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

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Chapter 10

General discussion

Although sexuality is important for health and wellbeing, the topic is often avoided in healthcare [1, 2]. Correspondingly, little is known about the impact that disease, treatment and associated factors can have on a person's sexual life. Within the field of sexuality in healthcare, sexual adverse drug reactions (sADRs) have often been named as potential risk factors for sexual issues [3]. However, few studies has been performed about sADRs. The limited literature available suggests that sADRs may occur with many drugs and have pivotal consequences for drug adherence and a person's quality of life [4, 5].

To improve the care and support for drug users who may experience sADRs, this thesis aimed to enhance our understanding of which drugs are related to sADRs (PART 1) and to explore the current practice and attitude of primary care providers regarding sADRs, with a special focus on the community pharmacy (PART 2). Several topics in the field of sADR research were entangled with both PART 1 and PART 2, such as gender differences and the consequences of sADR information provision. These topics, as well as methodological considerations and suggestions for future studies are discussed in PART 3 'Further considerations with regards to sADR and sADR research'.

PART 1 Characterisation of drugs that may cause sADRs and the population at risk for sADRs

sADR information in information leaflets

Data from registration trials are the primary source of ADR information for both professionals and patients. Therefore, to identify which drugs may cause sADRs, we systematically extracted the sADRs from a European and a Dutch database of Summary of Product Characteristics (SmPCs) (Chapter 2). With this method, we detected 346 drugs with at least one sADR registered in their SmPC. As hypothesized, the range of drugs was broad; it covered 13 of the 14 classes of the first level of the anatomical therapeutic chemical (ATC) classification system. Nonetheless, the majority of drugs registered with sADRs could be placed in two groups: drugs targeting the nervous system (ATC class N: 105 drugs) and drugs targeting the cardiovascular system (ATC class C: 89 drugs). These drugs were often already described in literature with association to sADRs [16-23]. The risk for sADRs was classified in the SmPCs as common (1–10% of users) for 82 drugs, and very common (>10%) for 16 drugs. Notably, the drugs were registered before 2016 on European level or before 2019 on Dutch level. The list published thus excludes drugs registered elsewhere or more recently, such as lisdexamfetamine (1–10% risk for decreased libido and erectile dysfunction). Nevertheless, most commonly used drugs have been on the European market for at least a decade and were thus assessed in Chapter 2.

sADR information in drug information leaflets deviates from clinical practice

The information and incidence rates as mentioned in the SmPC were not comprehensive. For instance, pharmacological class effects were mentioned in the SmPC of some drugs, and not for drugs with similar working mechanisms. The case of selective serotonin reuptake inhibitors (SSRIs) exemplifies this: non-registration studies have shown that 30–60% of users of SSRIs experience sADRs, whereas of the six SSRIs, only paroxetine and sertraline were registered with >10% risk for sADRs [24]. Even the SmPC texts for the same drug (e.g. generic brands), showed differences in which sADRs were found and which incidence rates were reported. In addition, for only 20 of the 346 drugs, gender differences in sADRs were explicitly stated in the SmPC. Lastly, for the majority of drugs with registered sADRs, the risk for sADRs was unknown. These inconsistencies and lack of detail raised the question whether SmPCs are the adequate source for sADR information.

Similarly, the US Food and Drug Administration (FDA) concluded that sADR information from registration trials likely did not reflect the incidence in clinical practice. For SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), they compared randomized controlled trials (RCT) published in literature databases with studies that were handed in for registration for the relevant drugs (in-house data) [6]. The real-world data showed consensus about the influence of the SSRIs and SNRIs on sexual function and sexual experiences. These influences were measured by two validated questionnaires. In the in-house data, only 11 trials could be found that relied on these questionnaires rather than unsolicited reporting. Those studies exhibited no consensus, reporting both positive and negative effects on sexual function [6]. Thus, even when registration trials utilized structured questionnaires to evaluate the effect of SSRIs and SNRIs on sexual function, no conclusions could be drawn from the divergent results. Two reasons for the discrepancy were suggested: publication bias (i.e. negative studies are less likely to be published) and less focus on the sexual function questionnaires because the registration trials included more endpoints.

Advantages and disadvantages of different sources for sADR information

Both the FDA findings and Chapter 2 showed deficits in the sADR information of SmPCs. Besides registration files, sADRs are also described in literature studies and pharmacovigilance data. Those sources have the advantage that they exhibit real-world data and, with some exceptions, conflicts of interest are not applicable. Nevertheless, they also have important limitations regarding sADRs. The available literature reviews about sADRs are few, incomplete and – similar to registration trials – have a high risk for publication bias. In addition, many of the studies that have been published were designed to show associations

between the incidence of sexual complaints and medication use, but not causal relationships. Pharmacovigilance data from spontaneous reporting, on the other hand, is mostly limited by underreporting of ADRs [7]. It should also be noted that besides specific limitations for each data source, all data sources share the limitation that culture and time periods also influence the reported incidence of sADRs [8].

Taking all limitations into consideration, we argued in this thesis that the SmPCs should be the starting point for an overview of drugs that can be associated with sADRs. Although the sADRs incidences in SmPCs were likely underreported, they have two main advantages: 1) This information source is available for every drug on the European market, thus representing the most complete overview of drugs, and 2) the study populations had comparatively few other risk factors for sexual problems. In addition, the SmPCs are the only source for drug information leaflets, which patients and healthcare providers may read to understand the risk about sADRs. At the same time, it should be acknowledged that the other information sources are also of crucial importance, to confirm and supplement the sADRs identified in registration trials. Especially potential interactive effects of other drugs or morbidities are currently not researched in registration trials, and thus not noted in SmPCs.

Supplementing sADRs information in SmPCs with social media data

To explore how the other information sources may supplement the findings from Chapter 2, we studied the reporting of drug-related sexual problems on an online medication platform, named mijnmedicijn.nl (Chapter 5). Social media such as this platform is increasingly investigated in the field of pharmacovigilance, with the assumption that more patients report their complaints on social media than at pharmacovigilance institutions. The first explorative studies indeed showed that one could capture the less frequently reported side effects from social media data [9]. Of note, these sources have the disadvantage that the reported adverse events (AEs) are not evaluated for causality with the drug in use by healthcare professionals. On mijnmedicijn.nl, we found 2408 sexual AEs (sAEs) that were reported for 189 drugs. The sAEs were posted in 3.9% of the patient-reported drug experiences. Similar to the findings of the SmPC study, the range of drugs associated with sexual complaints was broad, covering 11 of the 14 level 1 ATC classes, and most drugs were part of the drug classes N and C. However, when focusing on the number of sAE reports, after ATC class N (n=1341), not drug class C (n=178), but drug class G (drugs targeting genitourinary system and sex hormones; n=761) received most sAE reports. We also assessed which drugs received sAE disproportionally frequently. Of those 27 drugs with disproportional high sAE reporting, seven were registered with a low risk for sADRs

in their SmPC, thus showing a potential sAE underestimation in the registration trials. Especially antidepressants and contraceptives received significantly more sAE reports than would be expected from the incidence rate in their SmPCs. Furthermore, for 58 drugs for which sAEs were reported on mijnmedicijn.nl, no sADRs were found in their SmPCs.

Social media as a new pharmacovigilance source for sensitive side effects?

In comparison to the French Pharmacovigilance System (FPS), sAE were 18 times more often part of a report on mijnmedicijn.nl (sAEs in 3.9% vs 0.2% of reports) [10]. This suggests that an online medication platform may reflect the real-world frequency of sAEs better than pharmacovigilance institutions. However, to compare the sADR information that can be extracted from different types of pharmacovigilance sources, the quality of the report and the person reporting the sAE are also important factors. Indeed, the advantage of pharmacovigilance institutions is the more exhaustive report, with the possibility to reach a further understanding of the specific sADR (e.g. time of onset, severity of complaint, dose-dependency, etc.). On the other hand, healthcare professionals are the main source of ADR reporting, and they mostly report ADRs when these are severe and more objectively noticeable [11, 12]. The sADRs reported at FPS concerned for example more often anorgasmia or impotence whereas most sAE at mijnmedicijn.nl concerned the less objective symptom of decreased desire for sex. In other words, reporters for the two sources probably had different objectives to report a drug experience or side effect. Interestingly, the different pharmacovigilance sources also showed variance in the most common drugs for which sAE were reported. Lareb received considerably more sAE reports for statins and less sAE reports for hormonal contraceptives than mijnmedicijn.nl [20]. Because of these differences, the novel source of online platforms should not be seen as a replacement, but rather a complementary source. It does have the advantage that it likely reflects the real-world frequency better and elucidates which drugs patients associate their sexual complaints with, also when the association is doubtful.

Coherence of sADR information

Published studies about sADRs infrequently exhibit contradictory findings. For example, for classic antineoplastic drugs (e.g. cisplatin, cyclophosphamide, doxorubicin) sufficient evidence had shown a high risk for sexual problems, although this is not described in their SmPCs [13]. As a consequence, the current evidence about sADRs cannot be summarized in one apprehensible table. However, to exemplify how different information sources, with different findings, can be summarized and appraised, the evidence for sADR of four drug groups (antidepressants, cardiovascular and urological drugs and hormonal contracep-

tives) is described below. These drug groups were chosen because of the numerous studies published about their potential relationship to sexual function. They also highlight current issues with sADR studies, which are discussed below the drug-specific paragraphs.

Antidepressants

There is coherent evidence that antidepressants, especially SSRIs, can negatively impact sexual function. Less evident is the size of this effect. In the SmPCs, at least one sADRs was noted with an incidence rate of >10% of users for sertraline and paroxetine, an incidence rate of 1–10% for citalopram, escitalopram and fluoxetine and 0.1–1% for fluvoxamine (Chapter 2). Similarly, in the sADR studies of FPS and Lareb, paroxetine, citalopram, sertraline and fluoxetine showed the highest odds ratio for reporting sADRs [10, 14]. Notably, escitalopram and fluvoxamine were not, or only in one of the studies associated with an increased risk for sexual problems [10, 14]. In comparison, the findings of Chapter 5 showed more homogeneity, with sAEs mentioned in 8–17% of the SSRI experiences, also for escitalopram and fluvoxamine. In literature, the incidence of SSRI-induced sexual dysfunction ranged between 15% to 80% of users, depending on the population and methodology [15, 16]. In general, from the many published studies about this topic, it can be concluded that the SSRIs, the SNRIs and clomipramine all have a high risk for sADRs [15, 17]. The tricyclic antidepressants, with the exception of clomipramine, have an average risk for sADRs and for the other antidepressants, the few studies available showed a trend for a lower risk for sADRs [15, 17].

According to literature, antidepressants most often impact women's sexual arousal and men's sexual desire and orgasms [15]. In the SmPCs of SSRIs, and at FPS, problems with ejaculation were also commonly reported [10]. In contrast, at Lareb and in the online drug experiences (Chapter 5), ejaculation was barely mentioned by men using SSRIs [14]. Similarly, decreased arousal was also barely mentioned in the pharmacovigilance studies and in the online SSRI experiences, contrasting with the conclusions made in literature.

Cardiovascular drugs

A total of 89 drugs and drug combinations that target the cardiovascular system have sADRs described in their SmPC (Chapter 2). Most research about sADRs during cardiovascular drug treatment has focused on betablockers and their potential association with erectile dysfunction. The focus on erectile dysfunction is understandable since its pathophysiology often has a vascular component [18].

According to the European Society of Hypertension (ESH), the current evidence suggests that diuretics and beta-blockers have the strongest negative impact on erectile function,

and angiotensin receptor blockers (ARBs) and nebivolol have the most positive impact [18]. Baumhäkel *et al.* and Nicolai *et al.* reached similar conclusions in their reviews and added that alpha-blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers have no relevant, or even a positive effect [19, 20]. Nicolai *et al.* also stated that statins have a positive effect on sexual function [19].

Regarding these summaries, several important points should be acknowledged. Firstly, strong evidence for sADRs could not be found for any of the drugs, especially not for female users [18-20]. Even if enough evidence was found to summarize in guidelines and reviews, it is important to highlight that the 'neutral' effects in these reports are generally a summarization of both positive and negative effects on sexual function [18, 19]. Notably, a high risk for sADRs can also be registered coincidentally, as highlighted by the 1–10% risk in the SmPC of fosinopril, for which 1.0% of users reported sexual dysfunction in the clinical trials, in comparison to 1.1% among the placebo users [21]. Lastly, the majority of published studies about the association of cardiovascular drugs with sADRs were published in the 1980s and 1990s and were based on either spontaneous patient reports or otherwise assessed sexual dysfunction with non-specific indicators such as frequency of sexual contacts [20]. Although the SmPCs were published in a similar time period and also relied on spontaneous reporting, they generally provided more specific sADRs. When comparing the findings in Chapter 2 and Chapter 5 to those early trials, they do align with their conclusions that especially men had a small risk for erectile dysfunction and decreased libido during beta-blocker, spironolactone and thiazide treatment.

Hormonal contraceptives

One of the most significant findings of Chapter 5 is that women reported sAE five times more frequently for hormonal contraceptives than for other drugs. The sAEs generally concerned sexual desire. Ten of the 27 drugs with disproportional high numbers of reports with sAE were contraceptives, of which four were registered with a low risk (0.1–1%) in their SmPC. Indeed, for most contraceptives, the sADR incidence rate in the SmPC is 0.1–1% for decreased libido and 0.01–0.1% for increased libido. The exception are five contraceptives for which decreased libido is noted for 1–10% of users: the hormonal spiral and ring, the contraceptive injection and implant, and the 4th generation combination pill of estradiol with nomegestrol. Other sADRs mentioned in SmPC texts were anorgasmia, abnormal orgasms, dyspareunia and vulvovaginal dryness.

In literature, contradictory conclusions have been published about the topic. The few RCTs often showed neutral to negative effects on one or more domains of sexual function (generally on sexual desire, satisfaction and orgasm). However, more cohort and cross-

sectional studies were performed, in which also positive effects on sexual function were found. As a result, the 2019 position statement of the European Society of Sexual Medicine (ESSM) summarized the evidence as a positive to neutral effect of combined oral contraceptives (COCs) on sexual desire, a lower frequency of orgasms and insufficient evidence about potential effects on vaginal lubrication and atrophy [22]. Their conclusion about sexual desire is likely based on the systematic review of Pastor *et al.* (n=8422), which concluded that among COC users, 21.7% reported an increased libido, 63.6% no change in libido and 14.7% a decreased libido [23]. After the ESSM statement was developed, a meta-analysis by Huang *et al.* was published with contradictive results [24]. They examined the Female Sexual Function Index (FSFI) score for contraceptive users and found a small, non-significant decrease in the total FSFI score and a small, statistically significant decrease for the domain of desire [24].

Urological drugs

The two main drug groups used for male lower urinary tract symptoms and BPH, the alpha-blockers and 5-alpha reductase inhibitors (5-ARIs), are both associated with sADRs according to their SmPCs. Similarly, the Lareb study showed that alpha-blockers (mostly tamsulosin) were often related to ejaculation failure, ejaculation disorders and erectile dysfunctions [14]. Also on mijnmedicijn.nl, 38-40% of the male experiences with the 5-ARIs finasteride and dutasteride described sAEs. Interestingly, whereas sAE were common in the experiences with alpha-blockers tamsulosin (mentioned in 31% of the experiences) and silodosin (45%), barely any sAE were described for the alpha-blocker alfuzosin (4%). These findings concord with the registered incidences for alpha-blockers. For other types of urological drugs, such as oxybutynin and mirabegron, only rarely sADRs are described in their SmPCs and in pharmacovigilance studies.

Literature studies have revealed that 5-ARIs have a dose-dependent relationship with sADRs, which can present themselves as erectile dysfunction, decreased libido and according to their SmPCs, ejaculation disorders [25]. Interestingly, the two most recent meta-analysis about the effect of 5-ARIs on sexual function had similar inclusion criteria, but contradicted on whether finasteride and dutasteride differ in their risk for sADRs and whether after longer periods of time, the symptoms improve or worsen [25, 26]. Hopefully, future studies will indicate whether differences among the two drugs regarding their risk for sADRs exist. Also alpha-blockers showed a dose-dependent relationship with sADRs, in this case ejaculation disorders, which disappear 24 to 36 hours after discontinuation of treatment [27]. According to the latest reviews, the differences among the alpha-blockers are at least partly explained by their affinity and selectivity for the alpha 1-A receptor. Concordantly, silodosin and tamsulosin generally showed the highest risk for ejaculation problems, whereas doxazosin,

terazosin and alfuzosin have the lowest risk profile [27, 28]. It should also be noted that anejaculation, the most well-known sADR associated with these drugs, may also cause other issues in a man's sexual life. For example, 17% of men that experienced anejaculation during silodosin treatment also associated this with orgasmic problems [27].

Current issues in the reporting of sADRs

In the assimilation of the sAE information sources, several reasons arose for the divergencies in the available sAE information. These reasons highlight important current issues in collecting sADR information from patients. Firstly, the sources have different confounding risks for sexual problems in the study populations, which also have been handled differently in each study. Confounding by indication is the most well-known example, which makes differentiation between side effects of drug and disease difficult, especially for depression and cardiovascular diseases. The case of antihypertensives exemplifies this: the prevalence of erectile dysfunction is higher in patients treated for hypertension than in untreated patients, which suggests an important role of antihypertensives on erectile function. However, receiving treatment for hypertension is also associated with more severe forms of cardiovascular diseases and thus greater organ damage [15]. Accordingly, the ESH stated that the relationship between antihypertensive treatment and erectile dysfunction remains unclear [15]. Also for depression, about 40–50% of untreated patients noted lower sexual interest and arousal before they started antidepressants [29]. Because of this background risk, the exclusion criteria and baseline characteristics are extremely important for sADR studies. There are only a few exceptions of drugs for which the cause of sexual problems (drug vs. disease) is not difficult to untangle, such as the alpha blockers: sADRs related to this drug group diminish when the drug is discontinued for 1–2 days [27].

Besides the indication for the drug treatment, also multimorbidity and polypharmacy may explain differences in sADR incidences. Indeed, an increasing number of morbidities (and associated higher number of drugs in use) was shown to increases the risk for female sexual dysfunction by Appa *et al.* [30]. Sadly, no studies were identified that researched the effect of solely more drugs on the experience of sADRs. An increased risk for experiencing sADRs may be hypothesized based on the study by Appa *et al*. However, in Chapter 3, the discontinuation rates of a first dispense of drug with high sADR risk decreased with an increasing number of comorbidities, which suggests that patients with a high baseline risk may not experience or be bothered by additional sexual side effects. In Chapter 3 and 4 this theme was explored more in-depth, which is described below.

Another important factor in sADR reporting is the chosen study outcome for sADRs. As mentioned before, incidences for antidepressant-induced sexual dysfunction vary greatly,

depending on the population and method. Indeed, one meta-analysis showed a trend for higher sexual dysfunction rates in observational studies versus RCTs, and in prospective studies (incidences at 6 months) in comparison to cross-sectional surveys [17]. The authors of that meta-analysis noted that in the majority of RCTs, definitions of sexual dysfunction were vague, did not state whether or how specific sexual symptoms were combined into one outcome and did not state whether recording of sADRs occurred retrospectively or prospectively [15]. Also in the meta-analysis of Seretti and Chiesa, the outcome measure greatly impacted the reported incidence: direct inquiry without any specific questionnaire were associated with the lowest sADR percentages (paroxetine: 24–27% of users), and the changes in sexual functioning questionnaire (71%) and the psychotropic-related sexual dysfunction questionnaire (95%) with the highest percentages [16]. Similarly, other drug groups were investigated with non-explicit sADR outcomes: binary outcomes (did a sexual problem occur yes or no) were common for studies about ARIs and the frequency of sexual activity was utilized as a substitute for sexual dysfunction among beta-blocker users.

The SSRIs example highlights another problem: differences in how patients distinguish and appraise the experience of sADRs. As mentioned before, ejaculation issues were barely associated with SSRI use in literature. This is surprising, since the association between SSRI use and ejaculation function was so evident that the new SSRI dapoxetine was developed and registered for premature ejaculation disorders [31]. Accordingly, one could assume that more men on SSRI treatment experienced delayed ejaculation, but refrained from reporting this. Perhaps delayed ejaculation is a non-bothersome effect for some male users. Some of the online SSRI experiences indeed stated a positive experience with regards to delayed ejaculation. Another example of a different appraisal of sADR experiences is SSRI-induced decreased arousal, which was barely mentioned in online SSRI experiences and pharmacovigilance studies. In this case, it is more likely that the SSRI users could not distinguish between desire and arousal problems, describing them all as desire issues. Difficulties in understanding sexual function terms have been shown before, which was the reason why in Chapter 5, patient-reported sAE terms were utilized [32]. Another incongruent description concerns the worries and difficulties related to sADRs and a person's sexual life. For example, women who mentioned positive impacts of contraceptives on sexual function, did not mention more libido, but less worries about pregnancy and sexually transmittable diseases [33]. On the other hand, side effects or worries about health, including sADRs, made 10% of women stop their contraception method after 12 months and 22% after 36 months [34]. Also in low- and middle income countries, negative experiences regarding sexual function (e.g. decreased libido, lubrication, sexual enjoyment and more dyspareunia) were among the reasons for discontinuation of any contraceptive method [33]. It is clear that patients need a certain understanding of sexual function to

be able to describe their experience and find recognition in sADR descriptions. These findings thus advocate for reinforced shared decision making, in which all potential effects of sADRs should be explained.

Lastly, also the size of the drug group investigated is relevant for sADR information. The ESH, for example, summarized the effects for each major cardiovascular drug group, although more recent studies have shown that more refinement is appropriated: solely non-selective betablockers were associated with erectile dysfunction [35], and the third-generation beta-blocker nebivolol showed to have only a small risk for sexual dysfunction, even improving erectile function when this was negatively impacted by another betablocker [18, 36]. Also the references for these refinements need to be transparent. For the diuretics, the ESH did present a table stating that thiazide diuretics have a negative effect on erectile function (except for indapamide), loop diuretics a negative or neutral effect, mineralocorticoid receptor antagonists (MRAs) a negative effect and potassium-sparing non-MRAs a neutral effects [18]. However, their table cannot be verified, as references to information sources are missing, and, to our knowledge, no sADR information has been published elsewhere for loop diuretics and eplerenone. Distinguishing between the level of drug groups is thus highly relevant for adequate sADR information. In addition, it also provides alternatives within a drug group when sADRs are unacceptable for a specific drug.

Knowledge about the development of sADRs

The effect of drug treatments on sexual function can be explained by a combination of biological and psychological, and direct and indirect effects [4]. For some drug groups, pharmacological mechanisms have been described. For instance, drugs affecting the nervous system likely exert their effects through the availability of neurotransmitters, which influence one or more stages of the sexual response cycle, e.g. the 5HT-2A receptor negatively affects sexual function, the 5HT-2C receptor facilitates erection and the 5HT-1A receptor ejaculation [37]. The different affinities of antidepressants for specific serotonin, noradrenaline and dopamine receptors and their efficacies may thus explain why certain antidepressants have a higher risk for sADRs than others. Furthermore, the levels of sex hormones or stimulation of their receptors can explain how 5-ARI, contraceptives, the older anticonvulsants, spironolactone and statins can induce sADRs [19, 26, 38, 39]. This also holds true for prolactin levels, which dopamine antagonists appear to increase by blocking D2 receptors in the hypothalamic infundibular system [40]. In other cases, more integral systems may play a role, e.g. betablockers inhibiting the sympathetic nervous system, which is involved in the integration of erection, emission and ejaculation [19]. It should be noted that most direct effects on sexual function have not been verified in humans. Also indirect

effects are difficult to test, as they include a wide range of symptoms such as sedation, extrapyramidal effects, fatigue, weight gain, mood changes, and the nocebo effect [4, 37, 40]. Notably, the latter has only been documented for betablockers and 5-ARIs, and could (partly) be reversed with placebo treatment [41-43]. Lastly, it should be recognized that the time until occurrence of sADRs can also be delayed or even start after the treatment stopped. This has been described for SSRIs and finasteride, a rare phenomenon nowadays defined as post-SSRI sexual dysfunction and post-finasteride syndrome [44].

Knowledge about the treatment of sADRs

Since the effects of drugs on sexual function are still not fully understood, also the treatment of these sADRs remains unclear. Studies about SSRI-induced sADRs have suggested that for those drugs, the symptoms can be decreased or even resolved through waiting, reducing the dose, changing administration times, drug holidays, adjunct treatment and switching to another drug [15]. These strategies may also apply to other drugs, especially for drugs with dose-dependent relationships with sADRs (e.g. 5-ARI and alpha-blockers) and with short half-lives. Switching within the same drug class has also proven util for betablockers (to nebivolol) and hormonal contraceptive pills (any other pill, independent of androgen activity) [36, 45].

Description of the population at risk for sADRs

Many factors, such as the underlying disease indicators, psychological factors, culture and relationships play a role in the association between disease, treatment and sexual function and wellbeing [4]. Because of this, we should ask ourselves how can we extract the culprit(s) for sexual complaints if several risk factors exist. This is especially difficult if the individual is presented with multiple conditions and drug treatments. It is essential that the risk for sADRs is investigated in the increasingly multimorbid population with high rates of polypharmacy. In Chapter 3 we commenced this exploration of the population at risk for sADRs by estimating how many persons use drugs with a risk for sADRs according to their SmPC. Utilizing drug dispensing data, we found that 7.8% of the inhabitants of the Netherlands used a drug with 1–10% risk for sADRs and 2.1% a drug with >10% risk. Additional risk factors for decreased sexual function were common. For example, one of every three users of antidepressants was treated for cardiovascular diseases. In Chapter 4 we continued with a focus on the real-life setting of a multimorbid population by questioning these drug users about their sexual function and their perceived association with their drug treatments. However, a low response rate (9%) limited the generalisability of this study. Of the 44 responses that could be analysed (of which 21 females), 84% experienced

sexual complaints and more than 60% considered it possible or undoubtful that their drug treatments had negatively affected their sexual function. In most polypharmacy cases, several or all drugs were noted as the potential culprits by the patient. From these first explorations, it can be concluded that prescribers and pharmacists should be alert for sADRs in almost 1 in 10 of their patients, who frequently also have other risk factor for sexual complaints. In Dutch pharmacies, five to six patients start a drug with >10% risk for sADRs each month. Extra attention should be paid to this starting phase, especially for users of antidepressants with few additional medication treatments, because they showed the highest antidepressant discontinuation rates after the first dispense.

PART 2 sADRs in the community pharmacy: Current practice, attitude and possibilities

To our knowledge, how the topic of sADRs is handled in healthcare practice had not been researched before. Previous research did show that different healthcare professionals around the patient disagreed on who should counsel the patient about sADRs [46, 47]. To explore this role delegation regarding sADRs in primary care, we carried out four focus groups, with general practitioners (GPs), GP nurses, pharmacists and pharmacy technicians, in which the current practice, their own role and the role of the others regarding sADRs were discussed (Chapter 7). The study revealed that the discussion about sADRs was considered a shared responsibility between the prescriber, pharmacist and patient and mainly took place when the circumstances (e.g. availability of privacy and time) allowed this. Importantly, their perspective about responsibilities for sADRs did not reflect current practice, because of challenges that are common in healthcare practice (e.g. lack of time) or that occurred because of the sensitivity of sADRs. The pharmacy team mostly felt responsible for informing about sADRs and evaluating the drug treatment, although the latter process was not yet developed in most pharmacies.

Pharmacists have a unique position in primary care. Not only are they the most accessible healthcare provider in most neighbourhoods, their work tasks increasingly include more pharmaceutical care [48]. To understand the place of sADRs in the community pharmacy, we surveyed pharmacists in the Netherlands about their daily practice and attitude with regards to sADRs (Chapter 8). Similar to the questionnaire for drug users with a high risk for sADRs, the response rate was low (5%), limiting what can be concluded from the findings. If sADRs were discussed in the respondents' practices, this most likely happened during a first dispense of a high-risk drug or during medication reviews. About one-third of the respondents never or barely discuss sADRs during first dispenses of high-risk drugs,

and two-thirds reported that their pharmacy technicians never or barely discussed the topic. The latter is important to note, because the majority of the respondents assigned pharmacy technicians to the role for informing about potential sADRs. The responsibility for detecting sADRs was assigned to the patient or its partner and the main responsibility for detecting and discussing sADRs to the prescriber.

Barriers and facilitators for integrating sADR in primary care

The research described in Chapter 7 and 8 revealed many reasons why care for sADRs is challenging. These reasons can be divided in three groups: general barriers to change practice (e.g. lack of time, cultural or language barriers), barriers to discuss the sensitive topic of sexuality and barriers for sADRs specifically. Indeed, many of the barriers described in Chapter 7 and 8 concorded with those in previous research about sexuality in healthcare practice, e.g. not prioritizing sexuality in consultations, assuming the patient will bring up the topic, little awareness about sexuality in practice guidelines and not finding the right angle to start the conversation [2, 49-56]. For sADRs specifically, healthcare providers also considered it difficult to assess the causality with drug treatments, to have a conversation about this sensitive topic at the pharmacy counter (with little privacy) and to inform without deterring drug adherence or inducing nocebo effects. These barriers should be decreased or removed for potential interventions regarding sADR to succeed.

In Chapter 6 we described another study that aided in our understanding of how sADRs could be integrated in pharmacy practice. In this chapter, pharmacists in Northern-Ireland were interviewed, who provided nonprescription sildenafil, the only pharmacy-based service about sexual function. This service is available in countries such as the United Kingdom (UK) and New Zealand. Although this pharmacy service is not about sADRs specifically, lessons can be learned from their experience. Men who requested nonprescription sildenafil were often embarrassed and their answers were sometimes short or vague. Therefore, the first consultations were recalled as somewhat difficult or uncomfortable. With time, the pharmacists had found ways to make the patient feel at ease and to obtain the information that they needed from patients. They for example had learned how to always look friendly and confident and how to describe the technical terms with lay language. The pharmacists considered it rewarding to see signs that the service was working, and that they may have helped relationships by overcoming a taboo problem.

Exploring the potential of integrating sADR in primary care

To explore the potential of changing primary care practice to include sADRs, we collected information sources about sADRs, developed education materials and investigated how they would be used in primary care in a small explorative study with Pharmacotherapeutic Audit Meetings (PTAMs) (Chapter 9). PTAMs are already existing local collaborative groups of community pharmacists and GPs in the Netherlands, that meet 4 to 6 times per year to educate themselves and make agreements about pharmacotherapeutic topics of their own interest. In this case, we created education materials about sADRs, for which we incorporated lessons learned from the other chapters, such as the knowledge about which drugs may cause sADRs (Chapter 2), which patients are at risk for sADRs (Chapter 3), and barriers and facilitators experienced by pharmacists and GPs (Chapter 6 to 8). In addition, a short video about sADRs was created in collaboration with Kijksluiter, a company that summarizes drug information leaflets in short videos in plain language, specified for gender and age if relevant, and available in several languages. These visual drug information leaflets are referred to in many Dutch community pharmacies through links or QR codes. The video about sADRs was suggested as one of the potential agreements for the PTAM meeting.

The perspectives of a total of ten PTAM groups that had held a PTAM meeting about sADRs could be analyzed. The findings indicated that the PTAM about sADRs was generally appreciated by both the GPs and pharmacists for creating awareness about sADRs. The agreements mostly focused on incorporating sADRs in already existing processes, e.g. shared-decision making and chronic disease consultations in GP practices, and first drug dispenses and medication reviews in community pharmacies. In other words, adjustments were chosen that would burden the current healthcare practice the least. After three months, the majority considered informing about sADRs a normal part of their work. A before – after analysis showed that the PTAM about sADRs induced slight improvements in dealing with patient's sADRs. With the exception of one PTAM group, none of the agreements dealt with providing written or visual information about sADRs. When this choice was questioned in interviews with PTAM participants, it became clear that patient folders and the video about sADRs did not come to mind during the meeting and deviated from how the already existing processes were executed.

The PTAM about sADRs mostly created awareness about the topic and only slightly improved the information provision and discussion about sADRs. Education materials and related agreements about sADRs could thus be regarded as a first and crucial step in integrating sADRs in primary care, to create awareness before adjusting processes such as information provision. Notably, the PTAM materials about sADRs had one important

limitation according to the study participants; The agreements about changes in information provision of discussion of sADRs had to be monitored to maintain a high quality level of PTAM, which was more difficult for this novel type of agreements in comparison to the more common agreements about prescribing behavior.

PART 3 Further considerations with regards to sADR and sADR research

Gender differences in reporting sADR

In Chapter 5 it became evident that gender differences are an important, yet neglected theme regarding drug-induced sexual problems. The findings showed that women reported a higher total number of sAE than men (n=1383 vs. n=1025) but proportionally to all reports, men talked about sAE more often than women (sAE mentioned in 4.7% of all reports vs. 3.5%). The latter difference was especially noticeable for antidepressants and cardiovascular drugs. Other gender differences that were unveiled were a younger average age of the women reporting sAE (20–40 years vs. >40 years), and a higher proportion of sAE that concerned a change in desire in comparison to men (77% vs 42%). Of course, these differences can be partly explained by the high number of sAE reports for drugs with inherent sex differences, contraceptives (n=604) and drugs used for benign prostate hypertrophy (BPH) (n=118). Nevertheless, drugs that both genders use frequently also showed discrepancies, e.g. sAE in 22% of venlafaxine reports of men (n=102) and only 10% of reports of women (n=101). A comparison with the sADRs reported at the Dutch pharmacovigilance institution Lareb suggests that women and men also report their potential sADRs at different locations: at Lareb, the majority of reported drug-sADR associations were about men (n=1987; 72%) whereas most of the sAE reported at mijnmedicijn.nl concerned women [20]. In Chapter 5, several potential reasons for these gender differences were provided, including biological, social and cultural differences between the two sexes. Future research should explore which of these potential factors are relevant in practice, and more importantly, whether women and men identify sADRs to the same extent and if these sADR have a different impact on their lives.

sADRs and drug adherence

sADRs are considered one of the most difficult side effects to live with, and therefore decrease or deter treatment adherence [5, 57]. Consequently, treatment results can be negatively impacted, which can lead to fatal cases for drugs with narrow therapeutic

windows or which require strict adherence (e.g. anti-HIV medication). Sadly, little is known about the effects of potential sADRs on these types of drugs. It is important to note that in Chapter 4, many users of multiple drugs could not differentiate between the effects of separate drugs on sexual function. If sexual complaints are a reason for low drug adherence, and the drug user may not be able to differentiate between the separate drugs, the likelihood to be non-adherent to all drugs prescribed is high. It is therefore crucial to explore not only which drugs can cause sADRs, but also which drugs are associated with sexual symptoms by the drug users themselves. Indeed, although there is no consensus about the effects of antihypertensives and contraceptives on sexual function, many users of these drugs regard the association as proven [58]. Concordantly, in a recent observational study, about 40% of patients who started an antihypertensive treatment reported that the treatment had a negative impact on their sexual life [59]. This highlights the importance of adequate information provision about sADRs, not only to warn patients about sADRs, but also to lower the number of inaccurate associations and consequently, to improve drug adherence.

Adjusting information for drug users at risk for sADRs

For adequate information provision, it is vital to question the information preferences of the drug users themselves. Previous research with the Information about Medication Scale (SIMS) has shown that most patients want to receive information about how medication can impact their sexual life [46, 47, 60-63]. In addition, the majority of patients would like to talk with their healthcare provider about the potential impact of their health condition on sexuality, and prefer their healthcare provider to start this topic [58-62]. Importantly, the most suitable moment to receive information about the impact on sexuality – before, during or after treatment – differs for patients and their partners [63]. Therefore, patients' wishes may be best met when healthcare providers give the opportunity to talk about sexual function at various moments of the treatment. Furthermore, the small sample of drug users with a high risk for sADRs in Chapter 4 were questioned about their preferences for sADR information. Folders and websites were evidently their most preferred sources for sADR information. Importantly, almost half of the respondents did not want to discuss sADRs with their pharmacist, either because they did not regard the pharmacist as the right person to discuss sexual problems or because sexuality was considered not important or a private matter. If a pharmacist or pharmacy technician would mention sADRs during a consultation, most men would consider that natural or logic whereas half of the women would consider it uncomfortable. Furthermore, if a consultation about sADR should take place, the pharmacist should focus on advice about changing a drug with high risk for a drug with less risk for sADRs.

From the perspective of the drug user, sADR information is thus preferable provided in written format (folders or websites), and solution for sADR information provision should be gender-orientated and take into account that, at this moment, about half of the public would not feel comfortable discussing sADRs with the pharmacist. Having adequate, gender-specific information about sADR available from different healthcare providers is imperative.

A new vision about the best practice regarding sADR care

Although patients may wish to more extensively discuss the drug treatment and associated problems with their healthcare provider, this time is often not available. Healthcare practice has to accommodate many needs, with little resources. As a consequence, one should also consider the feasibility of any adjustments to the information provision and discussion about sADRs. On the other hand, saving time by placing more responsibility in the shoes of the patient is also undesirable. This balance was a recurrent topic in Chapter 7. Although the patient was considered responsible for reading the information leaflet or for detecting sADRs and discussing them with their healthcare provider, it was also recognized that many patients did not or could not take this responsibility. Indeed, in an increasingly complex healthcare system, a part of the patient population simply does not understand where to find the information they seek or where to report any health issues they experience. For this reason, some criticized the common phrase 'placing the patient central'. In response to this, we suggest that not the patient itself should be centralized in healthcare practice, but the process around the patient. In other words, the patient's perception, wishes and needs can be centralized in that their care is organized from the patient's viewpoint. This potential solution has also been adopted for the rise of patient-centered care paths or patient journeys [64, 65]. The conditions to make the patient care path as fitting as possible for both the patient and the current healthcare practice can be deducted from both the patients' and the healthcare providers' perspectives on what constitutes 'adequate care' and what deters from receiving and providing this care.

With regards to 'adequate sADR care', one of the most important notions of Chapter 7 and 8 was that the primary healthcare providers considered themselves responsible for informing about sADRs, but considered a shared responsibility with the patient for the detection of sADR. Of course, both informing and detecting are part of sADR care. However, as the first solely depends on the healthcare provider, this is more easily adjusted in practice. To adjust to the patient preferences mentioned above, and at the same time burden healthcare practice as little as possible, this information could be provided in written or visual format. Examples are reliable online information from healthcare professionals (in

the Netherlands: thuisarts.nl and apotheek.nl), updated information in SmPCs and drug information leaflets, and automatic referrals to reliable visual drug information such as Kijksluiter. In concordance, healthcare providers in Chapter 7 suggested a new format for the drug information leaflet; It should be easy to understand for patients with language barriers (e.g. with plain language, pictograms and translations to patient's native language), have a standard section about drug's influences on sexual life, as well as a gender-specific ADR section.

Importantly, 'adequate sADR care' has not been defined and it may be difficult to reach consensus about this topic. Indeed, for one PTAM group in Chapter 9, the best practice regarding sADRs signified lowering the risk for nocebo effects by not informing about sADRs at the start of a drug treatment. This vision contradicted partly with our study endpoint that assumed a higher frequency of informing about sADRs as best practice. We thus learned the lesson that in future studies, participants should always be asked about their own vision on the best practice regarding sADRs. Effectivity of an implemented change can be evaluated in those studies as how close the healthcare practice is towards the state of self-chosen best practice before and after the change. Furthermore, we learned that discussing sexual side effects can still be regarded as a taboo, for both patients and healthcare providers. This is exemplified by the low response rates in Chapters 4, 8 and 9, and the broad range of barriers in Chapters 6 and 7. As a consequence, a culture shift is needed before major changes can be expected regarding the discussion about sADRs. This may explain why increased awareness about sADRs and not further steps such as a change in behavior or agreement with other healthcare providers was the most valued effect of the PTAM about sADRs.

sADR care: what is the role of the pharmacist?

We hypothesized before that the development of pharmaceutical care may also aid in the integration of sexuality in healthcare practice. Most pharmacists that participated in the studies described in this thesis showed positive attitudes towards sADR care in the community pharmacy. They considered themselves responsible for sADR information provision and drug treatment evaluation and were willing to change their practice. Some pharmacists also considered it an opportunity for their own work field, for example by utilizing OTC sildenafil supply to refer men to other pharmacy services (e.g. smoking cessation scheme) or to their GP, or to develop a professional relationship with them. On the other hand, most pharmacists acknowledged that they did not provide the care they considered themselves responsible for, because of barriers that could be ordered in following domains of the Theoretical Domains Framework (TDF): 'Knowledge', 'Skills', 'Memory,

attention and decision processes', 'Environmental context and resources' and 'Social influences'. The most noted barrier was a lack of privacy at the pharmacy counter, which could easily be solved by taking the patient to a more private area such as the consultation room. In addition, training to improve knowledge about sADRs and communication skills about sensitive topics could resolve the knowledge and skills barriers. The other barriers are more difficult to tackle, mainly because they depend on other actors. Indeed, pharmacists will need support from patients, other healthcare providers (e.g. GPs and GP nurses) and policy makers to change their practice. Chapter 4 and 7 showed that both patients and GP nurses are still hesitant about discussing sADRs at the pharmacy counter and are thus not likely to provide this support. For the support of policy makers, sADR care needs to align with their policies, such as historically was the case for policies about care access, drug adherence, medication-related hospital admissions, and decreasing GP workload [66-68]. Chapter 6 described one example of such alignment in the field of sexual function: OTC sildenafil was approved in the UK because pharmacists would educate patients seeking OTC sildenafil about causes of sexual dysfunction and refer men to GPs, because sexual dysfunction is frequently indicative of cardiovascular disease and depression [69, 70]. Lastly, pharmacy teams themselves have to prioritize sADRs over other information and other tasks that may also need their attention. It can be concluded that pharmacy teams indeed have a unique potential to discuss sADRs and sexual dysfunction with patients, which has barely been utilized because of barriers that have been identified in this thesis, and are possible to address.

It could also be argued that sADRs are like any other ADR and as such, should already be part of healthcare practice. From that perspective, not the implementation of a new intervention, but the normalization of informing and discussing sADR should be aspired [71]. In Chapter 9, the Normalization Process Theory (NPT) questionnaire indicated that the participants of the PTAM about sADRs indeed considered sADRs as a normal part of the job. We therefore argue that for the integration of sADRs in healthcare practice, increased awareness will naturally lead to the normalization of sADRs being part of the responsibilities of the healthcare providers. However, for healthcare providers to act upon their responsibilities, and inform or discuss about sADRs, the barriers in the TDF domains described above should be tackled. To prioritize sADRs and to receive support to integrate sADRs in pharmacy processes, pharmacists and their teams have to once again change the story about their tasks and role towards the patient, towards themselves and towards society. The development of pharmaceutical care will provide the leaders that take up this task a hopeful message, as pharmacists have already successfully embraced a range of new tasks as part of their identity, such as medication reviews and treatment of minor ailments [72].

Potential solutions for improving sADRs care

In Chapter 6 to 9, several potential solutions for improving care for sADRs are suggested. As mentioned before, the most feasible potential change is providing information about sADRs, for example through drug information leaflets. With this change, a great part of the drug users might be reached, since utility rates of the patient information leaflets have increased greatly since their mandatory provision in most parts of the world [73-76]. However, it should be noted that in all studies, a small group (~10–30%) did or could not read the leaflet, and would thus not receive the sADR information if this was part of the leaflet [73-76]. Interestingly, patients' preferred information format, folders or websites, were not chosen by the PTAM groups. Possibly, subscription costs for video platforms, and interior instructions for the chain pharmacies deterred from choosing these options.

Although information provision may be the most feasible option for improved sADR care, many healthcare providers were concerned about the consequences of providing sADR information. They worried that it would induce nocebo effects or decrease drug adherence. Nocebo effects are indeed a potential consequence of ADR information. Importantly, the nocebo effect is relevant for all ADRs and not sADRs specifically. Little is known about whether the size of nocebo effects differs for specific drugs and specific ADRs and if and how the risk for nocebo effects can be lowered in healthcare practice. The first studies about the topic provide some potential mechanisms to decrease the risk, such as working with the patient's belief about medication and providing a choice between equivalent drugs [77, 78]. In other words, to decrease the risk for nocebo effects, the prescriber and pharmacist have to question the patients about their perspective on medication and their preferences regarding drug information. This could also solve the other barriers related to information provision: information overload and information-induced anxiety about medication. Drug adherence has indeed been associated with the amount of drug information provided [79]. For this reason, personalized information has been suggested, based on patients' preferences. It should, however, be noted that patients may not understand or be satisfied with their initial information preferences. This is exemplified by the study of Kusch *et al*., in which drug users often preferred as much drug information as possible [80]. When this information was provided, this was so overwhelming that many changed their initial preference to less information. Healthcare providers that share the concerns about providing sADRs information are thus advised to not assume negative consequences of this information, but instead have an open conversation with their patients about the appropriateness of providing ADR information for the individual. For community pharmacies, this may require mayor changes to the current pharmacy processes (Chapter 6). The focus group participants for example suggested information need consults for the frequent visitors of the pharmacy and different content and timing for the treatment

evaluation. Lastly, it should be noted that the patient may already experience sexual problems due to the condition for which the drug treatment is prescribed, in which case information about sADRs could be an ideal starting point to talk about how health and sexual function are intertwined.

Methodological considerations

For the research question of the first part of this thesis (which drugs cause sADRs and how), a positivist research paradigm was adopted [81]. This paradigm assumes that the researcher can objectively observe and measure with reliable and valid tools, to create knowledge in the shape of facts [81]. With this paradigm in mind, several limitations of the research performed and described in PART 1 should be discussed. First of all, because both mental and physical factors are necessary for an adequate sexual response, changes in sexual function are generally self-reported and thus less objective and reliable. The self-reporting methods assume that patients understand and can identify changes to their own sexual response. However, as discussed above in 'Current issues in the reporting of sADRs', we identified different appraisals of medication-induced changes to sexual function. Secondly, registration trials and pharmacovigilance studies are limited by underreporting and a lack of causality data, which hampers the generalizability of the results in Chapter 2 and 5. Indeed, for reliable measurements, validated sexual function questionnaires should be utilized, instead of the direct inquiry measurements or observational data that were investigated in those chapters. In addition, underreporting limits stratification and more specific prediction of sADR incidences. Also Chapter 4 is mostly limited by the low response rate, which decreases the accuracy of the incidences reported.

Historically, the research paradigms of pragmatism and interpretivism have often been adopted for understanding sexual function and its place in society. These paradigms utilize observational and interpretational work to understand and create a concept [81]. In the field of sexual medicine, the most important observational and interpretational work has been done in the 1960s, by Masters and Johnson [82]. Questionnaires that were based on adaptations of their linear sexual response model (desire – arousal – orgasm – resolution) have led the way to quantitative research on greater scale and consensus on several sexual medicine topics [3, 83-85]. Also the questionnaires utilized in PART 1 are all based on this model [86, 87]. However, in the past decades, new questions have arisen that could not be answered with the sexual response model, for example that placebo account for two-thirds of the treatment effect in drug trials for female sexual dysfunction, and the absence of an effective female version of sildenafil [88-90]. Also divergent findings between the drug experiences on mijnmedicijn.nl and studies that utilized sexual function questionnaires

based on the linear model indicated that drug users may not experience their sADRs as was theorized.

For the second part of this thesis (how to integrate sADRs in healthcare practice), the research paradigm of pragmatism was adopted [81]. PART 2 can also be seen as the explorative phase or development phase of implementation research, as described by the Medical Research Council (MRC) Framework [91]. It should be noted that we assumed the integration of sADRs in healthcare practice to be a complex intervention, because of the contextual difficulties in discussing sexuality in healthcare practice, and because of the flexibility to adapt to the local setting. Because there was no coherent understanding about the best practice regarding sADR care, the theory-based research perspective of the MRC Framework was adopted for most of the research in PART 2, which questions what works in which circumstances and how. As a result, mostly qualitative studies were performed. Inherent to qualitative designs, the sample of participants of Chapter 6, 7 and 9 may not be representative for the national populations. The questionnaire in Chapter 8 faced the same limitation, because of the low response rate. Nevertheless, the studies were also not designed to be representative, but to create a pragmatic view about how to integrate sADRs in healthcare practice. As such, PART 2 has successfully provided information and tools for future research in this direction.

Future studies

The findings of PART 1 highlight a gap of knowledge regarding the incidence of sADRs, which calls for future research on this topic. These future studies should especially focus on improving the detection of sADRs in clinical trials, as these are the cornerstone for ADR information for both healthcare professionals and patients. The FDA has published possible approaches on how to improve the evaluation of sexual dysfunction in clinical trials for antidepressants [92]. In their opinion, an adequate claim for a lower risk for sADRs addresses separate domains of sexual dysfunction (e.g. desire, arousal, orgasm) and in case of a no effect claim (no sADRs in comparison to placebo) the assay sensitivity is established with a positive control. In addition, to untangle the potential interactions between drug and depression, they argue that the potential sADRs should also be studied in patients with a history of depression, that are not in a current depression episode. Furthermore, arguments are made for stratification by gender, a detailed sexual history at baseline and an adequate statistical analysis plan in which 'no effect' is specified and would take multiple doses into account in case of a dose-response design. Although focused on SSRIs and SNRIs, their advice is also applicable for other drugs. To our knowledge, no trials that followed their advice have been published yet.

Of course, improvements in future clinical trials will not change the insecurities about the sADR information of already registered drugs, for which no superiority claims about sADRs are aspired. Improving that information will require a study of great scale in which side effects of a high number of drug users are collected with validated questionnaires, over a long period of time. A study of such magnitude and time span could also overcome the limitations encountered in this thesis and in relevant literature. Indeed, a prospective trial in which all drug users that start a new drug treatment are regularly questioned before, during and after the treatment about their sexual function would not be limited by under-reporting and a lack of causality data. In addition, with a high number of participants, effects can be stratified and predict the likelihood of experiencing a lower score on each sexual domain for specific baseline conditions, i.e. real-world incidences. Lastly, the trial could focus on several potential ADRs, with each scaled how bothersome they are for the drug user, to compare and improve the accuracy of the incidences.

Another important suggestion for future research concerns not the method, but the methodology. After 50 years of research with the sexual response model, it is time to question our assumptions that resulted from adopting this model. Perhaps the other models that have been proposed in the past decades, such as the Basson model [93] and the dual control model [94], concord better with the sexual dysfunction experiences of drug users. To question our interpretations that have become the standard in medical research, a research paradigm such as interpretivism is necessary. Besides an exploration of the more recent models, we also need to explore the increased attention to sexual wellbeing, satisfaction and pleasure, include non-binary and non-heterosexual perspectives and include more recent developments in medicine, such as the potential relevance of (pharmaco)genetics and personalized medicine for sexual function and sADRs [95, 96]. Furthermore, attention should go towards the new model of health by Huber *et al*., as it may influence societal viewpoints on what constitutes a sexual problem and the responsibility of healthcare concerning sexual health [97]. Indeed, from their integral health perspective, one could question the lack of importance given to sexual health in healthcare guidelines, practice and reimbursement systems.

The last suggestion for future research concerns implementation research, for both sADRs and sensitive topics in general. In PART 2, we identified that 'adequate sADR care' has not been defined and argued that for this care, a balance should be aspired in the responsibilities of patients versus healthcare providers, by organizing it from the perspective of the patient. In addition, education materials are necessary to increase awareness about sADRs, which our findings suggest would naturally lead to the normalization of sADRs being part of the responsibilities of healthcare providers (Chapter 9). For healthcare providers to inform

about and discuss sADRs, the next step after awareness creation is the design of an intervention that tackles the many barriers experienced for sADR care (Chapter 6–8). Sadly, we were unable to identify an intervention that could take the next step to feasibility and pilot testing (Chapter 9). Future studies are thus necessary to continue the integration of sADRs in healthcare practice. Our first explorations did provide two important lessons for this potential intervention: 1) it preferably incorporates sADRs in already existing processes, e.g. first drug dispenses, and 2) the low response rates and high motivation among study participants in comparison to their colleagues suggest great problems for the implementation of a potential effective intervention. Because of this, the implementation should be studied as a separate cycle, in which implementation outcomes are embedded in the method [98].

Similarly, we also stress the need for implementation research in primary care with regards to sensitive topics in general. Several barriers that were noted for sADRs, such as little privacy at the pharmacy counter, nocebo effects and information overload during first consultations, may also be relevant for other sensitive topics in primary care. As such, the problems faced in our research about sADRs would probably also impact research about other sensitive ADRs and other sensitive topics in the community pharmacy. Indeed, pharmacists that provided OTC sildenafil (Chapter 6) reported similar difficulties as pharmacists providing pharmacy-based care for patients with mental illness and addictions [99] and homeless persons [100]. In all cases, pharmacists were concerned about how these sensitive topics influenced their relationship with the patient. These sensitive topics are characterized by unique challenges, that have been little researched. Therefore, the implementation of potential services has to provide lessons for other sensitive topics to come. As such, we hope that the lessons learned in PART 2 of this thesis may be util for future research about sensitive topics in the community pharmacy. Such research will be necessary if community pharmacies are to become the 'health and wellbeing hubs' as envisioned by UK National Institute for Health and Care Excellence [101]. Certainly, this thesis highlighted that the sensitive topic of sexuality is intertwined with our health experience and consequently, should be a pivotal part of healthcare and future 'health hubs'.

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