Chapter 1

Introductory Chapter: Sexual Dysfunction - Introduction and Perspective

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The fifth *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) of the American Psychiatric Association [1] gives the following classifications of sexual dysfunctions: delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, substance-/medication-induced sexual dysfunction, other specified sexual dysfunction, and unspecified sexual dysfunction. It is evident that sexual dysfunctions constitute a heterogeneous group of disorders. They are characterized by clinically significant disturbances to respond sexually or experience sexual pleasure. Determining the character of the sexual dysfunction is a complex issue, which needs extensive clinical and psychological/psychiatric expertise in order to come to a correct clinical judgment and includes partner and relationship factors, individual vulnerability, psychiatric comorbidity, stressors, and cultural, religious, and medical factors.

Sexual functioning involves a complex interaction of biological, sociocultural, and psychological factors, which makes a clear diagnosis sometimes rather difficult. In any case, problems should be ruled out that are caused by interfering factors, like drugs, medicines, a medical condition (e.g., pelvic nerve damage) or external factors like partner violence, or other severe stressors.

In the present volume, four chapters are included that represent various aspects involved in sexual behavior and its dysfunctions in a very broad sense. These chapters also give a window on the complex issues involved in normal and dysfunctional sexual interactions.

In Chapter 2, the focus is on erectile disorder or erectile dysfunction. Erectile dysfunction (ED) is defined as a disorder that is characterized by the incapacity to sufficiently achieve and maintain an erection in order to enjoy a satisfactory sexual relationship. After premature ejaculation, it is the most frequent sexual dysfunction in men. Erectile disorder is frequently, but not always, associated with cardiovascular risk factors, and the authors describe and discuss an elegant

study in Spain, using a very extensive tool of methods and measures on a large cohort of males. The results indicate a high prevalence of erectile dysfunction in patients with high vascular risks. Improvement in erectile dysfunction was clearly associated with improved control of these cardiovascular risk factors. The study nicely illustrates the complexities involved in erectile problems and also in the difficulties in treating them properly. Moreover, the authors discuss the various factors that influence erectile functions like aging, lifestyle (smoking, diet), high blood pressure, atherosclerosis, and blood pressure medications. Although modifying lifestyle risk factors may help, in many cases patients also need medications to improve or correct erectile problems [2]. Phosphodiesterase type 5 inhibitors (PDE5i) have revolutionized ED treatment, although there are limitations in their use (e.g., diabetes and nerve injury patients often respond poorly to PDE5i). In the last decade, several new treatment strategies for the treatment of ED have been pursued, aiming at treating underlying microvascular abnormalities, restoring smooth muscle contractility, preventing cavernosal fibrosis, promoting endothelial revascularization, modulating neurohumoral pathways, and regenerating new penile tissue [3].

Hypogonadism is the decrease or absence of hormonal secretion from the gonads. In males, this condition is called androgen deficiency and is characterized by a decrease or absence of testosterone (T) secretion from the testes. T plays an essential role in normal male development starting from the very early stage in life (intrauterine) and is necessary for the emergence and maintenance of many male characteristics and functions, including body mass, bone density, libido, potency, and spermatogenesis. It is also indispensable for normal sexual functioning in adult life, and in puberty T is extremely important for a mature male phenotype at somatic and genital areas in the body. In Chapter 3, by Stolan and coworkers, an extensive overview is given on the role of T levels in normal sexual life and the dramatic effects of the consequences of hypogonadism, i.e., low T levels. Not only classical hypogonadic types, due to testicular disease or caused by central nervous system-, hypothalamic-, or hypophyseal-induced hypogonadism are described, but also the important partial T deficiency coinciding with aging is discussed. Apart from those, not only secondary T deficiency may occur due to problems associated with enhanced body weight (frequently seen in diabetes and metabolic syndrome) but also hypogonadism due to the chronic use of anabolic steroids or after long and intense stress exposure, even in young men. The authors describe therapeutic approaches to each kind of hypogonadism, based on individualized treatment including lifestyle changes, weight loss, exercising, and supplemental therapy. Because normal testosterone levels play a decisive role in various aspects of daily sex life, like daily sexual day dreaming or sexual fantasies, it is extremely evident how important normal T levels are for male sexual well-being. It can be easily seen that hypogonadism may lead to various complaints in daily life and in particular sexual complaints.

Mood disorders, and in particular major depression, are very often associated with sexual dysfunctions, both in male and in female patients. Such sexual dysfunctions cover the whole domain of sexual problems including libido, delayed ejaculations, erectile, and orgasmic disturbances. When major depression needs urgent treatment with an antidepressant, the latter often (and particularly with serotonergic antidepressants like selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs)) comes with additional sexual side effects. This makes the situation for the patient often unbearable

and frequently leads to ceasing the treatment. In Chapter 4 (Olivier and coworkers), the various factors that are involved in the complex interaction between the primary disorder (major depression) and the unwanted sexual dysfunctions (both caused by the disease itself and by the sexual side effects of the antidepressant) are described, primarily focused on men (mainly because the female domain is less well investigated). It appears extremely difficult to disentangle the intrinsic sexual problems associated with depression from those induced by the antidepressant. Sexual dysfunctions remain one of the important reasons to noncompliance to the drug treatment, even if the depressive mood is lifted and the patient feels better. One of the big challenges for research of new antidepressants is the design and development of such compounds without sexual side effects, although other side effects should also be avoided if possible. There is an ongoing heavy discussion on the therapeutic efficacy of antidepressants (and all other psychotropic agents) and their side effects [4]. This discussion and its implications make it very clear that we lack fundamental insight in the cause of psychiatric diseases (including depression) and that fundamental research into the mechanisms of action of "normal" functioning should lead to insight into pathological functioning. Only then, it might be possible to design and develop new psychotropic drugs, including antidepressants that are true "medicines" instead of drugs that merely treat "symptoms." Fundamental research of the brain is often difficult to perform directly in man, and animal research can be of utmost importance, although always caution should be used in the translation from animal to man because of sometimes large species differences. Chapter 4 also describes such an approach for sexual side effects of (novel) antidepressants. Because sexual side effects of antidepressants, at least in men, are relatively well described in the literature [5], those antidepressants can be used in a translational animal model that is sensitive to sexual side effects. The rat model reflects several aspects of the sexual side effects of classical antidepressants (tricyclics, SSRIs, SNRIs, NRIs), including delayed onset of action and disappearing of the sexual side effects after stopping treatment. Two recently introduced antidepressants vilazodone and vortioxetine, according to clinical studies [6, 7], exert no or less sexual side effects in depressed patients compared to classic antidepressants, especially the SSRIs. These two compounds had no sexual side effects in the rat model of sexual behavior used in Chapter 4. The model has considerable translational validity and can and will be used for future studies into sexual side effects of new antidepressants. Moreover, the model can also be used for fundamental research into the brain mechanisms and circuitry underlying sexual behavior. Understanding the normal functioning and inducing perturbations in this circuitry might help in finding new ways to treat side effects of novel and "real" psychotropic medicines.

A topic not dealt with in the present contributions but related to the use of antidepressants and the sexual inhibitory effects of the latter (notably the SSRIs) is premature ejaculation, one of the sexual dysfunctions mentioned in DSM-5. Premature ejaculation (PE) has been defined as persistent or recurrent ejaculation occurring during partnered sexual activity within approx. 1 minute following vaginal penetration and before the person wishes it. PE must be present for at least 6 months and must be present on practically all occasions of sexual activity and causes clinically significant distress in the individual. PE cannot be better explained by a nonsexual mental disorder or as a consequence of a severe relationship distress or other major stressors and is not caused by the effects of a substance/medication or another medical condition. PE can be lifelong or acquired, generalized, or situational and may have mild (intravaginal

ejaculation latency time (IELT) of 30–60 seconds), moderate (IELT of 15–30 seconds), or severe (IELT<15 seconds) effects. Treatment by selective serotonin reuptake inhibitors (SSRIs) has really led to a paradigm shift in the understanding and treatment of PE as all SSRIs exert ejaculation delaying effects in men with PE [8, 9]. Although the treatment of PE by SSRIs is "off-label," it is the present therapy used for PE, notwithstanding the nonsexual side effects and the need to take the medication daily and permanently [10]. An ideal anti-PE medication would be "on demand," that can be taken shortly (hours) before sexual activity. Although it still would come with side effects, it is assumed that many men may prefer the convenience of "on demand" dosing compared to daily and long-term dosing [11]. The search for an "on demand" treatment for PE has led to the development of dapoxetine, which has received approval for treatment of PE in many countries, although it has not been approved by the US Food and Drug Administration (FDA). Dapoxetine is a potent SSRI, and it is postulated that its rapid absorption and rapid appearance of peak plasma concentration combined with a relatively short half-life lead to an ideal pharmacokinetic profile for such an "on demand" profile. Dapoxetine has some minor "on demand" efficacy but clearly is not a breakthrough medicine in the treatment of PE [11]. Another SSRI, with a comparable profile as dapoxetine, DA-8031 is in development for PE, but efficacy data have not yet been elucidated [12, 13]. Several other approaches for treatment of PE are used or are in development, including local anesthetics (e.g., lidocaine) used as cream, gel, or spray, and are moderately effective in delaying ejaculation [10]. Several other compounds with various mechanisms of action (tramadol, α_1-adrenoceptor antagonists, oxytocin antagonists, modafinil, and botulin-A toxin) have been proposed in the treatment of PE but need extensive testing and will not reach the market soon.

Treatment of female sexual dysfunction lags behind the available male treatments (ED, PE, hypogonadism). Low sexual desire is the most common sexual complaint in women, and many females suffer from sexual dissatisfaction that often negatively interferes with quality of life. Initially, these sexual complaints were classified as hypoactive sexual desire disorder (HSDD) but have merged in DSM-5 with female sexual arousal disorder (FSAD) into the diagnosis of female sexual interest/arousal disorder (FSIAD). Most research up to now has been using HSDD as the most common sexual dysfunction disorder that affects many women all over the world. A recent study in the USA found that more than 7% of US women suffer from HSDD [14]. In 2012, the FDA approved flibanserin (Addyi™) for the treatment of premenstrual women with HSDD. Flibanserin is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist and has moderate pro-sexual activities [15]. Several other hormonal (testosterone) and pharmacological (buspirone, bupropion) drugs have been tested but have not led yet to approved pharmacotherapy for FSIAD. Currently, two drugs are under investigation for the treatment of FSIAD that combine a low dose of sublingual testosterone with either a PDE5i (sildenafil) or a partial 5-HT_{1A} receptor agonist (buspirone) [16]. Sublingual T is rapidly absorbed, induces a rapid peak in T, and is eliminated within 2–3 h [16]. However, T induces an increase in sexual motivation 3–6 h after administration (therapeutic window). Administration of either sildenafil or buspirone in such a way that their therapeutic window coincides with that induced by T leads to rather strong pro-sexual effects [16]. The (T + PDE5i) treatment (Lybrido) appears particularly active in women with HSDD/FSIAD due to a relatively insensitive system for sexual cues and the (T + buspirone) treatment (Lybridos) for

HSDD/FSIAD women due to dysfunctional activation of sexual inhibitory mechanisms [16]. In a small study in women with SSRI-induced sexual dysfunction, both drug combinations also showed promising results [17]. Further development of these promising drugs will take time, but at least it indicates the possibility to develop efficient and innovative pharmacotherapy for for FSIAD. Another potential medicine for FSIAD might come from influencing a completely different mechanism of action by bremelanotide, an agonist of melanocortin 3 (MC_3) and MC_4 receptors. Preliminary data are promising, but again further development need to show clear pro-sexual activity [15]. The positive message from all these developments is that the lack of effective medications to treat female sexual dysfunctions seems to come to an end.

Finally, in the last chapter by Egloff, various aspects of circumcision are described and discussed in a broad context. Biomedical, psychosomatic, psychotherapeutic, cultural, religious, clinical, and pharmacological aspects of circumcision are portrayed. The function of the foreskin, e.g., hygiene or protection of the glans penis, in normal (sexual) life is discussed, as well as in a clinical setting. Whether circumcision influences sexual behavior or may lead to sexual dysfunction, or, in contrast, improves sexual dysfunctions, is a matter of debate but certainly needs more research. The beauty of this chapter is that it adds a lot of additional facts and thoughts about the complexity of human sexuality.

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