunction, libido decreased*
C09AA	**ACE inhibitors[#]**	erectile dysfunction, *sexual dysfunction*
C10AA, C10BA, C10BX	**statins**	sexual dysfunction
C10AB08	**fibrates**	*erectile dysfunction*
G02CB, N04BA, N04BB, N04BC, N04BD, N04BX	**dopamine agonists**	hypersexuality, libido increased
G04BD04	**anticholineric therapy**	*erectile dysfunction*
G04BE	**PDE5 inhibitors**	priapism
N05AA02, N05AC01	**phenothiazine derivatives**	blood prolactin increased, erectile dysfunction
N05AB, N05AF, N05AG	**antipsychotics**	blood prolactin increased, erectile dysfunction. *priapism, ejaculation disorder, retrograde ejaculation*
N05CD01	**benzodiazepines**	*libido decreased*
N06AA12	**tricyclic antidepressants**	*libido increased*
S01ED	**ophthalmic beta-blockers**	sexual dysfunction, libido decreased, *erectile dysfunction*

Cursive: the ADRs mentioned in only one of the SmPCs concerning the drug class; [#]ACE: angiotensin converting enzyme; [$]In case for only one drug of the drug class the drug class effect is mentioned, the complete ATC code of that drug is shown in the table.

Table S2.3: Search terms used

Abnormal ejaculation	Female dyspareunia due to a general medical condition	Male sexual dysfunction NEC
Abnormal orgasm (female)	Female hypoactive sexual desire disorder due to a general medical condition	Orgasm abnormal
Abnormal orgasm (male)	Female orgasmic disorder	Orgasmic disorders and disturbances
Adrenal virilism	Female sexual dysfunction NEC	Other sexual deviation
Adrenogenital syndrome congenital	Frigidity	Other specified psychosexual disorder
Anorgasmia	Frigidity and impotence	Painful intercourse
Coitus painful	Frotteurism	Sexual aversion disorder
Congenital adrenal hyperplasia	Hyperestrogenism	Sexual desire disorders
Congenital adrenal hyperplasia - sodium losing form	Hyperoestrogenism	Sexual desire increased
Congenital adrenal hyperplasia - virilising form	Hypoactive sexual desire disorder	Sexual disorder NOS
Deep dyspareunia	Impotence	Sexual dysfunction
Erection and ejaculation conditions and disorders	Impotence of organic origin	Sexual dysfunction NEC
Sexual function and fertility disorders	Impotent	Sexual dysfunction NOS
Sexual function and fertility disorders NEC	Impotentia erigendi	Sexual dysfunctions, disturbances and gender identity disorders
Disturbance in arousal NOS	Inability to maintain erection	Sexual feeling decreased
Dyspareunia	Inability to orgasm	Sexual function abnormal
Dyspareunia (female excl psychogenic)	Inadequate lubrication	Sexual inhibition
Dyspareunia (male excl psychogenic)	Increased libido	Sexual problem
Dyspareunia NOS	Increased sexual arousal	Superficial dyspareunia
Dyspareunia psychogenic	Influence on libido	Unspecified psychosexual disorder
ejaculation disorder	Inhibited female orgasm	Vaginismus
Ejaculation decreased	Inhibited male orgasm	Vaginismus (excl psychogenic)
Ejaculation delayed	Lack of libido	Vaginismus psychogenic
Ejaculation disorder	Libido decreased	Impotence aggravated
Ejaculation disorder NOS	Libido disorder NOS	Priapism aggravated
Ejaculation failure	Libido increased	Spontaneous penile erection
Ejaculation inhibited	Libido lack	Psychogenic impotence
Ejaculation premature	Libido loss of	Organic impotence
Erectile disturbance	Loss of libido	Erectile dysfunction NOS
Erection decreased	Male dyspareunia due to a general medical condition	Organic erectile dysfunction
Erection failure	Male erectile disorder	Psychogenic erectile dysfunction
Erection inadequate	Male erectile disturbance due to general medical condition	Sexual function decreased
Erection increased	Male hypoactive sexual desire disorder due to a general medical condition	Orgasmic sensation decreased
Erection increased (exc priapism)	Male orgasmic disorder	Prolonged morning erection
Primary hypogenitalism	Erectile dysfunction	Hyperandrogenemia
Hypergonadotropic hypogonadism	Decreased genital sensation	Hyperandrogenaemia
Erection increased (excl priapism)	Female sexual arousal disorder	Dribbling ejaculation

Table S2.3 continues on next page.

Table S2.3: ***Continued***

Vaginal spasm	Lack of early morning erection	Weak ejaculation
Colpospasm	Hyperandrogenism	Anejaculation
Potency disturbance	Hypersexuality	Spontaneous ejaculation
Hypergonadism	Kluver-Bucy syndrome	Sexual desire disorder
Hypergenitalism	Post coital pain	Hyperprogesteronism
Nymphomania	Decreased frequency of erections	Hypoprogesteronism
Painful erection	HAIR-AN syndrome	Adrenal androgen deficiency
Delayed orgasm	Hyposexuality	Adrenal androgen excess
Female sexual dysfunction	Compulsive sexual behaviour	Primary gonadal failure
Male sexual dysfunction	Compulsive sexual behavior	Testosterone excess
Hypogonadism	Gonadal insufficiency	Excessive secretion of testosterone
Disturbance in sexual arousal	Erection prolonged	Genito-pelvic pain/penetration disorder
Sexual desire decreased	Luteinising hormone deficiency	Persistent genital arousal disorder
Painful orgasm	Follicle stimulating hormone deficiency	Restless genital syndrome
Immotile cilia syndrome	Luteinizing hormone deficiency	Impaired gonadal steroidogenesis
Libido disorder	Painful ejaculation	Peyronie's disease
Hyperprolactinemia	hyperprolactinaemia	Blood testosterone decreased
Hyperprolactinemia aggravated	Blood prolactin decreased	Blood testosterone free decreased
Hypoprolactinemia	Blood prolactin increased	Vulvovaginal dryness
Macroprolactinemia	Blood prolactin abnormal	

Table S2.4: Overview of drugs found with registered sexual adverse drug reactions

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
A	**Alimentary tract and metabolism**									
A02BA01	cimetidine				erectile dysfunction			2289	CBG	reported as reversibel
A02BA02	ranitidine					erectile dysfunction		93 531	CBG	reported as reversibel
A02BA03	famotidine					erectile dysfunction, libido decreased		1466	CBG	
A02BC03	lansoprazole				erectile dysfunction			11 487	CBG	
A03AX12	phloroglucinol		erectile dysfunction				sexual dysfunction, libido decreased, libido increased, ejaculation disorder, anorgasmia	NA	CBG	
A03FA01	metoclopramide			hyperprol-actinaemia				217 100	CBG	
A03FA03	domperidone			loss of libido			blood prolactin increased	95 017	CBG	In 45 clinical researches in which domperidone was used in high doses and during a longer period and different indications, the frequency of side effects was much higher. This was especially obvious for pharmacological as a consequence of a higher prolactin level.
A07EA06	budesonide		erectile dysfunction					18 764	CBG	reported as consequence of Cushing's syndrome which can lead to a disturbance of secretion of sex hormones
A08AA62	bupropion and naltrexone		ejaculation delayed (7)	libido disorder (7), erectile dysfunction (7), vulvovaginal dryness				NA	EMA	reported in subjects who received naltrexone; vulvovaginal dryness: reported in subjects who received naltrexone/bupropion
A10BD05	metformin and pioglitazone		erectile dysfunction					153	EMA	
A10BD10	metformin and saxagliptin			erectile dysfunction				46	EMA	reported in patients treated with saxagliptin with metformin
A10BG03	pioglitazone		erectile dysfunction					4684	both	reported for pioglitazone in combination therapy with metformin
A10BH03	saxagliptin			erectile dysfunction				1280	EMA	

A14AB01	nandrolone					libido increased, priapism, blood testosterone decreased	150	CBG	
A16AX06	miglustat	libido decreased					15	EMA	
B	**Blood and blood forming organs**								
B01AB01	heparin		priapism				1964	CBG	
B01AB06	nadroparin				priapism		115 900	CBG	
B01AB10	tinzaparin			priapism			7817	CBG	
B05BA02	fat emulsions				priapism		14	CBG	
B05BA10	combinations (parenteral nutrition)				priapism		586	CBG	
C	**Cardiovascular system**								
C01BA03	disopyramide					erectile dysfunction	1185	CBG	
C01BC03	propafenone		erectile dysfunction				1626	CBG	
C01BC04	flecainide				erectile dysfunction		43 141	CBG	
C01BD01	amiodarone				erectile dysfunction	libido decreased	27 815	CBG	
C01EB18	ranolazine			erectile dysfunction			NA	EMA	
C02AB01	methyldopa (levorotatory)		erectile dysfunction			hyperprolactinaemia, libido decreased	6303	CBG	
C02AC01	clonidine	erectile dysfunction				libido decreased	1626	CBG	
C02AC05	moxonidine		erectile dysfunction, loss of libido				1551	CBG	
C02CA04	doxazosin		erectile dysfunction		priapism (6), erection increased (6)	retrograde ejaculation	42 323	CBG	priapism and erection increased reported on basis of post marketing experiences with alpha-1-blockers like doxazosine

Table S2.4 continues on next page.

Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
C02CA06	urapidil					priapism		502	CBG	
C03AA03	hydrochlorothiazide			erectile dysfunction				650 050	CBG	
C03BA04	chlortalidone			erectile dysfunction				61 687	CBG	
C03DA01	spironalactone	libido decreased (3), erectile dysfunction (3)	libido decreased (4)					137 300	CBG	
C03EA01	hydrochlorothiazide and potassium-sparing agents						libido decreased (7), erectile dysfunction	45 351	CBG	libido decreased reported for amiloride
C07AA05	propanolol						erectile dysfunction	109 340	CBG	
C07AA07	sotalol		sexual dysfunction					97 663	CBG	
C07AB02	metoprolol				erectile dysfunction, peyronie's disease, sexual dysfunction	libido disorder		1 021 000	CBG	
C07AB03	atenolol				erectile dysfunction			90 030	CBG	
C07AB04	acebutolol						libido decreased	1414	CBG	
C07AB07	bisoprolol				erectile dysfunction			222 860	CBG	
C07AB08	celiprolol						libido decreased	3402	CBG	
C07AB12	nebivolol			erectile dysfunction				44 865	CBG	
C07AG01	labetalol		erectile dysfunction				ejaculation disorder	11 747	CBG	
C07AG02	carvedilol			erectile dysfunction				22 167	CBG	
C07BB02	metoprolol and thiazides				sexual dysfunction (7), erectile dysfunction			25 773	CBG	sexual dysfunction reported for metoprolol
C07BB07	bisoprolol and thiazides				erectile dysfunction			4887	CBG	

C07BB12	nebivolol and thiazides		erectile dysfunction				NA	CBG	erectile dysfunction reported for both nebivolol and hydrochlorothiazide separate
C07CB03	atenolol and other diuretics			erectile dysfunction			11 685	CBG	
C07FX05	metoprolol and ivabradine	libido disorder (7)		sexual dysfunction (7), erectile dysfunction (7)	peyronie's disease (7)		NA	CBG	libido disorder, sexual dysfunction, erectile dysfunction and peyronie's disease reported for metoprolol
C07FX06	carvedilol and ivabradine		erectile dysfunction (7)				NA	CBG	erectile dysfuncion reported for carvedilol
C08CA01	amlodipine		erectile dysfunction				558 710	CBG	
C08CA02	felodipine			erectile dysfunction, sexual dysfunction			9908	CBG	
C08CA03	isradipine				erectile dysfunction		1428	CBG	
C08CA05	nifedipine		erectile dysfunction				169 750	CBG	
C08DA01	verapamil				hyperprolactinaemia, erectile dysfunction		65 352	CBG	
C08DA51	verapamil, combinations (6)				erectile dysfunction	libido decreased, blood prolactin increased	NA	CBG	ADRs reported for phenylalkylamine calcium channel blockers
C08GA02	amlodipine and diuretics		erectile dysfunction (7)				463	CBG	erectile dysfunction reported for amlodipine
C09AA01	captopril				erectile dysfunction		14 733	CBG	
C09AA02	enalapril		erectile dysfunction				286 710	CBG	
C09AA03	lisinopril		erectile dysfunction				276 260	CBG	
C09AA04	perindopril		erectile dysfunction				318 070	CBG	
C09AA05	ramipril		libido decreased, erectile dysfunction				55 668	CBG	erectile dysfunction reported as transient
C09AA06	quinapril		erectile dysfunction				20 264	CBG	

Table S2.4 continues on next page.

Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
C09AA09	fosinopril (6)		sexual dysfunction	erectile dysfunction				56 423	CBG	erectile dysfunction and sexual dysfunction reported for ACE inhibitors and fosinopril
C09AA15	zofenapril (6)				erectile dysfunction			2592	CBG	erectile dysfunction reported for ACE inhibitors
C09BA01	captopril and diuretics					erectile dysfunction (7)		3581	CBG	erectile dysfunction reported for captopril
C09BA02	enalapril and diuretics			erectile dysfunction, libido decreased				47 617	CBG	libido decreased only reported for combinations with 12,5 mg or 25 mg hydrochlorothiazide
C09BA03	lisinopril and diuretics			erectile dysfunction (7)				30 927	CBG	erectile dysfunction reported for lisinopril
C09BA04	perindopril and diuretics			erectile dysfunction				35 813	CBG	
C09BA05	ramipril and diuretics			erectile dysfunction			libido decreased	3428	CBG	erectile dysfunction reported as transient
C09BA06	quinapril and diuretics			erectile dysfunction				3701	CBG	
C09BA07	benazepril and diuretics		erectile dysfunction (7)					NA	CBG	reported for thiazide diuretics (e.g. hydrochlorothiazide)
C09BA09	fosinopril and diuretics			sexual dysfunction (7)			libido disorder	5287	CBG	sexual disfunction reported for fosinopril
C09BA15	zofenapril and diuretics			erectile dysfunction				NA	CBG	
C09BB02	enalapril and lercanidipine			erectile dysfunction (7)				581	CBG	erectile dysfunction reported for enalapril and the combination of enalapril and lercanidipine
C09BB04	perindopril and amlodipine			erectile dysfunction				8300	CBG	erectile dysfunction reported for amlodipine and perindopril separate
C09BB10	trandolapril and verapamil (6)					erectile dysfunction	libido decreased, blood prolactin increased	169	CBG	blood prolactin increased reported for phenylalkylamine calcium channel blockers
C09BX01	perindopril, amlodipine and indapamide			erectile dysfunction				731	CBG	erectile dysfunction reported for amlodipine and perindopril separate

C09BX02	perindopril and bisoprolol		erectile dysfunction		10	CBG	erectile dysfunction reported for perindopril and bisoprolol separate
C09CA01	losartan			erectile dysfunction	236 650	CBG	
C09CA04	irbesartan		sexual dysfunction		128 600	both	
C09DA01	losartan and diuretics		libido decreased (7), erectile dysfunction (7)		81 694	CBG	reported for losartan
C09DA02	eprosartan and diuretics		libido disorder, sexual dysfunction		793	CBG	
C09DA03	valsartan and diuretics	erectile dysfunction (7)			78 658	CBG	reported for hydrochlorothiazide
C09DA04	irbesartan and diuretics		sexual dysfunction, libido disorder		65 483	both	
C09DA07	telmisartan and diuretics		erectile dysfunction		17 817	both	ADR reported from all clinical trials in patients treated with telmisartan and hydrochlorothiazide.
C09DA08	olmesartan medoxomil and diuretics		erectile dysfunction		5184	CBG	erectile dysfunction reported for both the combination and hydrochlorothiazide separate
C09DB01	valsartan and amlodipine		erectile dysfunction		8343	both	
C09DB02	olmesartan medoxomil and amlodipine		libido decreased, erectile dysfunction		3210	CBG	libido decreased only reported for the combination; erectile dysfunction reported for both the combination and amlodipine separate
C09DB04	amlodipine and telmisartan		erectile dysfunction		NA	EMA	
C09DX01	valsartan, amlodipine and hydrochlorothiazide	erectile dysfunction			8549	EMA	
C09DX03	olmesartan medoxomil, amlodipine and hydrochlorothiazide		erectile dysfunction, libido decreased		2802	CBG	erectile dysfunction reported for both the combination and amlodipine and hydrochlorothiazide separate; libido decreased reported for the combination of amlodipine and olmesartan
C09XA52	aliskiren and hydrochlorothiazide	erectile dysfunction (7)			1961	EMA	reported for hydrochlorothiazide
C10AA01	simvastatin			erectile dysfunction, sexual dysfunction (6)	1 075 000	CBG	sexual disfunction is reported for some statins

Table S2.4 continues on next page.

Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
C10AA03	pravastatin			sexual dysfunction				149 210	CBG	reported during clinical trials with pravastatin
C10AA04	fluvastatin						sexual dysfunction (6), erectile dysfunction	17 625	CBG	sexual disfunction is reported for some statins; erectile dysfunction based on post-marketing experiences
C10AA05	atorvastatin (6)						sexual dysfunction	544 150	CBG	sexual disfunction is reported for some statins
C10AA07	rosuvastatin (6)						sexual dysfunction	274 320	CBG	sexual disfunction is reported for some statins
C10AA08	pitavastatin (6)						sexual dysfunction	NA	CBG	sexual disfunction is reported for some statins
C10AB02	bezafibrate			erectile dysfunction				3095	CBG	
C10AB04	gemfibrozil				erectile dysfunction, libido decreased			12 662	CBG	
C10AB08	ciprofibrate (6)			erectile dysfunction				6357	CBG	Some cases of erectile dysfunction reported, just like other drugs in this pharmacological class
C10BA02	simvastatin and ezetimibe						erectile dysfunction, sexual dysfunction (6)	38 508	CBG	sexual disfunction is reported for some statins
C10BA03	pravastatin and fenofibrate			sexual dysfunction				NA	EMA	ADR reported with fenofibrate and with pravastatin.
C10BA04	simvastatin and fenofibrate			sexual dysfunction				NA	EMA	sexual dysfunction reported for medicinal products containing simvastatin or fenofibrate
C10BA05	atorvastatin and ezetimibe (6)						sexual dysfunction	4477	CBG	sexual disfunction is reported for some statins
C10BA06	rosuvastatin and ezetimibe (6)						sexual dysfunction	NA	CBG	sexual disfunction is reported for some statins
C10BX11	atorvastatin, amlodipine and perindopril			erectile dysfunction (7)			sexual dysfunction (6)	NA	CBG	erectile dysfunction reported for perindopril and amlodipine, sexual dysfunction for statins
C10BX15	atorvastatin and perindopril			erectile dysfunction (7)			sexual dysfunction (6)	NA	CBG	erectile dysfunction reported for perindopril, sexual dysfunction for statins

D	**Dermatologicals**							
D02BB02	afamelanotide		libido decreased			NA	EMA	
D06BB10	imiquimod		dyspareunia, erectile dysfunction			12 164	EMA	in patients treated for external genital warts
D06BB12	sinecatechins		dyspareunia			2095	CBG	
D10BA01	isotretinoin				sexual dysfunction, erectile dysfunction, libido decreased	24 894	CBG	
D11AX10	finasteride		ejaculation disorder, sexual dysfunction, libido decreased			NA	CBG	permanent sexual dysfunction (e.g. ejaculation disorder, erectile dysfunction, libido decreased) reported during postmarketing after stopping the treatment
G	**Genito-urinary system and sex hormones**							
G01AC05	dequalinium				vulvovaginal dryness	NA	CBG	
G02BA03	plastic IUD with progestogen	libido decreased				9254	CBG	
G02BB01	vaginal ring with progestogen and estrogen	libido decreased	dyspareunia, vulvovaginal dryness			2350	CBG	
G02CB01	bromocriptine (6)			hypersexuality, libido increased		777	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
G02CB03	cabergoline (6)		libido increased		hypersexuality	5907	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
G02CB04	quinagolide (6)				hypersexuality, libido increased	1111	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
G03AA07	levonorgestrel and ethinylestradiol		libido decreased, dyspareunia, vulvovaginal dryness, orgasm abnormal	libido increased		311 310	CBG	
G03AA09	desogestrel and ethinylestradiol		libido decreased	libido increased		10 214	CBG	
G03AA10	gestodene and ethinylestradiol		libido decreased	libido increased		2508	CBG	

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Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
G03AA11	norgestimate and ethinylestradiol			vulvovaginal dryness, libido increased, libido decreased				1016	CBG	
G03AA12	drospirenone and ethinylestradiol			libido increased, libido decreased, vulvovaginal dryness	dyspareunia, anorgasmia			18 755	CBG	
G03AA13	norelgestromin and ethinylestradiol			libido decreased, vulvovaginal dryness	libido increased			742	EMA	
G03AA14	nomegestrol and estradiol		libido decreased	dyspareunia, vulvovaginal dryness	libido increased			2001	EMA	
G03AA16	dienogest and ethinylestradiol				dyspareunia		libido decreased, libido increased	NA	CBG	
G03AB03	levonorgestrel and ethinylestradiol			libido decreased	libido increased			3442	CBG	
G03AB05	desogestrel and ethinylestradiol			libido decreased	libido increased			NA	CBG	
G03AB08	dienogest and estradiol			libido decreased, loss of libido, dyspareunia, vulvovaginal dryness	libido increased			328	CBG	
G03AC02	lynestrenol		libido decreased	vulvovaginal dryness	libido increased			NA	CBG	
G03AC06	medroxyprogesterone		libido decreased	anorgasmia, dyspareunia, vulvovaginal dryness				14 907	CBG	
G03AC08	etonogestrel		libido decreased					3827	CBG	
G03AC09	desogestrel		libido decreased					2567	CBG	
G03AD02	ulipristal			libido disorder	dyspareunia			NA	EMA	

G03BA03	testosterone			libido disorder, blood testosterone increased			erection increased, priapism	17 865	CBG	priapism reported for suppletion therapy with testosterone for hypogonadism
G03CA03	estradiol				libido decreased, libido increased	genito-pelvic pain/penetration disorder		34 112	CBG	
G03CC07	conjugated estrogens and bazedoxifene			libido disorder				78	EMA	
G03DB08	dienogest		loss of libido	vulvovaginal dryness				NA	CBG	
G03DC03	lynestrenol	libido decreased	libido increased					21 065	CBG	
G03FA01	norethisterone and estrogen						libido decreased, libido increased	2627	CBG	reported spontaneously post-marketing with a possible causal relationship
G03FA15	dienogest and estrogen			libido decreased, anorgasmia				NA	CBG	
G03HA01	cyproterone	libido decreased (3), erectile dysfunction (3)	libido decreased (4)					5064	CBG	
G03HB01	cyproterone and estrogen			libido decreased	libido increased			NA	CBG	
G04BD04	oxybutynin (6)					erectile dysfunction		24 075	both	ADR known to be associated with anticholinergic therapy
G04BD10	darifenacin			erectile dysfunction				7771	EMA	
G04BE01	alprostadil		spontaneous penile erection, erection increased, peyronie's disease	ejaculation disorder, erectile dysfunction, painful erection				NA	CBG	
G04BE03	sildenafil				priapism, erection increased		spontaneous penile erections (3)	1084	both	priapism only reported during postmarket surveillance; also in pediatric patients erection increased (incl. spontaneous penile erections (9%))
G04BE08	tadalafil			priapism, erection increased				348	both	
G04BE09	vardenafil			erection increased	priapism (6)			NA	both	priapism reported for vardenafil and all other PDE5 inhibitors.

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Table S2.4: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
G04BE10	avanafil				premature ejaculation, spontaneous penile erection		priapism (6)	NA	EMA	priapism reported for other PDE5 inhibitors.
G04BE30	combinations (of drugs used in erectile dysfunction)		erection increased					NA	CBG	
G04BX14	dapoxetine		erectile dysfunction, libido decreased	ejaculation disorder, male orgasmic disorder (3), anorgasmia, loss of libido				NA	CBG	
G04CA01	alfuzosin (6)						priapism	40 591	CBG	priapism reported on basis of post marketing experiences with alpha-1-blockers like alfuzosin
G04CA02	tamsulosin		ejaculation disorder, retrograde ejaculation, ejaculation failure, ejaculation delayed			priapism		211 230	CBG	
G04CA03	terazosin	erectile dysfunction	libido increased, priapism	libido decreased				966	CBG	
G04CA04	silodosin	ejaculation failure, retrograde ejaculation		libido decreased, erectile dysfunction				10 701	EMA	
G04CA52	tamsulosin and dutasteride		erectile dysfunction, libido decreased, ejaculation disorder			priapism (7)	retrograde ejaculation, ejaculation failure	38 587	CBG	erectile dysfunction, libido decreased and ejaculation disorder are thought to be caused by dutasteride and can last after the treatment. Priapism is only reported for tamsulosin. Retrograde ejaculation and ejaculation failure are thought to be caused by tamsulosin
G04CA53	tamsulosin and solifenacin		ejaculation disorder, retrograde ejaculation, ejaculation failure			priapism (7)		13 117	CBG	frequency of ejaculation disorders (incl. retrograde ejaculation) 1,5% for combination; priapism only reported for tamsulosin, ejaculation disorders for both the combination and tamsulosin.
G04CB01	finasteride		libido decreased, erectile dysfunction	ejaculation disorder				29 018	CBG	ejaculation disorder en libido decreased are reported after stopping treatment
G04CB02	dutasteride		ejaculation disorder, erectile dysfunction, libido decreased					28 477	CBG	erectile dysfunction, libido decreased and ejaculation disorder are thought to be caused by dutasteride and can last after the treatment.

H	**Systemic hormonal preparations, excluding sex hormones and insulins**						
H01AX01	pegvisomant		libido increased		330	EMA	
H01CA01	gonadorelin			priapism	NA	CBG	
H02AB07	prednisone			erectile dysfunction	14 319	CBG	
H02AB09	hydrocortisone			erectile dysfunction	12 161	CBG	
H05BX01	cinacalcet	blood testosterone decreased			5376	both	For patients with kidney failure the blood testosterone is often lower than normal. In a clinical study with ESRD-patients under dialyses the free testosterone was 31,3% (median) lower after a treatment of 6 months. In comparison the median for treatment with placebo was 16,3%. Over a period of 3 years there were no more decreases. Clinical significance is unknown.
H05BX02	paricalcitol		erectile dysfunction		NA	CBG	
J	**Antiinfectives for systemic use**						
J02AB02	ketoconazole			erectile dysfunction, blood testosterone decreased	104	EMA	
J02AC02	itraconazol			erectile dysfunction	65 900	CBG	
J04AK06	delamanid		libido increased		NA	EMA	the frequency for this event was lower for the combined delamanid plus optimalized background regime (OBR) group in comparison to the placebo plus OBR group.
J05AE01	saquinavir	libido decreased			30	EMA	
J05AE10	darunavir		libido decreased, erectile dysfunction		2159	both	
J05AP01	ribavirin (1)	libido decreased, sexual dysfunction (3), erectile dysfunction (3)			NA	both	
J05AP03	boceprevir	libido disorder, erectile dysfunction			NA	EMA	
J05AR06	emtricitabine, tenofovir disoproxil and efavirenz		libido decreased		2357	both	

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Table S2.4: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
J05AR10	lopinavir and ritonavir		erectile dysfunction	libido decreased, hypogonadism				314	both	
J05AR16	lamivudine and raltegravir			erectile dysfunction				NA	EMA	
J05AX08	raltegravir			erectile dysfunction				978	EMA	
L	**Antineoplastic and immunomodulating agents**									
L01AB01	busulfan						hypogonadism	NA	EMA	reported in post marketing with IV busulfan
L01AC01	thiotepa (2)	hypog-onadism						NA	EMA	
L01AX03	temozolamide			erectile dysfunction				NA	both	ADR reported for temozolamide + concomitant radiotherapy
L01BA01	methotrexate					loss of libido, erectile dysfunction		54	CBG	
L01BC06	capecitabine			libido decreased				NA	EMA	reported for monotherapy of capecitabine
L01BC53	tegafur, combinations			libido decreased, sexual inhibition, erectile dysfunction				NA	EMA	libido decreased is reported for the combination with cisplatin
L01DB11	pixantrone		spontaneous penile erection					NA	EMA	
L01XC11	ipilimumab			libido decreased, hypog-onadism, blood testosterone decreased	blood prolactin abnormal			NA	EMA	
L01XE01	imatinib			libido decreased, sexual dysfunction, erectile dysfunction				NA	both	
L01XE04	sunitinib		ejaculation disorder					NA	EMA	
L01XE05	sorafenib		erectile dysfunction					NA	EMA	
L01XE06	dasatinib			libido decreased				NA	EMA	
L01XE08	nilotinib			erectile dysfunction				NA	EMA	
L01XE16	crizotinib		blood testosterone decreased				hypogonadism	NA	EMA	

L01XE24	ponatinib			erectile dysfunction				NA	EMA	
L01XX11	estramustine						erectile dysfunction	NA	CBG	
L01XX23	mitotane						blood testosterone free decreased (3), blood testosterone decreased (4)	NA	EMA	
L01XX25	bexarotene						libido decreased, erectile dysfunction	NA	EMA	
L01XX32	bortezomib			erectile dysfunction	libido decreased			NA	both	
L01XX35	anagrelide			erectile dysfunction				NA	both	
L02AB02	medroxyprogesterone			loss of libido				356	CBG	
L02AE01	buserelin		erectile dysfunction, loss of libido					576	CBG	
L02AE02	leuprorelin	erectile dysfunction	dyspareunia	libido decreased, ejaculation disorder				14 073	CBG	
L02AE03	goserelin	libido decreased, erectile dysfunction (3), vulvovaginal dryness (4)						12 071	CBG	libido decreased is a pharmacological effect for which the therapy rarely needs to stop.
L02AE04	triptorelin	libido decreased, erectile dysfunction (3), vulvovaginal dryness (4), dyspareunia (4), ejaculation failure, ejaculation disorder	loss of libido				blood prolactin increased	2382	CBG	For 30-40% of the male patients erectile dysfunction and libido decreased should be expected, vulvovaginal dryness, dyspareunia, libido decreased for more than 20% of the female patients.
L02BB01	flutamide	libido decreased, erectile dysfunction				libido decreased	blood testosterone increased	81	CBG	libido decreased and erectile dysfunction were reported very common with combination therapy with LRHR agonists, libido decreased very rarely as monotherapy, as blood testosterone increased.
L02BB02	nilutamide	libido decreased, erectile dysfunction						249	CBG	

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Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
L02BB03	bicalutamide		erectile dysfunction, libido decreased					12 052	CBG	
L02BG04	letrozole			vulvovaginal dryness				11 816	CBG	
L02BX02	degarelix			ejaculation failure, libido decreased; erectile dysfunction				879	EMA	known physiological consequences of testosterone suppression
L03AB04	interferon alfa-2A				erectile dysfunction			80	CBG	
L03AB08	interferon beta-1b						erectile dysfunction	427	EMA	
L03AB10	peginterferon alfa-2b		libido decreased (1), sexual dysfunction, erectile dysfunction					134	EMA	libido decreased: reported for patients treated with peginterferon alfa-2b alone or in combination with ribavirin
L03AB11	peginterferon alfa-2a		libido decreased,erectile dysfunction					613	EMA	
L03AX03	BCG vaccine						dyspareunia	NA	CBG	
L03AX13	glatiramer acetate			erectile dysfunction, priapism				2101	CBG	
L04AA06	mycophenolic acid			erectile dysfunction				13 242	CBG	erectile dysfunction reported in one of the 372 patients.
L04AA18	everolimus		erectile dysfunction	hypog-onadisme (3)				605	CBG	
L04AA25	eculizumab			spontaneous penile erection				NA	EMA	
L04AA28	belatacept			libido increased, priapism				NA	EMA	
L04AB04	adalimumab			erectile dysfunction				NA	EMA	
L04AB05	certolizumab				sexual dysfunction			NA	EMA	
L04AX02	thalidomide						sexual dysfunction	NA	EMA	
L04AX03	methotrexate					libido decreased, erectile dysfunction		87 989	CBG	
L04AX04	lenalidomide		erectile dysfunction	loss of libido				NA	EMA	

M	**Musculo-skeletal system**							
M01AB05	diclofenac				erectile dysfunction	1 097 000	CBG	In rare cases erectile dysfunction is reported. A causal relationship with diclofenac is not shown yet
M03BX01	baclofen	sexual dysfunction			erectile dysfunction	20 163	CBG	priapism as withdrawal phenomenon
M03CA01	dantrolene			erectile dysfunction		576	CBG	
M04AA01	allopurinol			erectile dysfunction		135 670	CBG	
M04AA03	febuxostat		libido decreased, erectile dysfunction			1822	both	
M09AB02	collagenase	dyspareu-nia, painful erection, erectile dys-function	sexual dysfunction, sexual inhibition, peyronie's disease			NA	EMA	
N	**Nervous system**							
N01BB10	levobupivacaine				priapism	NA	CBG	This can be a symptom or complaint of the caudal syndrome
N01BB20	combinations (lidocaine, prilocaine)	erectile dysfunction	ejaculation failure			81 152	EMA	
N02AA01	morphine		erectile dysfunction, libido decreased			87 502	CBG	
N02AA03	hydromorphone		erectile dysfunction		libido decreased	824	CBG	Clinical symptoms are linked in different section in SmPC to an increase in blood prolactin and a decrease in cortisol and testosterone.
N02AA05	oxycodone		libido decreased, erectile dysfunction, hypogonadism			438 460	CBG	clinical symptoms are linked in different section in SmPC to an increase in blood prolactin and a decrease in cortisol and testosterone
N02AA55	oxycodone and naloxone		libido decreased, hypogonadism (7)		erectile dysfunction	NA	CBG	hypogonadism only mentioned for oxycodone
N02AB03	fentanyl		erectile dysfunction, sexual dysfunction	hypog-onadism		105 710	both	
N02AE01	buprenorphine		libido decreased	erectile dysfunction, sexual dysfunction		41 832	CBG	
N02AX06	tapentadol		sexual dysfunction			6464	CBG	

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Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
N02CX02	clonidine		erectile dysfunction				libido decreased	24 040	CBG	
N03AB02	phenytoin						peyronie's disease	6369	CBG	
N03AE01	clonazepam				loss of libido, erectile dysfunction			29 751	CBG	
N03AF01	carbamazepine					blood prolactin increased, libido decreased, sexual dysfunction, erectile dysfunction		37 424	CBG	
N03AG01	valproic acid			hyperandro-genism				54 017	CBG	
N03AX11	topiramate			erectile dysfunction, sexual dysfunction, libido decreased, loss of libido				19 861	CBG	
N03AX12	gabapentin		erectile dysfunction				ejaculation disorder, sexual dysfunction, anorgasmia, libido disorder	46 384	CBG	
N03AX16	pregabalin		libido decreased, erectile dysfunction	anorgasmia, ejaculation delayed, libido increased, sexual dysfunction				134 590	both	
N04BA02	levodopa and decarboxylase inhibitor (6)						libido increased, priapism, hypersexuality	36 932	both	Can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa; ADRs reported for other levodopa/carbidopa medicinal products.
N04BA03	levodopa, decarboxylase inhibitor and COMT inhibitor (6)						libido increased, hypersexuality	1996	EMA	disorders in impulse control are reported for patients treated with dopamine agonists
N04BB01	amantadine (6)						libido increased, hypersexuality	4504	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
N04BC01	bromocriptine (6)					hypersexuality, libido increased		38	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
N04BC02	pergolide (6)						libido increased, hypersexuality	111	CBG	disorders in impulse control are reported for patients treated with dopamine agonists

N04BC04	ropinirole (6)				libido increased, hypersexuality	13 366	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
N04BC05	pramipexole (6)		libido disorder, hypersexuality, libido increased			34 811	both	disorders in impulse control are reported for patients treated with dopamine agonists
N04BC07	apomorphine (6)				libido increased, hypersexuality	115	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
N04BC09	rotigotine	libido increased (6), libido disorder, hypersexuality (6)			erectile dysfunction	2998	EMA	disorders in impulse control are reported for patients treated with dopamine agonists
N04BD01	selegiline (6)				hypersexuality, libido increased	564	CBG	disorders in impulse control are reported for patients treated with dopamine agonists
N04BD02	rasagiline (6)				libido increased, hypersexuality, psychosexual dysfunction, compulsive sexual behavior	529	both	disorders in impulse control are reported for patients treated with dopamine agonists. Has been reported post-marketing with rasagiline and one case in the placebo controlled study.
N04BD03	safinamide		libido increased, erectile dysfunction	loss of libido, premature ejaculation		122	EMA	
N04BX01	tolcapone (6)				libido increased, hypersexuality	45	EMA	disorders in impulse control are reported for patients treated with dopamine agonists
N04BX02	entacopone (6)				libido increased, hypersexuality	1822	both	disorders in impulse control are reported for patients treated with dopamine agonists
N05AA02	levomepromazine (6)				erectile dysfunction, ejaculation disorder, priapism, retrograde ejaculation, hyperprolactinaemia	NA	CBG	phenothiazine derivatives are known to cause a dose depended increase of blood prolactin which can cause erectile dysfunction in men. Very rarely erectile dysfunction and ejaculation disorders (e.g. priapism and retrograde ejaculation) are possible for men.
N05AB02	fluphenazine (6)				ejaculation disorder, priapism, retrograde ejaculation, erectile dysfunction (3), libido disorder (4), blood prolactin increased	425	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin, which can give rise to erectile dysfunction in men who did not have sexual disorders before.

Table S2.4 continues on next page.

Table S2.4: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
N05AB03	perphenazine (6)						blood prolactin increased, erectile dysfunction, ejaculation disorder, priapism, retrograde ejaculation	1351	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin, which can give rise to erectile dysfunction in men who did not have sexual disorders before. Long treatment with phenothiazine derivates can give rise to erectile dysfunction and ejaculation disorders (e.g. priapism and retrograde ejaculation) for men.
N05AC01	periciazine (6)					erectile dysfunction, ejaculation disorder, priapism, retrograde ejaculation	blood prolactin increased	387	CBG	phenothiazine derivatives are known to cause a dose depended increase of blood prolactin which can cause erectile dysfunction in men. Very rarely erectile dysfunction and ejaculation disorders (e.g. priapism and retrograde ejaculation) are possible for men.
N05AD01	haloperidol		sexual dysfunction				loss of libido, libido decreased, priapism, erectile dysfunction, hyperprolactinaemia	58 208	CBG	
N05AD05	pipamperone						hyperprolactinaemia, priapism	15 032	CBG	
N05AD06	bromperidol	hyperprolacti-naemia					priapism, retrograde ejaculation, erectile dysfunction	853	CBG	
N05AD08	droperidol						hyperprolactinaemia	34	CBG	during long exposure with psychiatric indications isolated cases of hyperprolactinaemia are reported
N05AE03	sertindole		ejaculation disorder, erectile dysfunction	hyperprol-actinaemia				41	CBG	
N05AE05	lurisadone			blood prolactin increased			erectile dysfunction	437	EMA	

N05AF01	flupentixol (6)		libido decreased	ejaculation failure, erectile dysfunction	hyperprolacti-naemia	priapism, retrograde ejaculation	3682	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin, which can give rise to erectile dysfunction in men who did not have sexual disorders before; long treatment with phenothiazine derivates can give rise to erectile dysfunction and ejaculation disorders (e.g. priapism and retrograde ejaculation) for men
N05AF03	chlorprothixene		libido decreased	ejaculation failure, erectile dysfunction	hyperprolacti-naemia	priapism (6)	2484	CBG	cases of priapism are reported for use of antipsychotics
N05AF05	zuclopenthixol		libido decreased, ejaculation failure, erectile dysfunction	libido increased, female orgasmic disorder (4), vulvovaginal dryness	hyperprolactinaemia (6), priapism		5939	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin
N05AG01	fluspirilene			sexual dysfunction		hyperprolactinaemia (6), ejaculation disorder (6), erectile dysfunction (6), priapism (6), retrograde ejaculation (6)	93	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin; ejaculation disorder, erectile dysfunction, priapism and retrograde ejaculation known for antipsychotics.
N05AG02	pimozide		erectile dysfunction			libido decreased, hyperprolactinaemia (6)	5045	CBG	antipsychotics cause as a rule dose depended increase of blood prolactin
N05AG03	penfluridol					erectile dysfunction, blood prolactin increased (6), ejaculation disorder, priapism, retrograde ejaculation	4152	CBG	antipsychotics (dopamin antagonists) cause as a rule dose depended increase of blood prolactin, which can give rise to erectile dysfunction in men who did not have sexual disorders before
N05AH02	clozapine				priapism	retrograde ejaculation	14 052	CBG	unlike classic antipsychotics clozapine does not cause or causes only little rise in blood prolactin
N05AH03	olanzapine	blood prolactin increased	libido decreased, erectile dysfunction(3)		priapism		48 609	both	elevated plasma prolactin levels were reported in 47.4 % of adolescent patients; in clinical investigations until 12 weeks the upper limit of normal range of blood prolactin was exceeded for approximately 30% of the patients treated with olanzapine

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Table S2.4: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
N05AH04	quetiapine		hyperprol-actinaemia	sexual dysfunction	priapism			113 600	CBG	blood prolactin (patients older than 18 years): >20 µg/l (>869,56 pmol/l) for men; >30µg/l (>1304,34 pmol/l) for women at any time
N05AH05	asenapine			sexual dysfunction				NA	EMA	
N05AL01	sulpiride		hyperprol-actinaemia	erectile dysfunction, ejaculation disorder, priapism, retrograde ejaculation				2290	CBG	erectile dysfunction, ejaculation disorder, priapism and retrograde ejaculation reported as a result of hyperprolactinaemia
N05AL03	tiapride		hyperprol-actinaemia	orgasmic disorder, erectile dysfunction			sexual dysfunction	257	CBG	hyperprolactinaemia can cause erectile dysfunction in some cases
N05AX08	risperidone		hyperprol-actinaemia, libido decreased, erectile dys-function	anorgasmia, ejaculation disorder, sexual dysfunction	priapism			47 770	CBG	priapism not reported in clinical studies but seen in post marketing with risperidone; hyperprolactinaemia can cause erectile dysfunction and a decrease in libido in some cases
N05AX12	aripiprazole		erectile dysfunction	hyperprolactinaemia, hypersexuality, libido decreased, blood prolactin decreased, vulvovaginal dryness			priapism, blood prolactin increased	25 420	both	in clinical research and during the post marketing phase both a increase as decrease in blood prolactin were reported. Under adolescents (13-17 years) with schizophrenia who recieved during a maximum of 72 months 5 to 30 mg of aripiprazole, the incidence of decreased blood prolactin for women (< 3 ng/ml) and men (< 2 ng/ml) was respectively 25,6% and 45,0%. During two long term studies with adolescents (13-17 years) with schizophrenia or a bipolar disorder, the incidence of decreased blood prolactin was for females 37,0 % and for men 59,4 %

N05AX13	paliperidone	hyperprol-actinaemia	anorgasmia, libido decreased, sexual dysfunction, erectile dysfunction, ejaculation disorder	priapism		3268	both	priapism observed in post-marketing environment with paliperidone. In clinical studies for schizophrenia 67% of the patients treated with paliperidon showed an increase in blood prolactin. ADRs related to an increase in blood prolatin was reported in 2% of the patients. The maximum of average increase of blood prolactin was seen on day 15 of the treatment and was above the baseline until the end of the study.
N05BA01	diazepam			libido decreased, libido increased, erectile dysfunction		65 197	CBG	
N05BA04	oxazepam				libido decreased	147 140	CBG	
N05BA05	potassium clorazepate				libido decreased	7641	CBG	
N05BA06	lorazepam		erectile dysfunction, libido disorder, orgasmic disorder		disturbance in sexual arousal	58 654	CBG	
N05BA08	bromazepam	erectile dysfunc-tion, libido decreased, hyperprol-actinaemia	anorgasmia, ejaculation disorder, sexual dysfunction	priapism		6641	CBG	
N05BA09	clobazam		loss of libido		libido decreased	8766	CBG	
N05BA11	prazepam			libido decreased		673	CBG	
N05BA12	alprazolam	libido decreased, libido increased, sexual disfunction	ejaculation disorder, anorgasmia, hyperprolactinaemie			28 850	CBG	
N05CD01	flurazepam (6)				libido decreased	4765	CBG	a decrease in libido is known for benzodiazepines
N05CD02	nitrazepam				libido decreased	7403	CBG	
N05CD06	lormetazepam	libido decreased				15 444	CBG	
N05CD08	midazolam				libido disorder	59 890	CBG	

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Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
N05CD09	brotizolam			libido disorder				1135	CBG	
N05CD11	loprazolam						libido decreased	1090	CBG	
N05CF01	zopiclone					libido decreased		31 910	CBG	
N05CF02	zolpidem				libido disorder			27 767	CBG	
N05CH01	melatonin				libido increased, priapism			NA	EMA	
N06AA02	imipramine						libido disorder, erectile dysfunction	3628	CBG	
N06AA04	clomipramine	libido disorder, erectile dysfunction					ejaculation failure, ejaculation delayed, blood prolactin increased	27 300	CBG	
N06AA09	amytriptyline		libido decreased, erectile dysfunction					202 110	CBG	
N06AA10	nortriptyline		libido decreased, erectile dysfunction				orgasmic disorder (4), libido increased	49 141	CBG	
N06AA12	doxepin				libido increased (5, 6), libido decreased, orgasm abnormal (4), ejaculation disorder (3), erectile dysfunction (3)			1242	CBG	libido increased: reported for tricyclic antidepressants, but no causality found for doxepin
N06AA16	dosulepin						ejaculation disorder, erectile disfunction, orgasm abnormal (4)	848	CBG	
N06AA21	maprotiline		libido disorder, erectile dysfunction					1356	CBG	

N06AB03	fluoxetine		ejaculation disorder, ejaculation delayed, libido decreased, loss of libido, erectile dysfunction, retrograde ejaculation, premature ejaculation	sexual dysfunction, orgasmic disorder, anorgasmia	hyperprolactinaemia, priapism		54 540	CBG	
N06AB04	citalopram		ejaculation disorder, ejaculation failure, female orgasmic disorder, anorgasmia (4), erectile dysfunction, libido decreased, loss of libido	libido increased		priapism (3)	169 930	CBG	
N06AB05	paroxetine	sexual dysfunction			hyperprolacti-naemia	priapism	158 990	CBG	
N06AB06	sertraline	ejaculation disorder	erectile dysfunction	sexual dysfunction (4)	hyperprolactinaemia, priapism, premature ejaculation		83 644	CBG	during the treatment of social anxiety disorder sexual dysfunction (ejaculation disorder) was seen in 14% of men with sertraline in comparison to 0% of placebo
N06AB08	fluvoxamine			ejaculation delayed, ejaculation disorder		hyperprolactinaemia, anorgasmia	17 625	CBG	
N06AB10	escitalopram		anorgasmia (4), ejaculation disorder (3), erectile dysfunction (3), libido decreased			priapism (3)	65 727	CBG	
N06AF04	tranylcypromine				anorgasmia, erectile dysfunction, ejaculation disorder		1909	CBG	
N06AG02	moclobemide					blood prolactin increased	1056	CBG	
N06AX05	trazodone					priapism (6), loss of libido	12 711	CBG	as with other drugs with alpha sympatholytic action, very rare cases of priapism were reported

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Table S2.4: ***Continued***

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
N06AX16	venlafaxine		erectile dysfunction, ejaculation disorder (3), anorgasmia, libido decreased, orgasmic disorder (3)	orgasmic disorder (4)		blood prolactin increased		106 830	CBG	
N06AX21	duloxetine		ejaculation delayed, ejaculation disorder, libido decreased, erectile dysfunction, orgasm abnormal	sexual dysfunction	hyperprolacti-naemia			29 692	both	
N06AX26	vortioxetine						sexual dysfunction	3623	EMA	doses of 5 to 15 mg showed no difference to placebo. However, the 20 mg dose of vortioxetine was associated with an increase in treatment-emergent sexual dysfunction (TESD)
N06BA02	dexamfetamine						erectile dysfunction	27 772	CBG	
N06BA04	methylphenidate				libido disorder		priapism, erectile dysfunction, erection increased	196 250	CBG	long-term and painful erections have been reported that have been associated with products containing methylphenidate, especially with a change in the treatment regimen for methylphenidate
N06BA07	modafinil			libido decreased				2652	CBG	

N06BA09	atomoxetine	ejaculation disorder (1), erectile dysfunction (1), decreased libido (1)	orgasmic disorder (1), ejaculation failure (1)	priapism	4010	CBG	priapism also seen in pediatric patients; The following adverse reactions occurred in at least 2% of all patients slowly metabolising CYP2D6 ('poor metabolisers', PMs) and were statistically significantly more frequent in PMs compared to patients rapidly metabolising CYP2D6 (extensive metabolisers, EMs): erectile dysfunction (20.9% of PMs, 8.9% of EMs), ejaculation disorder (6.1% of PMs, 2.2% of EMs).
N07BA03	varenicline		libido decreased, libido increased	sexual dysfunction	NA	EMA	
N07BA04	cytisine		libido decreased		NA	CBG	
N07BB03	acamprosate	female sexual arousal disorder, erectile dysfunction, libido increased	libido decreased		3147	CBG	
N07BB04	naltrexone	ejaculation delayed, erectile dysfunction	libido disorder		4343	CBG	
N07BB05	nalmefene	libido decreased, loss of libido			918	EMA	
N07BC02	methadone	libido decreased, erectile dysfunction		blood prolactin increased	13 532	CBG	
N07BC51	buprenorphine, combinations	libido decreased, erectile dysfunction	ejaculation disorder		1340	both	
N07CA03	flunarizine		libido decreased		1464	CBG	
N07XX11	pitolisant		libido decreased		NA	EMA	
R	**Respiratory system**						
R06AD01	alimemazine (3)			erectile dysfunction	2151	CBG	

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Table S2.4: *Continued*

ATC	Substance	Very common	Common	Uncommon	Rare	Very rare	Unknown, not mentioned or no standard category	Users in the Netherlands (according to GIP)	SmPC source	Comment
R06AE07	cetirizine						erectile dysfunction	60 085	CBG	
S	**Sensory organs**									
S01EC01	acetazolamide						erectile dysfunction, libido decreased	30 998	CBG	erectile dysfunction mentioned in section 4.6 of SmPC
S01EC04	brinzolamide			libido decreased, erectile dysfunction			sexual dysfunction	9584	both	sexual disfunction observed in patients treated with brinzolamide and in patients treated with timolol.
S01ED01	timolol (6)						sexual dysfunction, libido decreased, erectile dysfunction, peyronie's disease	32 101	CBG	ADRs reported for the pharmacological class of ophthalmic beta-blockers
S01ED02	betaxolol (6)				libido decreased		sexual dysfunction	2007	CBG	ADRs reported for the pharmacological class of ophthalmic beta-blockers
S01ED05	carteolol (6)						erectile dysfunction, libido decreased, sexual dysfunction, peyronie's disease	961	CBG	ADRs reported for the pharmacological class of ophthalmic beta-blockers
S01ED51	timolol, combinations (6)						libido decreased, sexual dysfunction, peyronie's disease	102 550	both	observed in patients treated with timolol, ADRs reported for the pharmacological class of ophthalmic beta-blockers
V	**Various**									
V03AB21	potassium iodide						erectile dysfunction	NA	CBG	
V04CD04	corticorelin						blood prolactin increased	NA	CBG	
V09AX04	flutemetamol (18F)			erectile dysfunction				NA	EMA	

Explication of numbers and abbrevations: 1: ADR occurs in adults only; 2: ADR occurs in children only; 3: ADR occurs in men only; 4: ADR occurs in women only; 5: Doubtful relationship; 6: 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 (thus the ADR was reported for the drug or for drugs in the same pharmacological class); 7: Reported for one of the substances in a combination product, for (substance in comment); ADR: adverse drug reaction; ATC: anatomical therapeutic chemical; NA: no available data; GIP: Zorginstituut Nederland, GIP (2017), numbers based on national health insurance data; SmPC: Summary of Product Characteristics; EMA: substance found in PROTECT database, which lists the centrally authorised products at EMA; CBG: substance found at the website of the Dutch national registration authority (CBG); both: substance found at both the PROTECT database and the website of the Dutch national registration authority (CBG); very common: reported with an incidence >10%; common: reported with an incidence >1% and <10%; uncommon: reported with an incidence >0.1% and <1%; rare: reported with an incidence >0.01% and <0.1%; very rare: