Adverse drug reactions on sexual functioning: a systematic overview

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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 might 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 non-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 6 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% suspect

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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 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 requested 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 Product 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 ADRs 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)

Because 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 on 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 ADR 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). MedDRA is organized by the system organ class (SOC), divided into high-level group terms (HLGT), which are divided into 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 1 and 2. The MedDRA version in Dutch was used for the search of 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; Fig. 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 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 incidence 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.

TABLE 1

Most frequently used drugs with sexual adverse drug reactions in The Netherlands

	ATC	Drug	Uncommon	Rare	Unknown, not mentioned or no standard category	User numbers 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	Hydrochlorothiazide	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; uncommon: incidence >0.1% and <1%; rare: incidence >0.01% and <0.1%.

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 LLT and PT are mentioned only once in the tables, 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 ten drugs by a second researcher (MT). Analyses were performed with Microsoft Excel 2016 (Microsoft Corp., Redmond, WA).

Results

With 194 MedDRA search terms (Fig. 1) a total of 346 drugs were detected with at least one sexual ADR registered in the SmPC (see Table S3 in supplementary material online). 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 (Fig. 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 S1 in supplementary material online). 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 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). 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 in supplementary material online). However, the consistency of mentioning this pharmacological class effect in the individual SmPCs varied as seen for the statins: the pharma-

TABLE 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
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

Green = reported specifically for females; blue = reported specifically for men.
[a]ADR occurs in adults only.

cological 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. 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 the 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

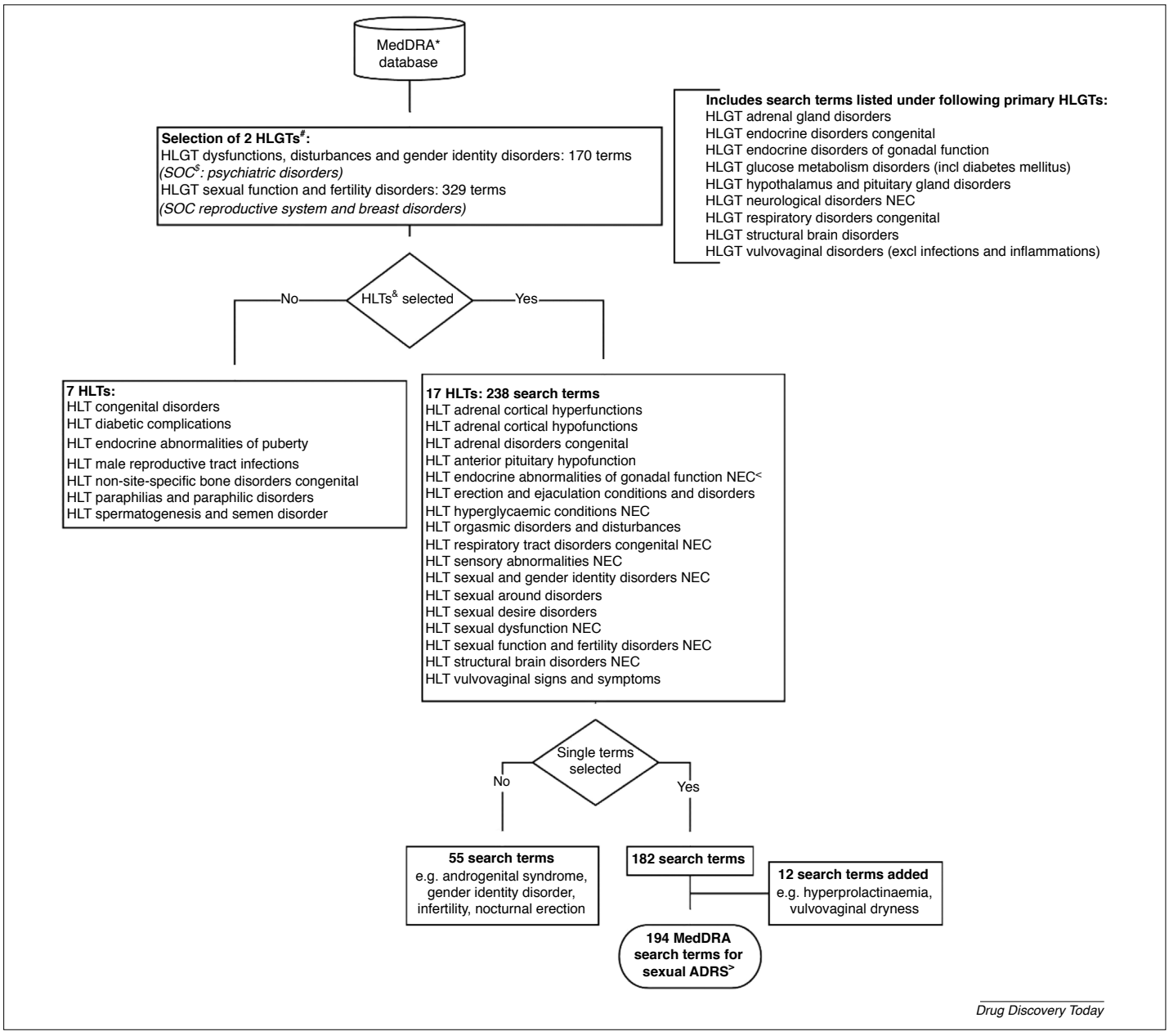

FIGURE 1

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. These terms were found relevant but are not listed under the two HGLTs. Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; HLGTs, high-level group terms; HLTs, high-level terms; NEC, not elsewhere classified; ADRs, adverse drug reactions.

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].

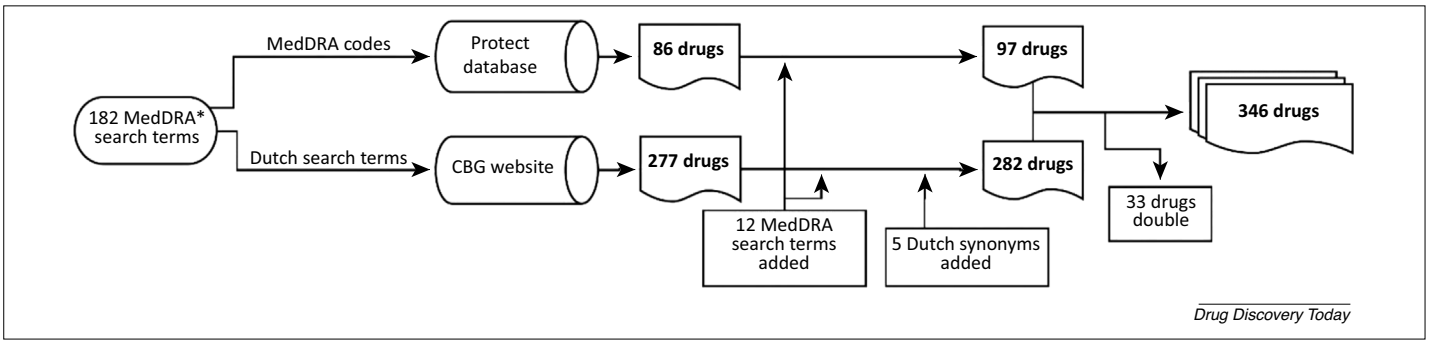

FIGURE 2

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.

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), anti-infectives for systemic use (J), musculoskeletal 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., confounding 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 as potential solutions [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 5ARIs, 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 well 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 can influence incidence rates as well, because sexual ADRs are perceived in other ways in different cultural backgrounds and in different times, for example the occurrence of a 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 because 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 has been more research attention 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 patient 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 functions. 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 review 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.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2019.01.012.

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