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

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Chapter 1

General introduction

'[Sexuality] is a central aspect of being human throughout life'

- World Health Organization, 2002

Sexuality is an integral part of a person's health, important from young to old, with or without medical conditions [1-4]. As a consequence, for many people, experiencing sexual problems can be very distressful and bothersome and has a negative impact on the quality of life. For instance, patients with mental health issues such as schizophrenia expressed that the subjective burden of sexual dysfunction can be as high as the burden of the disease itself [5]. Moreover, sexual problems can have a great impact on individuals' mental health and relationships, consequently being described as the most disturbing part of living with diabetes by women and heterosexual and gay men in different parts of the world [6-9]. Furthermore, relating sexual problems to a treatment is an important cause for treatment noncompliance [7, 10, 11] and drug-induced sexual problems that persisted after stopping the drug have been related to the breakup of relationships and with losing one's job [12]. However, contradictory to the importance of sexuality for health and wellbeing, the topic has been little investigated and most of us deter from talking about this part of our lives, also in healthcare [13-16].

Defining sexual health and sexuality

Our understanding of sexual health and sexuality are constructs that have been influenced by political, social and historical events, such as the struggle over reproductive rights and the impact of HIV and AIDS [17]. The current internationally recognized definition of sexual health is from the World Health Organization (WHO), who defined sexual health in 2002 as 'a state of physical, emotional, mental and social well-being in relation to sexuality' and 'not merely the absence of disease, dysfunction or infirmity' [18]. The definition also acknowledges the requirement of a positive and respectful approach to sexuality, the possibility of having pleasurable and safe sexual experiences, and the importance of respecting, protecting and fulfilling the sexual rights of all persons [18]. When the definition was drafted, the most debatable part of this understanding of sexual health was that it is a 'state' and not a dynamic process, which was eventually chosen to conform with the WHO definition of health [17]. According to the WHO definition, sexuality 'encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction' and 'is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships' [18].

Understanding sexual behaviour

In the last century, many different disciplines have contributed to our understanding of sexuality, of which the contribution of Masters and Johnson may be the most influential. Based on physiological observations, they proposed the sexual response model in 1966, which states that both men and women follow four stages in their sexual response: excitement/arousal, plateau, orgasm and resolution [19]. A decade later, Kaplan added sexual desire to their model and Robinson made the plateau phase part of the excitement phase [20, 21]. The revised model of sexual desire – arousal – orgasm (– resolution) became later known as a 'linear model', in which one stage precedes the next. In the 90s the validity of the linear model for women was questioned. Instead, a circular model was proposed, now known as the Basson model [22]. According to this model, motivation for sexual activities can occur for many reasons besides sexual desire (e.g. to feel closer to partner, to express love) and during sexual activity, arousal can lead to desire to continue. Moreover, positive feedback from the sexual activity (e.g. bonding) could also provide motivation for future sexual activities [22]. The circular model may be especially relatable for women with sexual dysfunction or sexual distress, since the majority of men and women with no dysfunction or distress considered the linear models to best describe their most experienced sexual response [23]. More recently, also the dual control model has been introduced, based on the interaction between sexual excitation and inhibition [24].

Defining sexual dysfunction

In contrast to sexual health and sexuality, no internationally agreed term nor definition for a problem regarding sexuality exist [25, 26]. One reason for this is that terms such as sexual function and dysfunction depend on social and medical attitudes about what is 'normal' and what is not [25]. In the medical field, a sexual dysfunction, such as orgasmic dysfunction or dyspareunia, refers to problems with the linear model for sexual response. Notably, not every sexual problem can be classified as sexual dysfunction. The international classification systems such as the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) state that the sexual problem should be associated with clinically significant distress for the individual, occur frequently and have been persistent or recurrent over a period of at least several months [18, 19]. Since the last editions of these classification systems (ICD-11 and DSM-V), it is acknowledged that sexual dysfunction often involves the interaction of physical and psychological factors. Additionally, both classification systems recognise other influences such as a partner, relationships, individual vulnerability, and cultural and religious factors

[27, 28]. Similar factors are also described in the WHO definition of sexuality [18] and in a conceptual framework by Verschuren et al. in relation to chronic disease [16]. In this framework, sexuality is divided into sexual functioning and sexual well-being. The first describes the physiological standards of the sexual response cycle, whereas sexual wellbeing concerns the person's subjective, individual experience of sexuality and its value in personal life. Importantly, sexual dysfunction and problems in sexual wellbeing can occur together, but both types could also be present independently [16].

Prevalence of sexual dysfunction

The reported prevalence of sexual dysfunction depends on the definition used, in addition to the different populations studied and different methods of data collection [29-31]. The International Consultation on Sexual Medicine Report of 2015 described the broad ranges of reported prevalence and concluded that at least one symptom of sexual dysfunction was present in 40–50% of women [29]. In men, sexual dysfunction usually occurred as one specific problem and was more age-dependent, with erectile dysfunction prevalence ranging between 50% and 100% (men aged 70–90 years), 20–24% (60–69 years), and 1–10% (younger than 40 years) [29].

The interrelatedness of health and sexual function

Prevalence studies have shown that a broad range of diseases (e.g. diabetes, depression) are associated to sexual dysfunction [16, 32, 33]. In addition, multimorbidity and poor health can also lower sexual satisfaction [1, 34]. These associations are bidirectional and are complexified by many influences on the physical and psychological component of both the disease and sexuality. For example, sexual dysfunction can be indicative of cardiovascular disease and depression [35]. A recent meta-analysis by Zhao et al. estimated that men with erectile dysfunction have a 43% increased risk of developing cardiovascular disease. For coronary heart disease, the risk increased to 59% [36]. Verschuren et al. showed the interrelatedness between disease and sexuality in their conceptual framework, displayed in Figure 1.1. As shown in the figure, the disease activity (the physical symptoms that characterize a disease, e.g. hyperglycaemia in diabetes), its complications and treatment may impact sexuality in direct, indirect or iatrogenic ways. Theoretically, a direct impact on sexual physiology can take place by any disease that affects vasocongestion or myotonia, thus diseases that affect arteries, central or peripheral nerves, musculoskeletal function and hormones [16]. Indirect effects are characterized by neurologic, vascular or hormonal

complications of the disease (e.g. diabetic neuropathy) or more general consequences of a chronic disease (e.g. pain, fatigue, changes to perception). The iatrogenic effects refer to surgical procedures (e.g. prostatectomy), side effects of medication and prescribed behaviours. These iatrogenic influences are also divided in either direct (e.g. inhibit or enhance sexual function) or indirect influences (e.g. change in body image because of weight gain) [16].

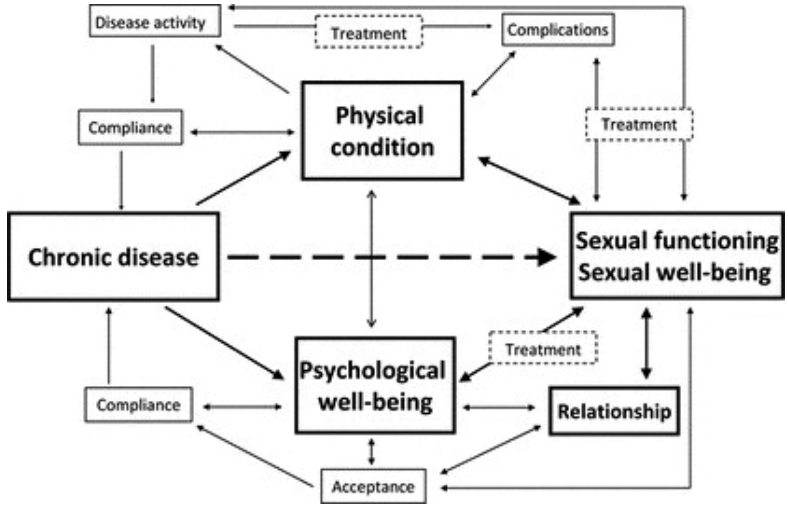

Figure 1.1: The generic conceptual framework about the impact of disease on sexual functioning and sexual well-being from Verschuren *et al*. [16].

Research about medication-induced sexual problems

Although the influence of some chronic diseases on sexual function have been well-documented, there is still a paucity of knowledge about other diseases and other relations within the framework of Verschuren et al. [16]. One of the little investigated topics is the influence of drug treatments on sexual function and well-being, especially in women. The few reviews that have summarized the literature on medication-induced sexual problems are outdated [37-40], published in national, not-English journals [41-44], lack a systemic design [45-49] or focused on specific drugs [50-54]. In addition, the research that has been done about medication-induced sexual problems was challenged by several complications. Firstly, a causality assessment is problematic because the potential sexual side effects are often also associated to the disease or symptoms to be treated, e.g. a decrease in desire can be caused by both the depression and the antidepressants [33]. The rise of polypharmacy further increases the complexity of a causality assessment to one specific

drug [34]. Secondly, associating a change in sexual function to a drug is more difficult when the baseline sexual function is unknown and when the research population has high rates of already existing sexual issues or high rates of sexual inactivity during the study period. In addition, it is probable that not all drug users related the drug to the potential sexual side effect or did not consider the change important, for example because in their culture the change was still within the boundaries of a 'normal sexual response'. Thirdly, the sensitivity of the topic deters many patients from spontaneously reporting potential sexual side effects. Indeed, direct questioning increased the reporting of sexual dysfunction from 14% to 58% among SSRI users and the reporting of orgasmic problems from 33% to 92% among clomipramine users [55, 56]. These challenges are acknowledged in the published reviews, which aim was generally to provide healthcare professionals with an overview of drugs for which they should be alert. Unfortunately, the lists covered only few drug groups, even though some estimated that more than 200 drugs may alter sexual function [47].

Differentiating between sexual adverse drug reactions and sexual adverse drug events

Research about medication-induced sexual problems has worked with vague and different definitions, which complicates the summarization of their results. However, unambiguous definitions can be deducted from the terminology utilized in the field of drug safety. They generally divide side effects from drugs in adverse drug reactions (ADRs) and adverse drug events (AEs). Both are abnormal symptoms, untoward or unplanned occurrences or unexpected deteriorations that occur during a drug treatment, at doses normally used in humans [57]. ADRs are evaluated by healthcare professionals to be probably attributed to the action of the drug treatment, whereas for AEs it is unknown whether there is a causal relationship. In a similar manner, sexual ADRs (sADRs) and sexual AEs (sAEs) would be defined as noxious and unintended changes in one or more phases of the sexual response and differentiated based on whether the change is probably related to the drug treatment. Notably, to comply with the terminology used within the field of drug safety, these definitions would focus solely on the sexual response cycle. Therefore, they include laboratory markers for a change in sexual response (e.g. hypo- or hypogonadism, changes in testosterone and prolactin) and exclude indirect effects (e.g. infection or irritation of the genitals) and fertility and menstruation changes.

Sexual adverse drug reactions in healthcare practice

Several actors influence how ADRs, including sADRs, are detected and informed about. For instance, researchers of clinical trials question the trial participants about ADRs, and assess and register the ADRs that occur during the drug treatment. Registration authorities such as the European Medicines Agency (EMA) regulate how these ADRs should be assessed and listed. If the drug is registered, the ADRs are listed in the Summary of Product Characteristics (SmPC). The SmPC is the official drug information on which the drug package leaflets are based, as well as the information provided by the prescriber and pharmacy team. Important information for patients, e.g. the very common or serious ADRs, is often also recorded in guidelines or standard operating procedures for the relevant healthcare professionals. Lastly, pharmacovigilance institutions assess AEs that may occur outside the controlled setting of the registration trials.

It is unknown in which manner effort was spent to collect sADRs by the above mentioned institutions and healthcare providers. Generally, the assessment of sADRs during registration trials has been based on 'unsolicited reporting'. Study participants proactively reported sADRs because researchers did not ask about them. As a result, the risk for sADRs may be underestimated in the drug information leaflets. For example, although 30–60% of users of selective serotonin reuptake inhibitors (SSRIs) reported sADRs in post-marketing studies, only 3–26% of users reported sADRs in registration studies (vs. 0–2% in placebo group) [58]. This general hesitation to report or discuss a sensitive topic such as sADRs probably also impacted healthcare providers. Physicians and nurses, for example, barely discuss sexuality with patients [59-65]. Reasons for this can be classified in three groups: healthcare providers' attitudes (e.g. cultural norms), patient factors (e.g. not finding a suitable moment to start the conversation) and organizational factors (e.g. lack of time, training or knowledge) [66, 67]. Patients, on the other hand, do wish to receive information about sADRs. For instance, Boons et al. showed that 44% of users of oral anticancer drugs wished to receive more information on the impact of these drugs on their sexual life [68]. Who should provide this information, has not been determined. For cardiac in-patients, most doctors, nurses and pharmacists believed that their own profession should counsel the patient about whether the medication will affect the patient's sex life [69]. Notably, the pharmacists' view in the latter study, that they are responsible for counselling patients, is part of a new development over the last decades: the transition of the pharmacy team from product-focused to patient-focused activities.

Sexual adverse drug reactions: A potential role for pharmacists

The new focus of pharmacy teams on patient care is known as pharmaceutical care, and is defined as '*the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes*' [70]. Information provision and advice about ADRs are important cornerstones of pharmaceutical care and thus part of pharmacist's daily practice and responsibilities [71, 72]. Under Dutch law, for example, pharmacists have a treatment agreement with patients (Dutch Medical Treatment Agreement Act, WGBO) and therefore the duty to inform the patient about their drug treatment for their informed consent. Other examples of new tasks of pharmacy teams are treatment optimization through medication reviews, advice and treatment for minor ailments, detecting and referring patients with undiagnosed health problems, educating patients about the importance of drug adherence and improving the quality of prescribing though local collaborations with prescribers.

The potential of pharmaceutical care could also be utilized in the emerging research field of integrating sexuality in healthcare practice. In fact, patients might discuss sexual health topics more readily with pharmacy teams than with other healthcare providers, as no appointment is needed in the community pharmacy. Because of the pharmacists' information duty, sADRs are the most relevant topic in the field of sexuality. In addition, sADRs could be integrated in any of the tasks mentioned above. It is therefore crucial that the potential role of the pharmacy team regarding sADRs is researched.

Aim and outline of this thesis

Research presented in this thesis will be undertaken with the general aim to improve the care and support for patients who may experience sADRs. This thesis can be divided in two parts.

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

Since the current available studies about sADRs are few and not complete, in **Chapter 2** we will first provide a systemic overview of the drugs at risk for sADRs according to their SmPC text. This overview will be utilised in **Chapter 3** to estimate with pharmacy dispensing data how many persons use drugs with a risk for sADRs. However, the risk for sADRs may be underestimated in drug information leaflets. Therefore, in **Chapter 4**, we will question the users of drugs with a high risk for sADRs according to the drug label

about their experience of drug-related sexual problems to roughly estimate the 'real-life' risk for sAE. In **Chapter 5**, we will take a step further by exploring whether patients may also experience sAE for other drugs than those presented in Chapter 2. Because of under-reporting issues in the field of pharmacovigilance, we will do this with a new trend in the field: the screening of online medical forums on which patients report their experiences with drugs. In addition, since females are often not adequately represented in clinical trials, we will also specifically look at gender-differences regarding online patient-reporting of sAE.

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

The only pharmacy-based service about sexual function is non-prescription sildenafil, available in only a few countries. In **Chapter 6** we will describe how pharmacists in Northern-Ireland experience this service, using a qualitative design. In primary care, both the general practitioner (GP) and the pharmacist provide drug information and thus information about sADRs. After recent role delegations to GP nurses and pharmacy technicians, these four types of healthcare professionals may have deviating views on the responsibilities of one another regarding sADRs. Therefore, in **Chapter 7**, we will present the results of online focus groups, one for each of these healthcare professionals, in which the current practice, their own role and the role of the others regarding sADRs are discussed. In addition, the participants will share their challenges to inform or discuss sADRs, as well as ideas for improvement. The findings from the qualitative studies presented in Chapter 5, 6 and 7 will be incorporated in a questionnaire previously used for different physicians and nurses, with the goal to describe pharmacists' current practice, knowledge and attitude towards sADRs. The results of this questionnaire will be summarized in **Chapter 8**. Finally, in **Chapter 9**, we will describe an explorative implementation study to improve the information provision and discussion of sADRs in primary care. For this study, education materials for already existing local collaborative groups of community pharmacists and GPs will be developed and tested.

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