Antipsychotic treatment and sexual functioning

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From mechanisms to clinical practice

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Table of contents

Chapter 1

Introduction

Introduction

As a clinician, I have seen a number of patients who reported sexual dysfunction during the use of antipsychotic medication, for example a decreased sexual desire, arousal problems (i.e. erectile dysfunction in men and lubrication problems in women), the inability to reach orgasm, or a decreased ejaculatory volume. I wondered how often such problems would arise, whether they would be the result of psychotropic medication, the psychiatric disorder or other factors, and if these problems could be alleviated.

The official pharmaceutical information on the different antipsychotics reports a low prevalence of sexual side effects (for most antipsychotics 0.1%-1% or sometimes 1%-10%) (Farmacotherapeutisch Kompas) suggesting a relatively modest scale of this problem. Still, antipsychotic-induced sexual dysfunction is clinically relevant and may be less infrequent than the pharmaceutical information suggests. Patients with sexual side effects see this as a serious problem that negatively influences their quality of life and treatment adherence (Finn, et al. 1990, Haddad & Sharma. 2007, Olfson, et al. 2005). And apart from the possible effects of psychotropic medication, social factors, psychological factors, somatic health and the degree of psychotic symptoms may also be related to sexual functioning in patients with severe mental illnesses (Marques, et al. 2012, Aizenberg, et al. 1995).

The literature suggests that both clinicians and patients may be reluctant to adequately discuss sexual functioning (Strauss & Gross. 1984), possibly also leading to an underestimation of this problem. Studies using spontaneous accounts of patients report a low prevalence (less than 10%) of sexual dysfunction related to treatment with antipsychotics. On the other hand, studies using structured interviews or self report questionnaires tend to report a much higher prevalence of sexual side effects related to treatment with antipsychotics (Knegtering, et al. 2003, Knegtering, et al. 2008, Lingjaerde, et al. 1987, Sullivan & Lukoff. 1990, Dossenbach, et al. 2005).

These experiences and the related clinical issues lead to the research questions described in this thesis. The aim is to shed more light on the prevalence of (antipsychotic-induced) sexual dysfunction, the factors and pharmacological mechanisms involved, the appropriate way to assess sexual dysfunction and discuss it with the patient, and the treatment strategies if available.

Outline of this thesis

This thesis will first explore which factors are involved in sexual dysfunction in patients with schizophrenia and related disorders, how patients and doctors weigh the burden of sexual side effects, the prevalence and different types of antipsychotic-induced sexual side effects, which mechanisms may be involved, and which treatment strategies for sexual side effects of antipsychotics are available (Chapter 2). It will then zoom in on the biological aspects of sexual functioning, especially regarding the biology that is influenced by psychotropic drugs. Based on preclinical and clinical studies in the literature, it will be discussed how insight in pharmacological mechanisms influencing sexual performance may lead to a better understanding and the generation of new hypotheses on biological mechanisms involved in sexuality (Chapter 3).

As talking about problems with sexual functioning and the systematic assessment of its presence in patients using psychotropic medication may not be optimal in daily clinical care (Strauss & Gross. 1984), we then explore the literature on the benefits and limitations of currently existing instruments in a systematic review (Chapter 4). Chapter 5 then describes the validation of an instrument for the assessment of sexual functioning in patients using antipsychotics that has been developed in the Department of Psychiatry of the University Medical Center Groningen.
To determine whether sexual functioning in patients can be influenced, three clinical trials are reported. The first is a randomized trial in which risperidone and aripiprazole are compared in their effect on sexual functioning (Chapter 6). The second study looks at the sexual side effects in patients using long-acting depot antipsychotics (Chapter 7). The third is a double-blind placebo-controlled crossover pilot study, which investigates the effect of tadalafil on erectile dysfunction in male patients using antipsychotics (Chapter 8). Also, a case report is presented, illustrating how insight in pharmacological mechanisms causing sexual dysfunction may guide treatment strategies (Chapter 9). Finally, we will elaborate on unanswered questions and challenges for future research (Chapter 10).

This thesis thus seeks to answer the following specified research questions:

- Which factors influence sexual functioning in patients with schizophrenia?
- How often do antipsychotics cause sexual side effects?
- Which sexual side effects of antipsychotics are reported by patients?
- Why is it important for clinicians to explicitly ask for sexual side effects?
- Which instruments are available to evaluate antipsychotic-induced sexual dysfunction?
- What are the differences between antipsychotics in their influence on sexual functioning?
- Can differences in antipsychotic-induced effects on sexual performance be understood from their pharmacological profile?
- What is the effect of the phosphodiesterase-5-inhibitor tadalafil on antipsychotic-induced erectile dysfunction?
- Which treatment strategies are available for antipsychotic-induced sexual dysfunction?
- What are challenges for future research?

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Chapter 2

The facts about sexual (dys)function in schizophrenia: an overview of clinically relevant findings

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Submitted

Abstract

A limited number of studies have evaluated sexual functioning in patients with schizophrenia. Most patients show an interest in sex that differs little from the general population. By contrast, psychiatric symptoms, institutionalization and psychotropic medication contribute to frequently occurring impairments in sexual functioning. Women with schizophrenia have a better social outcome, longer lasting (sexual) relationships and more offspring than men with schizophrenia. Still, in both sexes social and interpersonal impairments limit the development of stable sexual relationships.

Although patients consider sexual problems to be highly relevant, patients and clinicians are reluctant to discuss these spontaneously, leading to an underestimation of their prevalence and contributing to decreased adherence to treatment. Studies using structured interviews or questionnaires result in many more patients reporting sexual dysfunctions. A comparison of different antipsychotics showed high frequencies of sexual dysfunction for risperidone and classical antipsychotics, and lower frequencies for clozapine, olanzapine, quetiapine and aripiprazole.

It is suggested that decreased sexual desire in patients with schizophrenia may also be linked to the general reduction of initiative they experience, often referred to as negative symptoms. Still, antipsychotic medication may be the most prominent cause of sexual problems including reduced sexual desire. Postsynaptic dopamine antagonism, prolactin elevation and α_1-receptor blockade may be factors in the pathogenesis of antipsychotic-induced sexual dysfunction.

Strategies to treat antipsychotic-induced sexual dysfunction include lowering the dose or switching to a prolactin sparing antipsychotic. Also, the addition of a dopamine agonist or a phosphodiesterase-5 (PDE-5) inhibitor has shown some promising results, but evidence is currently scarce.

Introduction

Sexual dysfunction in patients with schizophrenia may be related to the disease itself (e.g. negative symptoms, decreased initiative and motivation), psychosocial factors, somatic health and the use of psychotropic medications (Aizenberg, et al. 1995, Marques, et al. 2012, Fujii, et al. 2010, Malik, et al. 2011). In particular, antipsychotic drugs have been associated with sexual dysfunction, such as decreased sexual desire, erectile dysfunction, anorgasmia, and decreased ejaculatory volume (Knegtering, et al. 2008, Baggaley. 2008). Studies using structured interviews or self report questionnaires have shown that 16% to 60% of the patients using antipsychotics experience sexual dysfunctions (Serretti & Chiesa. 2011). Sexual side effects have a considerable impact on quality of life and are probably a major factor in non-adherence to prescribed antipsychotic drugs (Baggaley. 2008, Olfson, et al. 2005, Haddad & Sharma. 2007, Finn, et al. 1990).

The aim of this article is to provide an overview of the literature on all aspects of sexual functioning that are relevant for clinicians who treat patients with psychotic disorders, including both the theoretical background and the practical implications. We will subsequently describe the relationship between schizophrenia and sexual dysfunction, the burden of sexual side effects as weighed by patients and doctors, the prevalence and different types of antipsychotic-induced sexual side effects, which mechanisms may be involved, and which treatment strategies for the sexual side of antipsychotics effects are available. No recent reviews have been published which cover these aspects from a clinical perspective.

Schizophrenia and sexual functioning

In the early 20th century it was believed that schizophrenia was caused by deficiencies in sex hormones (Jacobs & Bobek. 1991). Early psychoanalytic theories suggested that psychosis might derive from unconscious homosexual tendencies (Norman. 1948). Erotic sexual behaviors were also seen as possible causal factors for schizophrenia in pre-schizophrenic patients (Arieti. 1967). As these ideas were not based on any empirical research, they have gradually been abandoned.

According to case reports, some patients suffering from psychotic symptoms experience coenesthetic hallucinations (i.e. the sensation of bodily functions that are usually undetectable) of a sexual nature, erotomanic delusions, delusions related to sexual identity, the sexual act or pregnancy. Also, hypersexuality can occur during an acute psychotic episode. Such psychotic manifestations related to sexuality are uncommon and usually disappear after starting antipsychotic medication (Jacobs & Bobek. 1991, Akhtar & Thomson. 1980, Connolly & Gittleson. 1971).

According to Skopec et al. most patients with schizophrenia do not differ from controls in terms of actual sexual behavior (Skopec, et al. 1976). On the other hand, relationships of people with serious mental illness are characterized by less intimacy and commitment than in the general population (Perry & Wright. 2006).

Schizophrenia may influence sexual behavior in men and women in different ways (Verhulst & Schneidman. 1981). For example, women with schizophrenia have better social outcomes, as they date,

have sex, marry and raise children more often than men (McGlashan & Bardenstein. 1990). McEvoy et al. studied sexual activity and attitudes in chronic inpatients with schizophrenia (McEvoy, et al. 1983). A majority of female patients with chronic schizophrenia continued to be interested in sex. About one half of them wanted to become pregnant, but at the same time many of them were unaware of the limitations to their parenting abilities (McEvoy, et al. 1983).

Viewed from a social perspective, the sexual behavior of patients with schizophrenia was restricted in many ways before the 1950's. Extramarital sexual intercourse was socially frowned upon (Hilger, et al. 1983), and institutionalization in the Western world reinforced sexual inactivity by discouraging or even prohibiting sexual relationships. In the United States, for example, illegitimate pregnancies did occur among patients in psychiatric facilities, but only at one-fifth of the rate found among the general population (Wignall & Meredith. 1968).

Around the time that oral contraceptive medication became available, psychiatric institutions started to change their regulations, allowing more sexually mixed social activities and home passes (Wignall & Meredith. 1968). Particularly in the United States, the United Kingdom and Italy, de-institutionalization accelerated after the 1960's. In North America, beds in public psychiatric hospitals had decreased by 80 percent within ten years (Appleby, et al. 1993). Parallel to de-institutionalization, the relative fertility of women with a major mental illness increased (Odegard. 1980), as living in the community yielded more opportunities for sexual encounters (Nicholson, et al. 1996).

According to studies from the 1980's, patients with schizophrenia viewed institutionalization as an obstacle to sexuality; it took them longer to have a first date, first kiss, first coitus and first marriage (Raboch. 1984). In a population with institutionalized patients, both males and females with chronic schizophrenia showed diminished interest in sexual activity, decreased frequency of intercourse, and loss of satisfaction from sexual interactions, compared with controls (Lyketsos, et al. 1983). The lower frequency and lesser degree of satisfaction with sexual intercourse were related to the severity of psychopathology and the length of institutionalization. Interestingly, sexual dreams and fantasies among these patients did not differ significantly from dreams and fantasies in the control group (Lyketsos, et al. 1983).

In summary, only a limited number of studies have evaluated sexual functioning in patients with schizophrenia. To which degree schizophrenia is linked to problematic sexual behavior has yet to be established. It is clear that institutionalization and psychotropic medication often impair sexual functioning. Still, most patients with schizophrenia show an interest in sex that differs little from the general population. In comparison to men, women with schizophrenia tend to have a better social outcome, as reflected not only in longer lasting (sexual) relationships but also in more often having offspring. On the whole, however, due to social and interpersonal impairments, patients with schizophrenia are not frequently involved in long and stable sexual relationships.

The burden of sexual complaints from the patient's and doctor's perspective

Sexual side effects are of major importance to patients and lead to decreased adherence to therapy and reduced quality of life (Baggaley. 2008, Haddad & Sharma. 2007, Finn, et al. 1990). Nonetheless, patients and clinicians are equally reluctant to discuss these matters (Strauss & Gross. 1984).

In a study by Finn et al., 41 patients with schizophrenia were asked to compare the subjective burden caused by their psychotic symptoms with that caused by other symptoms or side effects (Finn, et al. 1990). The burden of symptoms could be rated from 1 (mild) to 5 (most serious). Patients rated prosecutory hallucinations as a heavy burden (frequency in patients reporting the symptom 66%, and the corresponding burden 4.3). Significantly, the burden of erectile dysfunction (frequency 34%, burden 4.5) and absence of ejaculation or painful ejaculation (frequency 12%, burden 4.0) was rated in the same range.

Strauss and Gross interviewed 86 psychiatrists on the importance of sexual side effects of psychopharmacological treatment (Strauss & Gross. 1984). Most psychiatrists considered sexual side effects to be clinically relevant in two out of three patients, and felt that these side effects were likely to influence treatment adherence in a negative way. Although the psychiatrists were convinced that most patients would not discuss sexual side effects spontaneously, only 10% had actually asked their patients about this.

Studies using spontaneous accounts of patients report low incidences of sexual dysfunction related to treatment with antipsychotics; actually less than 10% of the patients report sexual dysfunction spontaneously when asked about side effects. On the other hand, studies using structured interviews or self report questionnaires tend to report a prevalence of 30-60% for sexual side effects related to treatment with antipsychotics (Knegtering, et al. 2008, Knegtering, et al. 2003, Lingjaerde, et al. 1987, Sullivan & Lukoff. 1990, Dossenbach, et al. 2005). This emphasizes that direct questioning about sexual functioning including sexual side effects is necessary to avoid underestimating their frequency among patients with schizophrenia and related psychotic disorders.

In summary, patients with schizophrenia consider sexual problems to be highly relevant. It affects their quality of life and treatment adherence negatively. Still, both clinicians and patients seem to be reluctant to discuss these issues. Therefore, in clinical practice, the frequency and impact of sexual problems is probably underestimated.

Prevalence of sexual dysfunction in patients with schizophrenia

In patients with schizophrenia, changes in sexual performance may result either from the primary illness, from antipsychotic treatment or from the social consequences such as stigmatization and discrimination (Nestoros, et al. 1981).

A review comparing different antipsychotics with regard to sexual dysfunction concluded that risperidone induces sexual dysfunction most frequently, followed by typical antipsychotics (haloperidol), olanzapine, quetiapine; the lowest frequency is found for aripiprazole (Baggaley. 2008). Knegtering et

al. found a comparable order (risperidone, typical antipsychotics, clozapine, olanzapine, quetiapine, aripiprazole), based on previous studies by this research group, all of which used the same design and questionnaire (Knegtering, et al. 2008, Knegtering, et al. 2003, Knegtering, et al. 2004, Knegtering, et al. 2006, de Boer, et al. 2011).

In 2011, a meta-analysis was published about sexual dysfunction in psychiatric populations of patients taking antipsychotics. In contrast to other findings, it was found that quetiapine, ziprasidone, perphenazine, aripiprazole, olanzapine, risperidone, haloperidol, clozapine and thioridazine had an incrementally increasing impact on sexual function ranging from 16% (quetiapine) to 60% (thioridazine). It was noted that the quality of the included studies showed large variation, and the findings related to aripiprazole, clozapine, perphenazine and thioridazine should be considered with caution as replication was very limited (Serretti & Chiesa. 2011).

Also in 2011, a large multicenter randomized trial was published by Malik et al. (Malik, et al. 2011), the EUFEST study (European First Episode Schizophrenia Trial). Rates of sexual dysfunction at baseline were comparable with rates after 12 months. In contrast to other studies, there were no significant differences in rates of sexual dysfunction between the different medications. A higher score of negative symptoms as measured with the Positive and Negative Syndrome Scale (PANSS), was associated with libido reduction, although some other studies did not find this association (Malik, et al. 2011). In a Japanese study (352 outpatients with schizophrenia) no differences in rates of sexual dysfunction were found between medication groups (risperidone, olanzapine, aripiprazole, haloperidol) (Fujii, et al. 2010).

Although not all studies agree, sexual side effects may not subside over time (Malik, et al. 2011). This emphasizes the importance of treatment strategies for sexual side effects.

In summary, studies using questionnaires suggest that 16% to 60% of the patients report sexual dysfunction, possibly related to the use of antipsychotics. In most studies, frequencies of sexual dysfunction differ between different types of medication. Conflicting results between studies may result from differences in the study design and questionnaires used.

Types of sexual dysfunction in patients with schizophrenia

A commonly used classification of stages in sexual response is: sexual desire (thoughts, interest), sexual arousal/plateau (feeling sexually excited as well as physiological effects, e.g. erection or lubrication), orgasm (peak in pleasure; mentally as well as physiologically) and resolution/refraction (Meston & Frohlich. 2000). In the following section, an overview will be given of clinical studies on different types of sexual dysfunction reported during use of antipsychotics.

Sexual desire

Sexual desire is a term commonly defined as interest in sexual objects or sexual experiences. There is no objective physiological criterion for desire. It is generally inferred from the self-reported frequency of sexual thoughts, fantasies, dreams, wishes and interest in initiating and/or engaging in sexual experiences (Meston & Frohlich. 2000).

A meta-analysis shows that 12-38% of patients using antipsychotics experience a reduction of sexual desire (ranging from 12% for aripiprazole to 38% for clozapine) (Serretti & Chiesa. 2011). Knegtering et al. report 6-50% (ranging from 6% for aripiprazole to 50% for risperidone) (Knegtering, et al. 2008, de Boer, et al. 2011).

Medicated as well as unmedicated patients with schizophrenia often report a decrease in sexual desire. In a study by Aizenberg (1995), patients with schizophrenia reported significantly more frequent sexual desire reduction versus unaffected controls, while sexual desire was reduced in patients using antipsychotics as well as in those not using antipsychotics (Aizenberg, et al. 1995). The 'disease-related' sexual desire reduction might be induced by an unknown underlying process, the patients' psychotic symptoms or as part of the general loss of initiative and activity level (i.e. negative symptoms).

Sexual arousal

Sexual arousal is closely connected to sexual desire. It is defined both in subjective terms, like feeling sexually excited, and objective physiological terms like erection and lubrication. Patients being treated with antipsychotics often report being less easily sexually aroused (Aizenberg, et al. 1995).

Sexual arousal: erectile dysfunction

Erection describes the non-flaccid state of the penis and is in most cases the physiological expression of sexual arousal. Erectile dysfunction refers to the inability of men to achieve and/or maintain erection. In clinical practice patients often report problems related to a delayed, shortened or diminished ability to reach full erection. Although erections often co-occur with the subjective feelings of sexual excitement, they can also occur without arousal, for instance during Rapid Eye Movement (REM) sleep.

In many studies assessing arousal, questionnaires are used to evaluate quantitative (duration, frequency) and qualitative (rigidity) aspects of erection. More objective ways to study erection include for instance a mechanical strain gauge that measures the penile circumference. Such objective evaluations are complex, and given the taboos surrounding sexuality, not readily accepted in routine clinical practice or clinical trials evaluating side effects. This explains why studies evaluating sexual side effects in patients using antipsychotics on the whole relied on questionnaires.

The meta-analysis of Serretti and Chiesa (2011) shows that 7-46% of patients using antipsychotics experience dysfunction of arousal, like erection and lubrication (ranging from 7% for aripiprazole to 46% for thioridazine) (Serretti & Chiesa. 2011). Knegtering et al. report 0-39% (ranging from 0% for aripiprazole to 39% for risperidone) (Knegtering, et al. 2008, de Boer, et al. 2011).

Aizenberg et al. found that in patients with schizophrenia who had a sexual partner, erection was reduced in quality or time during coitus. Patients using antipsychotics experienced significantly more erection disturbance compared to patients without antipsychotics, both during sexual intercourse and during masturbation. At the same time, no change occurred in waking erections (an expression of REM sleep correlated erections) in these patients (Aizenberg, et al. 1995).

Sexual arousal: priapism

Priapism is a painful, prolonged and sustained erection of the penis and is a urologic emergency. How priapism exactly results from treatment with antipsychotics remains unclear, but α-adrenergic receptors seem to be involved (Compton & Miller. 2001, Sood, et al. 2008). The onset can be sexual stimulation, but the condition itself persists long after sexual excitement has subsided. Priapism is an emergency that needs immediate attention as it can lead to long-term devastating consequences such as erectile dysfunction, urinary retention and gangrene. Even with treatment, 40-50% of patients can become impotent owing to ischemia and fibrosis of the corpora cavernosa (Compton & Miller. 2001, Sood, et al. 2008, Patel, et al. 1996).

Priapism related to treatment with antipsychotics is a rarely occurring effect and has shown up only in case reports, which relate priapism to many different antipsychotics, such as haloperidol, clozapine, risperidone, olanzapine, aripirazole and quetiapine. Antipsychotics with strong α_1- and α_2-antagonistic properties seem to induce priapism most frequently (Compton & Miller. 2001, Sood, et al. 2008). Risperidone has a high affinity, followed by clozapine and quetiapine. Olanzapine has the lowest affinity for the adrenergic receptors. The only exception is ziprasidone with a high affinity, but there are just a few case reports in the literature. A possible explanation may be that this drug has not been available as long as other atypical antipsychotics (Sood, et al. 2008). Most sexual side effects of medications are reversible. In contrast, although priapism is rare, it should be treated immediately as it may result in irreversible sexual dysfunctions.

Clitoral priapism is an even less frequently reported side effect. In antipsychotics, it has only been reported with olanzapine (Bucur & Mahmood. 2004).

Sexual arousal: vaginal lubrication

Vaginal lubrication is the excretion of a lubricating fluid by the vaginal wall that facilitates sexual intercourse. It is associated with increased vaginal blood flow and sexual arousal. Although vaginal lubrication in women may be viewed as the physiological equivalent of erection, it has hardly been studied in relation to schizophrenia or antipsychotic medication. Lubrication can be evaluated indirectly by measuring vaginal blood flow using for instance photopletysmography, or by indirect measures of heat dissipation and Doppler techniques (Munarriz, et al. 2003). Measuring vaginal blood flow requires the insertion of a tampon shaped device into the vagina. These instruments are too intrusive to be used in routine clinical practice or clinical research.

Studies suggest that women report diminished lubrication in frequencies that are comparable to the frequency of erectile dysfunction reported by men treated with the same antipsychotics (Knegtering, et al. 2008, Serretti & Chiesa. 2011).

Orgasm

Orgasm is characterized by a peak in sexual pleasure accompanied by rhythmic contractions of the genital and reproductive organs, cardiovascular and respiratory changes and a release of sexual tension

(Meston & Frohlich. 2000). Physiological measurements of orgasm, like fluctuations in rectal pressure, are infrequently described (Meston & Frohlich. 2000, van Netten, et al. 2008). Also, this method is too invasive for use in clinical trials on patients using antipsychotics.

The meta-analysis of Serretti and Chiesa shows that 4-49% of patients using antipsychotics experience orgasm dysfunction (ranging from 4% for aripiprazole to 49% for thioridazine) (Serretti & Chiesa. 2011). Knegtering et al. report 3-46% (ranging from 3% for olanzapine to 46% for risperidone) (Knegtering, et al. 2008, de Boer, et al. 2011).

In studies evaluating sexual dysfunctions, orgasm is evaluated as an individual item in questionnaires. Most studies assess the degree to which the patient indicates he or she is capable of experiencing an orgasm, but some studies also noted a disturbance in the quality of the orgasm (Ghadirian, et al. 1982). In the study of Aizenberg, patients using clozapine reported the quality of their orgasm had improved, unlike patients using classical antipsychotics (Aizenberg, et al. 1995).

Ejaculation

Ejaculation is the emission of semen during orgasm in men. Ejaculation disturbances consist of a change in consistence or volume of the ejaculate. Most commonly reported in patients treated with antipsychotics is a decreased ejaculatory volume (DEV). Terms in the literature related to DEV are aspermia, anejaculation, dry ejaculation or retrograde ejaculation. It has been stated that retrograde ejaculation and aspermia are often used wrongly as synonyms (Shader & Elkins. 1980). Aspermia can be defined as the absence of ejaculate in the presence of erection, muscular ejaculation and orgasm (Girgis, et al. 1968). Retrograde ejaculation refers to the ejaculate being released into the bladder during orgasm as can be shown by analyzing the urine for the presence of semen after orgasm.

Decreased ejaculatory volume (DEV) is frequently (8-58%) reported in patients treated with antipsychotics (Serretti & Chiesa. 2011). Knegtering et al. report 7-40% (ranging from 0% for aripiprazole to 40% for risperidone) (Knegtering, et al. 2008, de Boer, et al. 2011).

DEV and dry ejaculation are reportedly related to the use of several antipsychotics like thioridazine, chlorpromazine, sertindole, risperidone and olanzapine (Knegtering, et al. 2008, Patel, et al. 1996, Shader & Elkins. 1980, Girgis, et al. 1968, Kotin, et al. 1976, van Bruggen, et al. 2009, van Kammen, et al. 1996). Although the mechanisms are not fully known, antipsychotics with α-blocking properties and possibly also calcium channel blockers are thought to be most likely to induce DEV.

Spontaneous ejaculation is a rare condition that has been described with zuclopentixol, trifluoperazine, thiothixene and risperidone (Gitlin. 1994, Ichikawa, et al. 2001, Keitner & Selub. 1983).

Menstrual disturbance, galactorrhea and gynecomastia

Although menstrual disturbance, gynecomastia and galactorrhea are not in themselves sexual dysfunctions, they do tend to coincide with some of the sexual dysfunctions since they may originate at least partly from the same source: high serum prolactin levels (Ouwehand, et al. 2012). The literature suggests that lowering prolactin levels with a dopamine agonist or switching to a prolactin sparing

antipsychotic will often be successful in treating antipsychotic-induced menstrual disturbance and galactorrhea.

Other aspects of sexual functioning

Besides the aspects of sexual functioning discussed above, some studies have tried to evaluate the subjective judgment of patients about the overall quality of their sexual experience. Aizenberg included items in his questionnaire such as 'enjoyment of sex' and 'sexual satisfaction' (Aizenberg, et al. 1995) and found that these were significantly higher in patients treated with clozapine than in those treated with classical antipsychotics (Aizenberg, et al. 2001). As mentioned in the section on orgasm, the study of Ghadirian et al. included one item about change in the quality of orgasm (Ghadirian, et al. 1982).
Some studies mention pain during orgasm (Ghadirian, et al. 1982) or painful ejaculation (odynorgasmia) (Berger. 1979, Donnellan, et al. 2001). On the whole, pain during orgasm seems to be extremely rare and is absent as item in most studies, while the patho-physiological mechanisms in relation to treatment with antipsychotics remain unclear.

Pharmacological mechanisms in antipsychotic-induced sexual dysfunction

The pathogenetic mechanisms of antipsychotic-associated sexual dysfunction are not fully understood. Postsynaptic dopamine antagonism, α_1-antagonism and prolactin elevation are likely to be involved (Knegtering, et al. 2008, Meston & Frohlich. 2000). Most antipsychotics are potent postsynaptic dopamine antagonists and can cause sustained elevation of the anterior pituitary hormone, prolactin (Knegtering, et al. 2008, Ghadirian, et al. 1982). Dopamine is an important neurotransmitter in brain areas and circuits involved in attention and salience of stimuli, and in experiencing motivation and rewards, including sexual motivation (desire) and probably also sexual reward. Sexual reward is experienced primarily during orgasm, but other stages of sexual functioning also seem to be involved in reward-related learning (Meston & Frohlich. 2000, Giuliano & Allard. 2001). However, it has to be noted that perspectives on the role of dopamine have changed in recent years: dopamine is now suggested to be more important in the anticipation of reward than reward itself (Bressan & Crippa. 2005).
Dopamine blockade is probably a major factor in antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008). A second factor possibly involved in the inhibition of sexual behavior by dopamine antagonists may be the associated hyperprolactinemia (Knegtering, et al. 2008, Meston & Frohlich. 2000). Dopaminergic activity controls the production of prolactin in the pituitary gland. While dopamine antagonists decrease levels of dopaminergic output, prolactin levels are increased. Prolactin in turn has an inhibiting effect on the tuberoinfundibular dopaminergic neurons, thereby completing the feedback mechanism between dopamine and prolactin (Fitzgerald & Dinan. 2008).
Antipsychotic-induced hyperprolactinemia has been associated with a number of side effects including galactorrhea, menstrual disturbances, amenorrhea, and sexual dysfunction (Knegtering, et al. 2008, Dickson & Glazer. 1999, Hummer & Huber. 2004, Shim, et al. 2007, Rettenbacher, et al. 2010), although

some studies only confirm this for subgroups of patients (Westheide, et al. 2007, Nakonezny, et al. 2007), or do not find an association between prolactin levels and sexual dysfunction (Howes, et al. 2007). In contrast to risperidone and classical antipsychotics, clozapine, quetiapine and olanzapine do not appear to cause sustained elevated levels of prolactin. The reports available suggest that patients using these antipsychotics may have comparatively lower rates of sexual dysfunction (Aizenberg, et al. 1995, Knegtering, et al. 2008, Baggaley. 2008, Serretti & Chiesa. 2011, Knegtering, et al. 2004, Knegtering, et al. 2006, de Boer, et al. 2011, Knegtering, et al. 2007).

Besides having affinity for the dopamine receptor, antipsychotics interact with many neurotransmitter systems in the brain and other parts of the body. Affinity for the serotonergic, noradrenergic, histaminic and cholinergic/muscarinic neurotransmitter systems differs among the various groups of antipsychotics (Leysen & Gommeren. 1984, Richtand, et al. 2008, Correll. 2010). Agonistic serotonergic effects, for instance on 5-HT_2 receptors, are associated with a decreased ability to achieve orgasm. By contrast, agonism of the 5-HT_{1a} receptors, and possibly also antagonism of the 5-HT_{2a} and 5-HT_{2c} receptors appear to have a stimulating effect on sexual performance (Kennedy & Rizvi. 2009, Gelenberg, et al. 2000). The α_1 receptors are thought to be involved in erection, lubrication and ejaculation (Sood, et al. 2008, Thompson, et al. 1990, Sanbe, et al. 2007). Some antipsychotics also have α_2-blocking properties. In treatment with antipsychotics a clear relationship between these properties and sexual performance has not been described. In theory, as in the α_2-blocking yohimbine, they may stimulate erection (Smith, et al. 1987, Tallentire, et al. 1996). Antihistaminic effects like sedation may have indirect effects on sexual function.

Table 1 shows the effects of neurotransmitters on sexual functioning. Table 2 shows the affinity of several antipsychotics for the neurotransmitters and represents global receptor affinity based on different studies, showing the large variation in pharmacological properties of frequently used antipsychotics which partly explain differential effects on sexual functioning (Leysen & Gommeren. 1984, Richtand, et al. 2008, Correll. 2010, Schotte, et al. 1996, Richelson & Souder. 2000).

Table 1. Main effects of antipsychotics on sexual functioning

	Effects on sexual response
D_2 agonism	Increased sexual desire (anticipation of reward)
D_2 antagonism	Decreased sexual desire, sexual activity, erection and ejaculation
5-HT_2 agonism	Delay of orgasm
5-HT_{1a} agonism	Activation of sexual behavior, facilitation of orgasm
5-HT_{2a} and 5-HT_{2c} antagonism	Probable stimulation of sexual behavior
α_1 antagonism	Central effect: decrease of erection, lubrication and ejaculation Peripheral effect: may have a stimulating effect on e.g. erection
α_2 antagonism	Stimulation of erection
H_1 antagonism	Indirect effect on sexual performance through sedation
M_1 antagonism	Decreased erection and lubrication

D = dopamine receptor; 5-HT = serotonin receptor; α = alpha-adrenergic receptor (or alpha-adrenoceptor); H = histamine receptor; M = muscarinic receptor (a subtype of acetylcholine receptor).

Table 2. Receptor-binding affinity profiles of most antipsychotics discussed in this article

	D_1	D_2	$5HT_{1a}$	$5HT_{2a}$	$5HT_{2c}$	α_1	α_2	H_1	M_1
Amisulpride	?	+++	0	0	0	0	0	0	?
Aripiprazole*	+	++++	+++	++	++	++	++	++	0
Chlorpromazine	+	+++	0	+++	++	+++	?	+++	+
Clozapine	+	+	+	+++	++	+++	+	+++	+++
Haloperidol	++	+++	0	+	0	++	++	+	0
Olanzapine	++	++	0	+++	++	++	+	++++	+++
Paliperidone	+	+++	+	+++	++	+++	++	+++	+
Perphenazine	?	++++	+	+++	+	++	+	+++	0
Pimozide	0	+++	+	++	0	+	?	0	0
Quetiapine	+	+	+	+	0	++	+	++	+
Risperidone	++	+++	+	++++	++	+++	+++	+++	0
Sertindole	?	+++	++	++++	++++	+++	+	+	0
Thioridazine	++	++	+	++	++	+++	?	++	+
Ziprasidone	++	+++	++	++++	++	+++	+	+++	+

* = Partial dopamine agonist; D = dopamine receptor; 5HT = serotonin receptor; α = alpha-adrenergic receptor (or alpha-adrenoceptor); H = histamine receptor; M = muscarinic receptor (a subtype of acetylcholine receptor). Affinity for receptors: 0 = absent or very low (Ki value >1000); + = low (Ki value 100-1000); ++ = moderate (Ki value 10-100); +++ = high (Ki value 1-10); ++++ = very high (Ki value <1); ? = unknown.

Other pharmacological mechanisms

Besides the affinity for the D_2 receptor and other receptors, other pharmacological mechanisms may also influence treatment effects and side effects of antipsychotics, e.g. passage of the blood brain barrier, metabolization in the liver and presence of an active metabolite.

Passage of the blood brain barrier influences the ratio between the amount of the antipsychotic in the brain and peripheral blood. This may be influenced by the lipophility of a drug and the extent to which an antipsychotic may be actively moved through transporting systems in the blood brain barrier (Kapur, et al. 2002). In general, high lipophility of medication predicts good penetration in the brain. Antipsychotics with a poor passage of the blood brain barrier (e.g. risperidone, paliperidone and amisulpride), have to be dosed relatively highly to accomplish a central effect, leading to a high peripheral level. The pituitary gland produces prolactin that is regulated by dopamine. The location of the pituitary gland outside the blood brain barrier leads to a considerable rise in prolactin blood levels for hydrophilic antipsychotics due to a higher peripheral-to-central D_2 receptor occupancy. If an antipsychotic has active metabolites with an affinity to D_2 receptors, it is important that they have a central-to-peripheral ratio as good as that of the parent drug, if not better (Kapur, et al. 2002). This is not the case for the metabolite of risperidone, 9-hydroxyrisperidone. This may explain why risperidone, through its hydrophilic metabolite, 9-OH-risperidone, elevates prolactin more than would be expected based on the affinity of the parent compound risperidone for the D_2 receptor (Knegtering, et al. 2008, Knegtering, et al. 2005, Melkersson. 2005). Meanwhile, 9-OH-hydroxyrisperidone has been registered as

a separate antipsychotic, namely paliperidone. Evidence about paliperidone and sexual dysfunction is still very scarce. It may be hypothesized that detrimental effects on sexual functioning and the increase of prolactin levels will be comparable to or exceed those of risperidone, but to date (2013), there are no studies to support this.

It seems that the central-to-peripheral ratio of D_2 occupancy outweighs the impact of other pharmacodynamic considerations such as the modulation of prolactin levels by the serotonin-dopamine interactions in ensuring prolactin-sparing effects (Kapur, et al. 2002). This leads to the conclusion that dopamine antagonism and prolactin levels are the most important factors in antipsychotic-induced sexual dysfunction.

Treatment strategies for antipsychotic-induced sexual dysfunction

Knowing the underlying mechanisms of sexual (dys)function in patients with a severe mental illness being treated with antipsychotics may help to give well informed clinical guidance.

Clinicians should actively and routinely ask about undesired treatment effects of antipsychotics, including effects on sexual performance. In clinical consultation, psychological, social, symptom and medication related aspects of sexual performance should be disentangled. Also, it is important to try to understand the influence of sexuality on the individual's overall quality of life, in order to assess the need for adjusting treatment. Explaining to the patient which factors may be involved and outlining the possible treatment alternatives may lead to a shared decision whether to accept a diminished sexual performance or to try to find a solution. Possible treatment alternatives should be discussed.

Knowledge about the different pharmacological properties of antipsychotics related to sexual performance may be helpful in choosing an antipsychotic with a low risk of inducing sexual side effects. A limited number of studies have focused on treatment strategies to reduce sexual dysfunction in patients treated with antipsychotics. Lowering the dose, switching to an antipsychotic with less detrimental effects on sexual functioning, or using adjunctive therapy with, for example, a dopamine agonist or phosphodiesterase-5-inhibitor are the main treatment options. The risk that psychiatric symptoms might increase during one of these treatment options should be evaluated in each individual patient. In most studies on switching strategies of antipsychotics or adding a dopamine agonist, an increase in psychotic symptoms is not frequently reported (Haddad & Wieck. 2004, Nunes, et al. 2012). In our clinical experience, switching medication in collaboration with the patient, with the explicit aim of finding the best tolerated antipsychotic that is still effective, nearly always leads to a better outcome, although sometimes a return to the original antipsychotic may be necessary.

The review of Nunes (Nunes, et al. 2012) describes randomized, double-blind controlled studies of treatment aimed to improve sexual dysfunction and/or decrease prolactin levels. Improvement of erectile functioning is described for adjunctive treatment with sildenafil (Gopalakrishnan, et al. 2006) and lodenafil (Nunes, et al. 2013). Lowering of elevated prolactin levels and reinstatement of menstruation are reported for adjunctive therapy with aripiprazole (Shim, et al. 2007). Adding selegiline (Kodesh, et al. 2003) or cyproheptadine (Lee, et al. 1995) did not seem to improve sexual function. The switch from

risperidone to quetiapine was demonstrated in two randomized controlled studies, with one showing improvement in sexual functioning and lowering of prolactin levels (Nakonezny, et al. 2007, Byerly, et al. 2008).

Open label studies reported improved sexual functioning for adjunctive therapy with aripiprazole, vardenafil, peony-glycyrrhiza-decoction, carbegoline, amantadine, shakuyaku-kanzo-to and imipramine. Open label studies described improvement in sexual performance when switching from antipsychotics that are strong dopamine antagonists (which often lead to elevated prolactin levels) to aripiprazole, ziprasidone, olanzapine and quetiapine (prolactin sparing antipsychotics); the switch to aripiprazole was the most studied strategy (Nunes, et al. 2012).

In summary, strategies to treat antipsychotic-induced sexual dysfunction include lowering the dose, switching to a prolactin sparing antipsychotic, adding a dopamine agonist or a phosphodiesterase-5 (PDE-5) inhibitor (Nunes, et al. 2012). These options are shown in Figure 1.

Conclusion

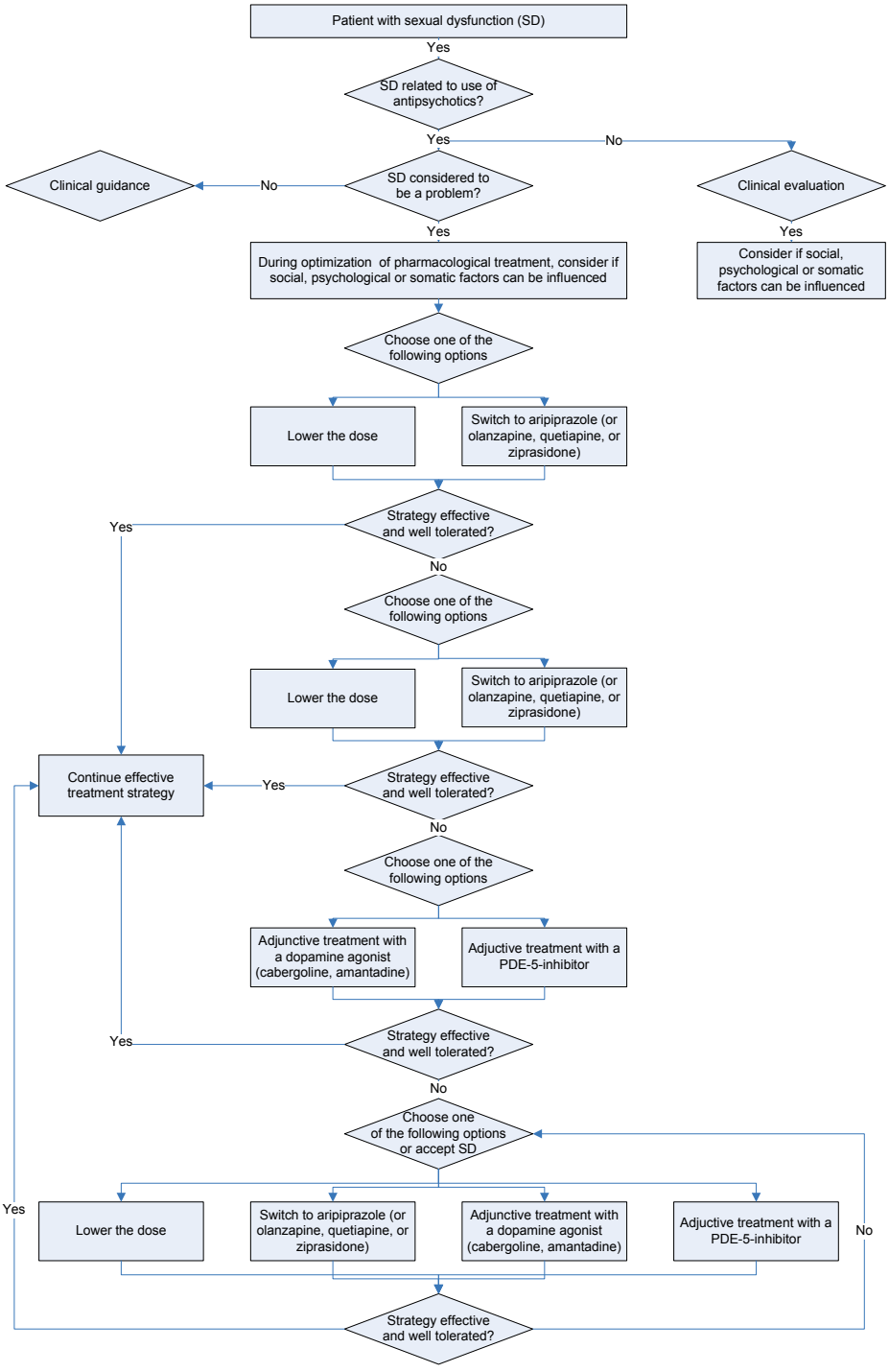
A limited number of studies have evaluated sexual functioning in patients with schizophrenia. Most patients with schizophrenia show an interest in sex that differs little from the general population. In contrast, psychiatric symptoms, institutionalization and psychotropic medication contribute to frequently occurring impairments in sexual functioning. Women with schizophrenia have a better social outcome, longer lasting (sexual) relationships and more offspring than men. Still, in both sexes social and interpersonal impairments limit the development of stable sexual relationships.

Although patients consider sexual problems to be highly relevant, patients and clinicians are reluctant to discuss these spontaneously, leading to underestimation of their prevalence and contributing to decreased adherence to treatment. Studies using structured interviews or questionnaires result in many more patients reporting sexual dysfunctions. A comparison of different antipsychotics showed that high frequencies of sexual dysfunction were found for risperidone and classical antipsychotics, and lower frequencies for clozapine, olanzapine, quetiapine and aripiprazole.

It is suggested that reduced sexual desire in patients with schizophrenia may also be linked to the general reduction of initiative they experience, often referred to as negative symptoms. Still, antipsychotic medication may be the most prominent cause of sexual problems including reduced sexual desire. Postsynaptic dopamine antagonism, prolactin elevation and α_1-receptor blockade may be factors in the pathogenesis of antipsychotic-induced sexual dysfunction.

Strategies to treat antipsychotic-induced sexual dysfunction include lowering the dose or switching to a prolactin sparing antipsychotic. Also, the addition of a dopamine agonist or a phosphodiesterase-5 (PDE-5) inhibitor has shown some promising results, but evidence is currently scarce.

Figure 1. Treatment strategies in antipsychotic-induced sexual dysfunction



Future research

The fact that sexual side effects may not subside over time emphasizes the importance of effective treatment strategies for these side effects. As research on this topic is limited, this should be a focus of future research.

Second, more research is needed on the possible interaction between sexual side effects and the symptoms of schizophrenia, e.g. negative symptoms, lack of motivation and initiative. There may be an overlap in underlying neurobiological mechanisms.

Third, the variation in outcome between different studies could be the result of the study design and the instruments used. Future studies should use instruments that are validated for patients using antipsychotics. These questionnaires are relatively short and are simply formulated, thereby taking into account the cognitive symptoms that many patients with a psychotic disorder experience.

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Chapter 3

From effects of psychotropic medication to mechanisms of sexual functioning: a clinically oriented review

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Submitted

Abstract

This review of the mechanisms involved in sexual functioning describes clinical and preclinical research on the effects of psychotropic medication with the aim of providing a clinically useful and comprehensive but also concise overview of findings.

We show that dopamine has a central role in neuronal networks involved in the anticipation of reward and motivation for sexual activity. Dopaminergic networks interact with many other neuronal networks involving miscellaneous neurotransmitters.

Noradrenalin primarily has a stimulating effect on sexual functioning in the central nervous system, but too high levels of noradrenergic transmission lead to a general fear response, thereby inhibiting sexual functioning. Contrarily, in the peripheral nervous system lowering of noradrenalin levels (e.g. by alpha-1 antagonism) stimulates erection, vaginal lubrication and ejaculation, probably by decreasing the smooth muscle tone and increased vasodilatation.

Serotonergic activity is involved especially in sexual satiety and often results in a decreased ability to achieve orgasm/ejaculation, partly through inhibition of dopamine release in the mesolimbic tract. Postsynaptic antagonism of 5-HT_2 receptors has stimulating effects on sexual behavior, especially for the 5-HT_{2C} receptor. In line with this, agonistic effects on the presynaptic 5-HT_{1A} receptor result in a decreased serotonergic transmission also leading to stimulation of sexual behavior.

Opioids are associated with the experience of sexual reward and sexual satiety after orgasm. Low amounts of opioids increase dopaminergic neurotransmission in the mesolimbic system, increasing the 'wanting' of the sexual response cycle.

Neurogenic nitric oxide (NO) is considered to be the most important factor for relaxation of penile vessels and corpora cavernosa, which induces erection. NO is probably also an important factor in clitoral vasocongestion. In the central nervous system, via increased production of NO, glutamate increases dopamine release in the medial preoptic area (mPOA).

GABA, (endo)cannabinoids, acetylcholine and histamine have been suggested to influence sexual performance but evidence is limited.

In conclusion, this review described what psychotropic medication learns us about sexual functioning. Using the wanting-liking-inhibition model in animal as well as human research will improve the translation of results between both fields, increasing our understanding of different aspects of behavior, including sexual behavior.

Introduction

Sexual functioning is a complex process, involving biological, psychological and social determinants. Biological aspects include (age-related) endocrine function and neuronal functioning expressed in neurotransmission in specific brain areas and brain-circuits (Meston & Frohlich. 2000). In order to study sexual functioning and its (patho)physiology, different research methods exist. First, information is available from animal research, in which sexual behavior of animals can be studied while influencing the social situation, endocrine functioning or neurotransmitter functioning by pharmacological challenges. These animal studies increase the insight in the possible influences of social interaction, hormones, gender, aging, neuronal systems and medications on animal sexual behavior. Second, psychological, physiological and neuroimaging studies in humans have also yielded important information, including studies that investigated the functioning of brain areas and circuits related to different stages of sexual performance. Third, studying sexual performance in patients using psychotropic agents prescribed in psychiatry or neurology, may also increase our understanding of human sexual physiology and pathophysiology. These medications often target the dopaminergic and serotonergic system, undoubtedly involved in sexual physiology (Pfaus. 2009).

This review will focus on biological aspects of sexual functioning, especially regarding the biology that is influenced by psychotropic drugs. As a framework, we will first describe different phases of sexual behaviour, followed by a description of the role of neurotransmitters and neuropeptides in sexual functioning underscored by the effects of psychopharmacological drugs. We will finish with discussing how insight in pharmacological mechanisms influencing sexual performance may lead to new hypotheses on biological mechanisms involved in human sexuality. In addition, a better understanding of the mechanisms involved will also enable us to develop treatment strategies to improve sexual functioning, or to diminish the undesired effects of medications on sexual performance in clinical practice.

Literature searches

We searched PubMed using different combinations of the following search terms: "animal", "human", "clinical", "preclinical", "sexual", "sexual function", "sexual dysfunction", "appetitive", "consummatory", "wanting", "liking", "inhibition", "pleasure cycle", "reward", "incentive salience", "neurotransmitter", "receptor", "dopamine", "noradrenalin", "norepinephrine", "serotonin", "opioid", "(endo)cannabinoid", "nitric oxide", "glutamate", "GABA", "acetylcholine", "histamine", "prolactin", "testosterone", "oxytocin", "antidepressant", "antipsychotic", "acute", "chronic", "central", "peripheral", "medial preoptic area", "hypothalamus", "nucleus accumbens", "ventral tegmental area", "medial prefrontal cortex", "striatum".

First, to obtain a global overview of the field, we selected reviews about sexual functioning in humans and sexual functioning in animals. This provided an overview of the main neurotransmitters and other factors that are involved in normal sexual functioning, as well as information about the different stages of sexual functioning. Second, we selected reviews about the influence of psychotropic medication (e.g. antidepressants, antipsychotics) on sexual functioning in humans and animals. Third, for each

neurotransmitter we searched for more specific articles not included in the review papers and fourth, we specifically searched for literature describing the interactions between the different neurotransmitters and other factors (like hormones or duration of treatment with psychotropic medication).
Articles were selected by the first author (MB). In case of uncertainty inclusion was discussed with the last author (HK). All retrieved studies were checked for cross-references that were retreived when they fulfilled the search criteria. Finally, we structured, summarized and integrated this abundance of knowledge and descibed this according to neutransmitter-systems in the present report.

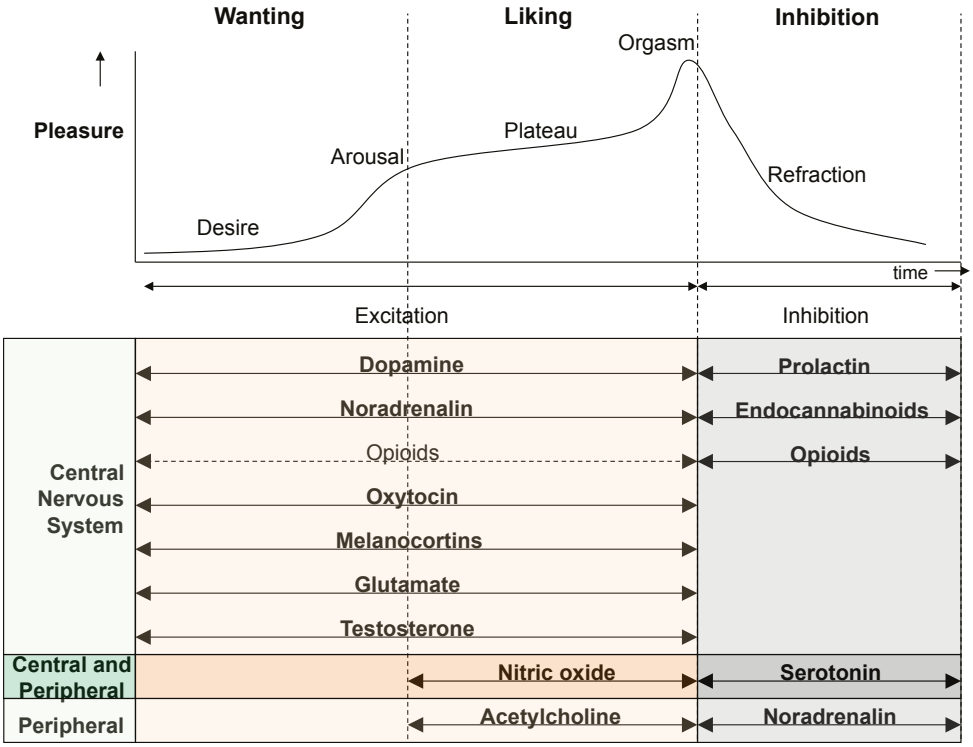
Distinguishing phases of sexual behaviour: the sexual pleasure cycle

As a framework, the most relevant models for sexual response are described. In general, models describe dichotomies, for instance processes of excitation and inhibition, and the result of the balance between these factors on sexual functioning. Alternatively, a cycle that moves through sequences of sexual behavior from initiation to termination is also found in the literature.
An important dichotomous model describes the sexual response along an "appetitive" vs. "consummatory" continuum. The terms "appetitive" and "consummatory" distinguish measures of sexual desire or arousal (appetitive) from "performance" measures of masturbation or copulation (consummatory) (Pfaus. 1996). Although this dichotomy has been helpful, it is rather artificial as there seems to be a more continuous stream of behaviors focusing on a particular incentive or goal. In most cases it is impossible to draw an exact line between where the appetitive phase of sexual behavior ends and the consummatory phase begins (Ball & Balthazart. 2008). In studies on sexual behavior this overlap in appetitive and consummative behavior should be recognized when analyzing sexual behavior (Pfaus. 1996).
The response cycle concept was a model introduced by Masters and Johnson in their Excitation, Plateau, Orgasm, Resolution (EPOR)-model, in which individuals move from excitement (a mix of genital responses and emotional desire for sex), through a plateau of arousal as sexual activity ensues, to an apex of excitement (called orgasm), and then to a resolution or refractory phase, in which sexual behavior is temporary inhibited (Masters & Johnson. 1966, Meston & Frohlich. 2000). Kaplan (1977) and Lief (1977) proposed a variation on this model in their work on inhibited sexual desire: sexual desire, arousal, orgasm and refraction (Kaplan. 1977, Lief. 1977). This model has been used since 1980 in the classification of mental disorders DSM-III, DSM-IV and DSM-IV-TR and in many clinical studies as well. Still, more recent findings suggest that these stages cannot be distinguished strictly either. This is the reason why Levin adjusted the sexual response cycle in terms of the following four major phases: sexual desire, arousal and desire (a 'combination' phase), orgasm and refraction (Levin, 2001). The recently published DSM-5 (American Psychiatric Association, 2013) also combines different stages, e.g. in "sexual interest/arousal disorder".
A recent reconceptualization has been to relate the sexual response cycle to other "pleasure cycles" that have elements of "wanting", "liking", and "inhibition" (Georgiadis & Kringelbach. 2012, Georgiadis, et al. 2012, Kringelbach & Berridge. 2009, Berridge, et al. 2009). This conceptualization essentially distinguishes the appetitive behaviors as a part of the more general "wanting" system, the consummatory behavior as a part of the "liking" system, and the "inhibition" after sex as a feedback system that blunts wanting and

liking. In the pleasure cycle of "wanting", "liking", and "inhibition", sexual responses follow a pattern similar to other motivations like thirst, feeding, and drug use or addiction, in which an individual wants or craves, likes (or dislikes), and experiences feedback in satiety or satisfaction of the need state (Georgiadis & Kringelbach. 2012). A synonym of "wanting" is "incentive salience", which means that a reward-predicting incentive causes motivation that promotes approach toward and consumption of rewards.

When the model of "sexual desire", "arousal", "orgasm" and "refraction" is compared to "wanting", "liking" and "inhibition", wanting corresponds with sexual desire and partly with arousal, liking corresponds partly with arousal and with orgasm, while refraction corresponds with inhibition. We therefore consider a translation of previous models to the model of "wanting", "liking" and "inhibition", which is possible for most stages of sexual functioning except arousal, as this stage contains aspects of both wanting and liking.

Figure 1. Excitatory and inhibitory neurtransmitters in the central and peripheral nervous system during the sexual response cycle



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Different aspects of sexual functioning can be modeled in the "wanting", "liking", "inhibition" pleasure cycle. The effects of psychotropic drugs on excitatory and inhibitory neurotransmitters in most cases show a distinction between excitatory and inhibitory actions on sexual functioning. This figure also illustrates that a dichotomous distinction of the effects of excitatory neurotransmitters on "wanting" and "liking" is difficult, as most excitatory neurotransmitters are thought to be involved in both "wanting" and "liking", although possibly in different degrees.

In contrast to the model of "sexual desire", "arousal", "orgasm" and "refraction", the "wanting", "liking", "inhibition" model makes it possible to compare aspects of sexual functioning with other behaviors and to compare animal and human research. This allows comparisons in behavior patterns both in terms of the behaviors that are expressed in each phase and the neuroanatomical and neurochemical systems that underlie them. Similarly, medications that will be described in this article may influence one or more aspects of wanting, liking and inhibition. The behavior effects of medications could be used for this reason to validate or improve models for sexual performance.

Although sexual functioning in animal and clinical studies has mostly been described in terms of sexual desire, arousal, orgasm and refraction and these terms will be used in this review, at the end of the review, we will summarize the main results in terms of "wanting", "liking" and "inhibition". The different stages of sexual functioning are shown in Figure 1, including the effects of the neurotransmitters that will be described.

Mechanisms in the brain in normal sexual functioning

The level of sexual excitation is the result of a combination of inhibitory and excitatory factors. Sexual excitation involves the activation of brain areas including noradrenalin as neurotransmitter and is modulated by the hormone oxytocin. Dopaminergic areas and melanocortin hormones are involved in the attention for sexual cues and sexual desire (wanting). The hypothalamus and limbic system are activated in response to sexual cues and stimulation.

Inhibitory mechanisms include endogenous opioids, endocannabinoids and serotonin. Endogenous opioids are released in the cortex, limbic system, hypothalamus and midbrain during an orgasm or other sexual reward. Endocannabinoids mediate sedation while serotonin is associated with refractoriness and sexual satiety (Pfaus. 2009).

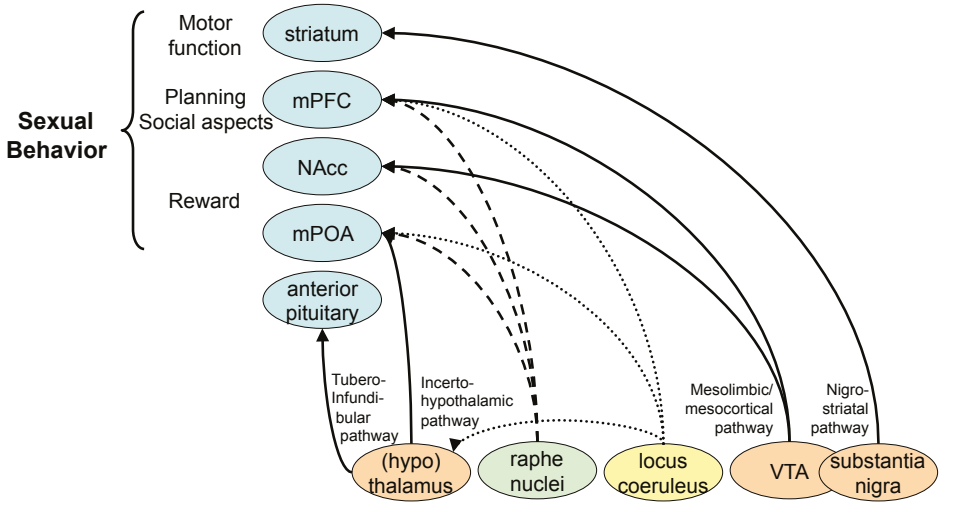
Sexual excitation can be primed internally by steroid hormone (testosterone, estrogen, progesterone) actions or externally by sexual incentives or drugs that activate excitatory neurochemical systems (Pfaus. 2009). Thus, some (steroid) hormones enhance the sensitivity of parts of the brain for sexual incentives. Steroid hormones have primarily slow, genomically mediated effects. Copulation requires rapid somatomotor interactions between two active individuals. The means by which the slow hormonal effects are translated into rapid, interactive behaviors includes the up-regulation of enzymes and receptors that allow neurotransmitters to activate (or inhibit) neurons that integrate and execute the behaviors (Hull & Dominguez. 2006). Pharmacological agents affect mainly these rapid changes in neurotransmitter function.

Apart from neurotransmitters and hormones, previous sexual experiences are also important in sexual functioning. These experiences may influence the interaction between neurotransmitters, brain areas and hormones in current sexual behavior (Pfaus, et al. 2012). Evidence from rats and humans shows that pleasurable sexual experiences early in life facilitate later sexual functioning and reduce the risk for sexual dysfunction. Social deprivation or traumatic sexual experiences early in life likely compromise future sexual behavior. A more detailed description of these associations can be found in reviews of Pfaus (Pfaus. 2009) and Meston and Frohlich (Meston & Frohlich. 2000).

Role of neurotransmitters and neuropeptides in sexual functioning

In the following sections, the effects of individual or interacting neurotransmitters in brain areas involved in sexual functioning will be discussed. Figure 2 shows pathways of dopamine, serotonin and noradrenalin in the central nervous system involved in sexual functioning.

Figure 2. Pathways of dopamine, serotonin and noradrenalin in the central nervous system involved in sexual functioning



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Dopamine

Function of dopamine

Dopaminergic neurons are involved in the control of motor activity in the striatum and in cognitive and emotional processes in the frontal and limbic areas of the brain. Dopamine is also an important neurotransmitter in brain areas and circuits involved in experiencing motivation (mesocortical tracts), salience or rewards (mesolimbic tracts). This includes sexual motivation (desire) and sexual reward. Sexual reward is experienced during orgasm, but also during other stages of sexual functioning, contributing to reward-related learning of sexual behavior (Meston & Frohlich. 2000, Giuliano & Allard. 2001). Perspectives on the role of dopamine are still under debate as some researchers suggest that the dopamine system may be primarily involved in anticipation of reward, more than reward itself (Bressan & Crippa. 2005).

Three major dopamine circuits are involved in sexual arousal and desire: 1) the diencephalic (i.e. incertohypothalamic and tuberoinfundibular) dopamine system with terminals in the medial preoptic area (mPOA) of the anterior hypothalamus; 2) the mesolimbic and mesocortical dopamine system with terminals in the nucleus accumbens (NAcc), other limbic regions, and the medial prefrontal cortex, respectively, and 3) the nigrostriatal pathway, with terminals in the striatum (caudate and putamen) (Pfaus. 2009). The NAcc and mPOA are also important regions in actual sexual functioning.

The functioning of the dopamine system in sexual activity is facilitated by noradrenergic activity and priming by steroid hormones. A general noradrenergic tone in the forebrain is important for the control of (sexual) arousal and in the autonomic nervous system for the control of genital blood flow. The influence of noradrenalin on the DA system will be discussed in more detail later.

Dopamine release in rats seems to be facilitated by nitric oxide, while testosterone is thought to potentiate the synthesis of nitric oxide that controls dopamine release (Becker. 1990, Sanderson, et al. 2008, Sato, et al. 2005). These interactions between dopamine, nitric oxide and testosterone especially occur in the mPOA. Besides that, glutamatergic inputs to the mPOA increase the amount of dopamine in the mPOA via increased production of nitric oxide. At least in male rats, glutamate, nitric oxide and dopamine interact in the mPOA to facilitate mating and to enhance future sexual responsiveness (Hull & Dominguez. 2006, Will, et al. 2014). Figure 3 shows the central role of the mPOA in sexual functioning, including other influencing neurotransmitters that will be described in more detail later.

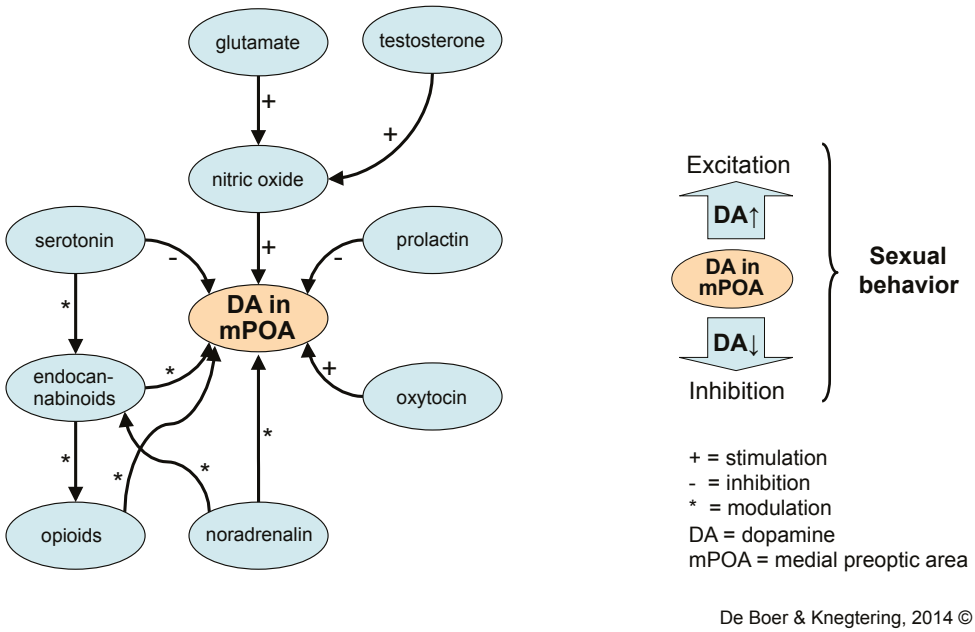
Pharmacology: Dopamine agonism and antagonism

Dopamine agonists, like levodopa, apomorphine and bromocriptine, are mainly used in the treatment of Parkinson's disease. Some dopamine agonists are also applied for the treatment of hyperprolactinemia. It is reported that dopamine agonists simulate sexual excitement and arousal in both rats and humans (Pfaus. 2009, van Deelen, et al. 2002, Uitti, et al. 1989). Apomorphine, a dopamine-D_1/D_2agonist facilitates erection in men with normal and decreased erectile capacity as well as in rats with decreased erectile functioning. The effects of dopamine-induced erection in male rats can be blocked by dopamine antagonists like haloperidol. In patients with Parkinson's disease levodopa treatment can provoke sexual hyperactivity (van Deelen, et al. 2002, Uitti, et al. 1989). Other medications with dopamine agonistic properties, like buproprion and stimulants like methylphenidate have been reported to improve sexual functioning in patients suffering from depression or ADHD. Moll and Brown recently reviewed how effects of monoamine pharmacologic agents may be used in treatment of sexual dysfunction. They concluded that most research on this topic was about SSRI-induced sexual dysfunction. Of the dopaminergic agents, the addition of buproprion showed the most convincing results to reduce SSRI-induced sexual dysfunction (Moll & Brown. 2011).

Stimulants, such as the drugs methamphetamine and cocaine, increase dopaminergic neurotransmission and have a stimulating effect on sexual behavior in humans after acute administration. In contrast, after chronic use, sexual functioning may be impaired. An explanation for this observation may lie in downregulation of dopaminergic receptors during chronic use. Methylphenidate only seems to have a stimulating effect on sexual functioning during acute intravenous administration, but not during

longterm oral use. In animal research, corroborative results have been reported (Frohmader, et al. 2010). Dopamine blockade is a major factor in antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008). Most antipsychotics are postsynaptic dopamine antagonists that inhibit the effects of endogenous dopamine diffusely in the brain and frequently cause sexual dysfunction in patients treated for a psychotic disorder (16-60%). A decreased level of sexual desire is most frequently reported, but also other stages of sexual functioning are influenced (Serretti & Chiesa. 2011). Comparable inhibitory effects of antipsychotics on sexual functioning are reported in rats (Pfaus. 2009).

Figure 3. Interaction between neurotransmitters involved in sexual functioning: focus on the central role of the mPOA



A second factor possibly involved in the inhibition of sexual behavior by dopamine antagonists is the associated hyperprolactinemia (Meston & Frohlich. 2000, Knegtering, et al. 2008), as dopaminergic activity is the main controlling pathway in the production of prolactin in the pituitary gland. When dopamine antagonists decrease levels of dopaminergic output, prolactin levels are increased. Prolactin in turn has an inhibiting effect on the tuberoinfundibular dopaminergic neurons (Fitzgerald & Dinan. 2008), thereby inhibiting sexual behavior. In normal sexual functioning, the level of prolactin increases during orgasm and is thought to be involved in sexual satiety after orgasm. A definitive conclusion to which degree antipsychotic-induced sexual dysfunction may be related prolactin elevation is still under debate (De Hert, et al. 2014).

Many dopamine antagonists (often used as antipsychotics) not only interact with dopamine, but also with other neurotransmitter systems in the central en peripheral nervous system, like serotonergic,

noradrenergic, histaminic and cholinergic/muscarinic neurotransmitter systems (Leysen & Gommeren. 1984, Richtand, et al. 2008, Correll. 2010). These may also influence sexual functioning as will be discussed later.

Neurons that are part of the dopaminergic system may show fluctuating firing patterns. In one state, dopaminergic neurons in the ventral tegmental area and substantia nigra fire at relatively low frequencies (tonic activity). Periodically, dopamine neurons fire at much higher frequencies for short repeating periods, which is often referred to as "burst firing" or "phasic activity". Burst firing is associated with anticipation of reward, or experience of new rewards. Medications with dopamine antagonistic, agonistic or partial antagonistic effects (e.g. used as antipsychotics, moodstabilizers or antiparkinsonian medication) on dopaminergic neurons have differential effects on tonic and phasic activity of the dopaminergic system, although exact influences remain understudied. Unfortunately, it is not yet known whether the influence of antipsychotics or antidepressants on sexual performance may be explained by their influence on the firing pattern of dopaminergic neurons (Hamamura & Harada. 2007, Heien & Wightman. 2006, de Boer, et al. 2011). Furthermore, it has been suggested that the ratio between dopamine D_1 and D_2 activity influences sexual functioning in rats (Hull & Dominguez. 2006, Graham & Pfaus. 2010, Hull, et al. 1989) and may be disturbed in patients with schizophrenia (Hess, et al. 1987, Seeman, et al. 1989), but evidence is limited.

Noradrenalin

Function of noradrenalin

Central noradrenergic systems are involved in general arousal and in the control of autonomic outflow of the central nervous system. Noradrenergic cell bodies arise in the locus coeruleus at the border of the midbrain and brainstem and project to almost all forerbrain regions, including the hypothalamus, limbic and motor systems, and cortex. Noradrenalin release in different regions of the brain is involved in different aspects of motivation (Moore & Bloom. 1979). The association between noradrenalin-levels and sexual functioning is characterized by an inverted U shaped relation. High levels of noradrenergic transmission lead to a general fear response, which inhibits sexual functioning (Green, et al. 1957). However, a decreased noradrenergic tone may contribute to a decrease in sexual desire due to insufficient general arousal (Pfaus. 2009). An intermediate level of noradrenalin transmission optimizes sexual functioning.

Noradrenalin binds to two receptor classes, namely alpha and beta receptors. The alpha subtypes are further classified into alpha-1 (postsynaptically) and alpha-2 subtypes (mainly presynaptically). In the peripheral nervous system, noradrenalin contracts both corpora cavernosa and penile vessels via stimulation of the alpha-1 adrenoceptors (Pfaus. 2009, Andersson. 2011, Sanbe, et al. 2007). Alpha-1 antagonism in the peripheral nervous system seems to stimulate erection, vaginal lubrication and ejaculation (Maggi, et al. 2000) by decreasing the smooth muscle tone and increased vasodilatation. Furthermore, central alpha-1 antagonism has been shown to decrease sexual functioning.

Pharmacology: Noradrenalin agonism and antagonism

It has been suggested that peripheral alpha-1 antagonists like tamsulosin or doxazosin, often used for treatment of lower urinary tract symptoms, could improve erection (Gur, et al. 2008).

Antipsychotics with alpha-1-antagonistic properties are associated with priapism and diminished ejaculatory volume (DEV) (Sanbe, et al. 2007, Thompson, et al. 1990, Sood, et al. 2008). The mechanisms involved in priapism and DEV are not totally clear, but these may be primarily the result of peripheral alpha-1 antagonism, although central effects may be involved too.

Activation of *presynaptic* alpha-2 receptors reduces noradrenalin transmission, while antagonism of presynaptic alpha-2 receptors will increase noradrenalin transmission. The alpha-2 antagonist yohimbine stimulates erection in humans and rats (Smith, et al. 1987, Tallentire, et al. 1996), while the alpha-2 agonist clonidine leads to a decreased sympathetic tone, sedation and decreased sexual functioning in rats (Clark & Smith. 1990). There are indications in quails that dopaminergic effects in the mPOA are mediated mainly through the activation of alpha-2 receptors, which means that when dopamine levels increase too much, it is controlled by this mechanism (Cornil, et al. 2005).

Beta blockers like propranolol block peripheral and central noradrenergic beta receptors and have negative effects on copulatory behavior, e.g. when injected in the mPOA of rats. This may be reversed through exercise, which increases noradrenalin in the brain (Thom, et al. 2009).

Some antidepressants like reboxetine specifically increase the amount of central noradrenalin (possibly improving sexual functioning). However, most antidepressants also increase the amount of serotonin, which makes it difficult to determine a specific effect of the increase of noradrenalin on sexual functioning. The prevalence of sexual dysfunction is significantly lower in patients using reboxetine compared with e.g. serotonin re-uptake inhibitors (SSRIs), and is comparable with sexual functioning during placebo treatment (Clayton, et al. 2003, Langworth, et al. 2006). Reboxetine is a noradrenalin re-uptake inhibitor that mainly acts on the noradrenalin transporter, thereby increasing the level of central noradrenalin. In some studies, improved sexual functioning during use of reboxetine has been reported (Baldwin, et al. 2006). Treatment with the dopamine- and noradrenalin re-uptake inhibitor bupropion, with known effects of increased dopamine and noradrenalin levels, is associated with low levels of sexual dysfunction and beneficial effects on sexual dysfunction. This was found in both animal and human studies (Moll & Brown. 2011, Abler, et al. 2011, Moreira. 2011).

Serotonin

Function of serotonin

Serotonin is located throughout the body and plays an important role in numerous physiological processes, like gastrointestinal smooth muscle contraction, learning and memory, and vasoconstriction. Serotonergic neurons arise in the raphe nuclei of the midbrain and send extensive axonal projections to the brainstem, midbrain and forebrain areas, including the hypothalamus, limbic system, hippocampus and cortex, and down the spinal cord to lower lumbar and sacral regions that control genital reflexes (Pfaus. 2009, Moll & Brown. 2011).

The effects of serotonin in the central nervous system on sexual behavior are complex (Rosen, R. C. et al. 1999). Serotonin is released during orgasm/ejaculation. Serotonergic neurons generally have inhibitory effects on sexual function and are therefore thought to be involved in sexual satiety. Animal studies suggest that serotonin release in the lateral hypothalamus may explain this inhibition of sexual behavior, partly through inhibition of dopamine release in the mesolimbic tract (Pfaus. 2009, Bijlsma, et al. 2013). In rats and humans agonism of the presynaptic 5-HT_{1A} receptors and antagonism of the postsynaptic 5-HT_2 receptors (mainly the 5-HT_{2C} and possibly also the 5-HT_{2A}) seems to facilitate copulatory behavior (Moll & Brown. 2011).

Pharmacology: Serotonin agonism and antagonism

Serotonin re-uptake inhibitors (SSRIs) increase serotonergic neurotransmission and are often prescribed for treatment of depression and anxiety. Delayed or inhibited orgasm/ejaculation are common side effects of serotonin re-uptake inhibitors (SSRIs) (Kennedy & Rizvi. 2009). When healthy non-depressed volunteers use SSRI's, they report sexual dysfunction in approximately the same frequencies as patients, especially delayed orgasm (Montejo, et al. 2010, Nafziger, et al. 1999). In a randomized double-blind placebo-controlled study in 48 men receiving fluoxetine, citalopram or placebo, treatment with citalopram and fluoxetine delayed ejaculation/orgasm, but the difference relative to placebo was statistically significant for citalopram only. Citalopram and fluoxetine did not affect sexual desire, and did not directly affect penile erection as objectively assessed by the RigiScan (a mechanical strain gauge that measures the penile circumference). Impairment in the subjective assessment of erectile function was statistically significant for citalopram and was interpreted as a consequence of delayed ejaculation (Madeo, et al. 2008). The effect of SSRIs of delaying orgasm/ejaculation is clinically used in the treatment of premature ejaculation (Giuliano & Clement. 2012).

Serotonergic drugs that reduce sexual dysfunction are often agonists of the 5-HT_{1A} receptor and/or antagonists for the 5-HT_2 receptor. Examples are cyproheptadine (5-HT_2 antagonist), mirtazapine (5-HT_{2A} antagonist, 5-HT_{2C} antagonist, 5-HT_3 antagonist, alpha-2 antagonist), buspirone (5-HT_{1A} partial agonist, alpha-2 agonist, D_2 agonist), flibanserin (5-HT_{1A} agonist, 5-HT_{2A} antagonist, D_4 partial agonist). A more detailed description of these aspects was reviewed by Moll and Brown (Moll & Brown. 2011). Currently available 5-HT_{1A} receptor agonists activate both presynaptic autoreceptors and postsynaptic receptors. Several studies suggest that the stimulating effects of 5-HT_{1A} agonists on sexual functioning are explained by activation of postsynaptic receptors (Bijlsma, et al. 2013).

Some antipsychotics, like risperidone and haloperidol, are antagonists for the D_2 receptors as well as the 5-HT_2 receptors. This would theoretically promote different effects on sexual functioning, e.g. an inhibition of "wanting" due to dopamine antagonism, and an increase of "liking" due to antagonism of the 5-HT_2 receptors. In line with this hypothesis, in female rats, haloperidol indeed enhanced lordosis ("liking") while concomitantly solicitations ("wanting") were abolished (Grierson, et al. 1988). In clinical practice, most antipsychotics are reported to cause sexual dysfunction in humans (Serretti & Chiesa. 2011), suggesting that the antagonism for the D_2 receptor dominates the clinical outcome in terms of sexual functioning.

MDMA (3,4-methyleendioxymethamfetamine = ecstasy) often used as a recreational drug, induces an acute release of serotonin and to a lesser degree dopamine and noradrenalin. Users mainly report enhanced pleasure in physical closeness and sexual arousal, but impairment of sexual functioning like erectile functioning and a delay in experiencing orgasm, corresponding with the serotonergic effects (Frohmader, et al. 2010).

For different patients different combinations of pharmacological interventions may lead to an optimal result, but evidence is still limited. As sexual functioning is influenced by many factors, it can be hypothesized that the combination of different medications (e.g. influencing serotonin and nitric oxide) would provide more optimal treatment strategies for sexual dysfunction. Clinical studies of combination strategies are still scarce. In women with high (sexual) inhibition, a combination of a low dose of testosterone followed by a 5-HT_{1A} receptor agonist increased sexual performance. In these patients, a low dose of testosterone followed by a phosphodiesterase-5-inhibitor did not increase sexual perfomance. In contrast, women with an insensitivity for sexual cues may benefit from a combination of a low dose of testosterone and a phosphodiesterase-5-inhibitor (Bloemers, et al. 2013, Poels, et al. 2013, van Rooij, et al. 2013). The underlying mechanisms may be that testosterone stimulates sexual desire or initiative, a 5-HT_{1A} receptor agonist decreases anxiety and stimulates sexual functioning and a phosphodiesterase-5-inhibitor stimulates arousal.

Opioids

Function of opioids

Opioids can be involved in both sexual reward and sexual satiety. Endogenous opioid activation forms the basis of sexual reward, which also sensitizes hypothalamic and mesolimbic dopamine systems in the presence of cues that predict sexual reward (Pfaus, et al. 2012). Evidence indicates that the MPOA plays a crucial role in the expression of opioid mediated sex-reward in male and female animals (Paredes. 2013). Besides that, opioids are released at relatively low levels during sexual desire and arousal in the ventral tegmental area and help to disinhibit dopaminergic neurons, thereby increasing dopamine release in mesolimbic terminals. The level of opioids increases during orgasm/ejaculation in rats and is believed to contribute to the induction of sexual satiety (Pfaus. 2009).

Pfaus suggests that in any motivational system, rewards should be considered a dynamic function with an inverted U-shaped relationship to ongoing behavior. Low rewards do not induce the continuation of behavior; moderate levels induce the reinforcement of behavior, while higher reward levels tend to induce inhibitory feedback that characterizes satiety (Pfaus. 2009).

Pharmacology: Opioid agonism and antagonism

Opiates like heroin produce a rush of euphoria followed by a prolonged period of relaxation, a state that has been referred to as a 'pharmacogenic orgasm' in the drug addict (Chessick. 1960). Opioids induce, when used continuously, a decline in sexual arousal and desire in male and female animals and humans. Furthermore, opiates inhibit the ability to achieve orgasm in those who are able to generate enough sexual arousal to sustain sexual intercourse (Frohmader, et al. 2010, Teusch, et al. 1995, Pfaus & Gorzalka. 1987).

When opiates are chronically used as analgesics, they frequently cause sexual dysfunction in humans. In contrast, some animal research reports a stimulating effect of acute administration of morphine on sexual arousal and motivation in male rats (Frohmader, et al. 2010). It is hypothesized that in chronic use, impaired sexual functioning may also be due to the effects that opioids have on the endocrine system, since the chronic effects of opioid administration increase prolactin, decrease testosterone, estradiol and oxytocin levels, and also influence other hormones (Vuong, et al. 2010). Another explanation may be downregulation of opioid receptors in chronic opiate use, leading to a decreased ability to experience sexual reward.

Injections of the nonselective opioid receptor antagonists naloxone or naltrexone reverse the sexual inhibition displayed by male rats after reaching sexual exhaustion (i.e. when opioid levels are endogenously high) (Rodriguez-Manzo & Fernandez-Guasti. 1995). In line with the possible role of opiods in experiencing reward mediated learning of sexual behavior, a decrease in sexual activity in rats has been reported when naloxone was administered during the first few sexual experiences (Pfaus. 2009, Rodriguez-Manzo & Fernandez-Guasti. 1995). This suggests that when the experience of reward is inhibited during the first sexual experiences, the animals learn that sexual activity is not rewarding, leading to a decrease of future sexual activity. In humans, evidence for this interaction, although clinically probably very important, is limited (Orri, et al. 2013).

(Endo)cannabinoids

Cortical, limbic, hypothalamic and motor regions contain medium to high density of cannabinoid 1 (CB1) receptors and neurons that produce endocannabinoids. This system induces a natural anxiolytic and sedative effect that counteracts stress activation through the modulation of dopamine and noradrenalin release. The cannabinoid system itself is modulated by brain opioid and serotonin release, other important neurotransmitters that inhibit sexual functioning (Pfaus. 2009, Gorzalka, et al. 2010). Agents influencing the cannabinoid receptor (like THC/marijuana) are used for anxiolysis or sedation/relaxation in recreational and medicinal use (Gorzalka, et al. 2010).

The influence of cannabis intake on sexual behavior and arousability appear to be dose-dependent in both men and women, although women are far more consistent in reporting facilitatory effects. In acute use, effects seem to be facilitating sexual activity while after chronic use, more detrimental effects are reported, e.g. erectile dysfunction (Frohmader, et al. 2010).

Nitric oxide

Neurogenic nitric oxide (NO) is considered to be the most important factor (neurotransmitter) for relaxation of penile vessels and corpora cavernosa, which induces erection. NO is probably also an important factor in clitoral vasocongestion (Andersson. 2011, Creed, et al. 1991). NO leads to the production of cyclic guanosinemonophosphate (cGMP) in the smooth muscle cells of the penis, which leads to relaxation of these smooth muscle cells and an increased blood flow into the penis. The ('active') cGMP is metabolized to ('inactive') 5'CMP by the enzyme phosphodiesterase-5 (PDE-5). Therefore, PDE-

5 inhibitors like sildenafil, vardenalfil or tadalafil facilitate erection by restoring a sufficient amount of cGMP. PDE-5-inhibitors also improve sexual functioning in women (Nurnberg, et al. 2008, van der Made, et al. 2009), but may be less effective than in men (Chivers & Rosen. 2010). As mentioned previously, in women, the context of sexual inhibition may be decisive in whether a PDE-5 inhibitor may be helpful in sexual activities (Bloemers, et al. 2013, Poels, et al. 2013, van Rooij, et al. 2013).
Originally PDE-5-inhibitors are thought to enhance erection through peripheral mechanisms, but also central mechanisms, involving the glutamate and dopamine system, may contribute to their action (Reneerkens, et al. 2012).

Glutamate

Glutamate is the major excitatory neurotransmitter in the brain of humans and vertebrate animals, which is also involved in learning (Kuriyama, et al. 2011, Kuriyama, et al. 2013). Glutamatergic neurons involve many different post- and presynaptic receptor systems and receptors on glia cells (AMPA, Kianate, NMDA, mGluR) in the brain (Nakanishi, et al. 1998). Networks of interacting neurons using miscellaneous neurotransmitters interact with each other, thereby influencing behavior, including sexual behavior. The mPOA serves as an important integrative site of the input from many networks, in which glutamate is involved. Glutamatergic neurons contain NO in postsynaptic second messenger systems that play an important role in the mPOA. Gonadal hormones regulate dopamine release in the mPOA of male rats in part by increasing nitric oxide synthase (NOS) in the mPOA, leading to the production of more NO, which increases dopamine release (Hull & Dominguez. 2006, Will, et al. 2014).
Extracellular glutamate in the mPOA increases during copulation, especially during ejaculation, and increased glutamate facilitates copulation and genital reflexes (Hull & Dominguez. 2006). In theory, modulation of glutamatergic neurons, for instance through NOS or mGLUR (metabotropic glutamate receptor), may influence sexual performance (Li, et al. 2013). However, it is not clear whether psychotrophic substances acting on the glutamate system indeed influence sexual performance in humans.

GABA

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain of humans and vertebrate animals. Glutamate is a precursor for GABA. GABAergic neurotransmission is involved in a decrease of male sexual behavior in animals (Meston & Frohlich. 2000, Bernardi, et al. 2012).
In humans, although many studies have been published on sexual side effects of psychopharmacological treatment, only a minority relate to mood stabilizers and anxiolytic drugs known to act on GABAergic neurotransmission. These studies are in general of poor quality leading to inconclusive evidence. Few studies suggest detrimental effects of anticonvulsants on sexual performance, but their mechanism might be better explained by alterations in sex hormone levels than its direct effects on GABA (La Torre, et al. 2014). Further research of effects on sexual performance is needed to better understand pharmacological effects of mood stabilizers and anxiolytic drugs, both in animals and humans.

Acetylcholine

The human corpus cavernosum is innervated by cholinergic nerves. Administration of exogenous acetylcholine chloride to precontracted corpus cavernosum results in a relaxation of the smooth muscles in men. This is in line with the notion that acetylcholine has a facilitatory role in erection and ejaculation. Reliable information about the effects of acetylcholine on sexual behavior in women is currently unavailable (Meston & Frohlich. 2000). In addition, little is known about possible central *anti*cholinergic effects, which often occur as adverse effect of antidepressants and antipsychotics, which may contribute to inhibition of sexual functioning (Floody. 2011, Canevelli, et al. 2012).

Histamine

Histamine receptors are present peripherally as well as in the central nervous system. Information about the influence of histamine on sexual functioning is again limited (White & Rumbold. 1988, Uckert, et al. 2012). Injection of histamine in the corpora cavernosa induces full or partial erections in the majority of men with psychogenic erectile dysfunction, while histamine antagonists are associated with a decrease of sexual functioning (White & Rumbold. 1988). The exact effects of central agonism or antagonism of histamine receptors on sexual functioning remains unknown. An indirect negative result of antihistaminergic medication (e.g. anti-allergy medication, some antipsychotics or some antidepressants (Correll. 2010)) on sexual functioning may primarily be caused by their sedating effects.

Summary

This review of the mechanisms involved in sexual functioning describes clinical and preclinical research on the effects of psychotropic medication with the aim of providing a clinically useful and comprehensive but also concise overview of findings.

We show that dopamine has a central role in neuronal networks involved in the anticipation of reward and motivation for sexual activity. Dopaminergic networks interact with many other neuronal networks involving miscellaneous neurotransmitters. An important integrative site is the mPOA, where dopaminergic mechanisms and other mechanisms interact with each other (Figure 3). In line with this, influencing dopaminergic transmission often affects sexual functioning. Dopaminergic systems appear be involved in a final common pathway in the central nervous system, modulating sexual performance including attentional, emotional and motor aspects of sexual behavior. Pharmacological agents as well as disorders influencing the dopaminergic system often have an effect on sexual functioning. Furthermore, the majority of non-dopaminergic systems influencing sexual performance systems seem to do this, at least partly, by their modulating influences on dopaminergic mechanisms.

Noradrenalin primarily has a stimulating effect on sexual functioning in the central nervous system, but too high levels of noradrenergic transmission lead to a general fear response, thereby inhibiting sexual functioning. Contrarily, in the peripheral nervous system lowering of noradrenalin levels (e.g. by alpha-1 antagonism) stimulates erection, vaginal lubrication and ejaculation, probably by decreasing the smooth muscle tone and increased vasodilatation.

Serotonergic activity is involved especially in sexual satiety and often results in a decreased ability to achieve orgasm/ejaculation, partly through inhibition of dopamine release in the mesolimbic tract. Postsynaptic antagonism of 5-HT_2 receptors has stimulating effects on sexual behavior, especially for the 5-HT_{2C} receptor. In line with this, agonistic effects on the presynaptic 5-HT_{1A} receptor result in a decreased serotonergic transmission also leading to stimulation of sexual behavior.

Opioids are associated with the experience of sexual reward and sexual satiety after orgasm. Low amounts of opioids increase dopaminergic neurotransmission in the mesolimbic system, increasing the 'wanting' of the sexual response cycle.

Neurogenic nitric oxide (NO) is considered to be the most important factor for relaxation of penile vessels and corpora cavernosa, which induces erection. NO is probably also an important factor in clitoral vasocongestion. In the central nervous system, glutamatergic neurons contain NO in postsynaptic second messenger systems that play an important role in the mPOA: via increased production of NO, glutamate increases dopamine release in the mPOA.

GABA, (endo)cannabinoids, acetylcholine and histamine have been suggested to influence sexual performance but evidence is limited.

Discussion

As outlined above, sexual functioning is influenced by many factors, among which are neuronal networks and their neurotransmitters, hormones, social factors, psychological factors, previous sexual experience, psychiatric symptoms (e.g. anxiety, depression, psychosis) and combinations of these. Contradicting findings in the source literature may often be explained by the difficulty to control for the diversity of interacting factors in sexual performance.

In this review, animal as well as human (clinical) research has been described. The findings of animal and human research frequently appear to support each other. Still, the reader has to be careful to translate results from one field to another. Medication in rats is often administered in specific areas in the brain, while in humans medication is administered systemically which may give different effects and more various effects involving interacting systems, potentially confounding the results. Also, brains of rats and humans are different in many aspects. Still, the model of "wanting, liking, inhibition" appears to be helpful and facilitates comparisons between preclinical and clinical research to describe the stages of sexual functioning.

A complicating aspect in understanding mechanisms of neurotransmitters influencing sexual behavior is the difference between effects of acute and chronic administration of many drugs. For instance, drugs like methamphetamine and cocaine increase dopaminergic neurotransmission and have a stimulating effect on sexual behavior in humans after acute administration. In contrast, after chronic use, sexual functioning may be impaired. An explanation for this observation may lie in downregulation of dopaminergic receptors during chronic use.

For some neurotransmitter systems there is no linear but for instance an inverted U-shaped dose-effect relation of medication on output, including sexual functioning. For some neurotransmitters an optimal stimulating or rewarding effect has been described for intermediate levels (e.g. opioids, noradrenalin), while low or high levels impair (or do not stimulate) sexual functioning.
Another complicating mechanism in studying sexual behavior is the non-linear dose-respons relation in reward related behavior. Low (anticipated) rewards may not induce the initiation or continuation of behavior. In contrast (anticipated) moderate levels may induce initiation and reinforcement of behavior, while higher or continuous reward levels may induce inhibitory feedback that characterizes satiety.

Limitations

Some limitations are specifically related to the structure of this review. This review focused on many neurotransmitter systems involved in sexual functioning, based on results from animal as well as clinical research. As we wanted to provide a comprehensive, clinically oriented and concise overview of the different mechanisms, it was not possible to describe all aspects in detail. Particularly for animal studies it was not possible to mention all original studies, including the differences in the circumstances in which these studies have been performed, which may have influenced the results. However, no other recent overviews are available that describe the influence of all neurotransmitters involved in sexual functioning in both animals and humans. Despite the complexity of this endeavour, we provided an integrated overall image of this field, which may encourage the interested reader to search for more details in the original articles.

Clinical implications

Evidence from pharmacological studies as described here improves our understanding of possible mechanisms involved in sexual functioning. This can be helpful in the development of treatment strategies to influence sexual functioning, or to decrease undesired effects of medications. However, when patients complain about sexual problems, it is important for clinicians to systematically evaluate possible causal and influencing factors as well as the burden of sexual dysfunction with the patient. When treatment is desired, psychological and medication options should be considered, but here we focus on psychotropic-induced sexual dysfunction.
When psychotropic medication is a likely cause of sexual dysfunction, knowledge as described in this review is crucial. In view of the central role of dopamine in sexual functioning, it is important to restore dopaminergic function when this is impaired (e.g. during treatment with antipsychotics). Moreover, impaired dopaminergic function not only influences sexual functioning, but may also impair subjective well-being and increase anhedonia (de Haan, et al. 2005, Liemburg, et al. 2011), probably by disturbing the anticipation for reward. However, when dopaminergic function is intact or when it is not possible to restore dopaminergic function, other neurotransmitters can be considered as causal mechanisms impairing sexual performance and/or as possible treatment targets.

More specifically, when sexual functioning is impaired by antipsychotics or antidepressants, the first treatment options to diminish the effects on dopamine or serotonine, respectively, are lowering the dose or switching to an antipsychotic or antidepressant with less detrimental effects on sexual functioning. Of note, antiparkinsonian medication (dopamine agonists) could lead to hypersexuality, for which lowering the dose could also be considered. Furthermore, for antidepressant-induced sexual dysfunction, most evidence is available for adjunctive treatment with a PDE-5 inhibitor (like sildenafil) or bupropion. Also, adjunctive treatment with a dopamine agonist or 5-HT_2 antagonist (like mirtazapine) has been investigated. For antipsychotic-induced sexual dysfunction, adjunctive treatment with a dopamine agonist, aripiprazole or a PDE-5 inhibitor could be considered (Taylor. 2006, Taylor, et al. 2013, Nunes, et al. 2012).

Knowledge of the underlying pharmacological mechanisms of psychotropic-induced sexual dysfunction is important as insight into these mechanisms helps clinicians together with their patients to design tailor made treatment strategies to reduce undesired effects of medications, especially undesired effects on sexual performance.

Future research

With the present review the multifactorial nature of sexual (dys)function is discussed, including the interaction between different factors. For future research on sexual dysfunction, it may be better to focus on combination strategies targeting specific phases in the wanting-liking-inhibition model, like the combination of hormonal and pharmacological treatment, for instance a low dose of testosterone with a 5-HT_{1A} receptor agonist or a low dose of testosterone with a phosphodiesterase-5-inhibitor. These strategies have been investigated in women with hyposexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) (Bloemers, et al. 2013, Poels, et al. 2013, van Rooij, et al. 2013). Other useful treatment strategies may be well designed interventions combining pharmacological and psychological treatment. Furthermore, more research is needed on interactions between networks using different neurotransmitters, including the context of hormones and social behavior.

In conclusion, this review described what psychotropic medication learns us about sexual functioning. Using the wanting-liking-inhibition model in animal as well as human research will improve the translation of results between both fields, increasing our understanding of different aspects of behavior, including sexual behavior.

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Chapter 4

A systematic review of instruments to measure sexual functioning in patients using antipsychotics

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Abstract

Sexual dysfunction is a frequent side effect of antipsychotics, but there is only scant information about the psychometric properties and clinical usefulness of currently existing questionnaires. This systematic review compares the psychometric properties and content of questionnaires for assessment of sexual functioning in patients using antipsychotics. A systematic literature search was performed using three electronic databases (PubMed, Embase and PsycINFO) with predefined search terms. We identified six validated instruments for assessment of sexual functioning in patients using antipsychotics: the Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS), the Arizona Sexual Experience Scale (ASEX), the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), the Changes in Sexual Function Questionnaire-14 (CSFQ-14), the Nagoya Sexual Function Questionnaire (NSFQ) and the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ).

The ASFQ, CSFQ-14 and PRSexDQ cover all stages of sexual functioning, which makes these questionnaires preferable above the other three described questionnaires. The ASFQ and PRSexDQ are clinician-administered and ask for a change in sexual functioning related to medication. The ASFQ assesses improvement as well as deterioration of sexual functioning, and includes items about hyperprolactinemia. The CSFQ-14 is useful when self-report is desired, but contains more items.

Introduction

Sexual dysfunction in patients with schizophrenia or other psychotic disorders may be related to the disease itself, as well as to psychosocial factors, physical health and the use of psychotropic medications (Aizenberg, et al. 1995, Dickson & Glazer. 1999). Antipsychotics have been associated with sexual dysfunction, such as decreased sexual desire, erectile dysfunction, anorgasmia, and decreased ejaculatory volume (Knegtering, et al. 2008, Smith. 2003). Besides postsynaptic dopamine antagonism, prolactin elevation may be a factor in the pathogenesis of antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008).

Sexual side effects have a considerable impact on quality of life and are a major factor in non-adherence to prescribed antipsychotic drugs (Olfson, et al. 2005, Finn, et al. 1990). Sexual dysfunction is rarely reported spontaneously, leading to underestimation of its prevalence. In contrast, studies using structured interviews or questionnaires show that 16% to 60% of the patients using antipsychotics experience sexual dysfunction (Knegtering, et al. 2008, Serretti & Chiesa. 2011). Although antipsychotics are also prescribed for e.g. mood disorders or anxiety disorders, the vast majority of research on antipsychotics has been performed in patients with a psychotic disorder. Therefore, the focus of this review will be on this diagnostic category.

Many general questionnaires are available for evaluation of sexual functioning (Rizvi, et al. 2011), but for the evaluation of side effects and sexual performance in patients with psychosis, cognitive symptoms have to be taken into account. From the literature, it is known that the majority of patients with a psychotic disorder experience significant neurocognitive deficits, which impairs the patient's insight in the symptomatology of the psychotic disorder and it's impact on functioning in daily life in some cases (Saperstein, et al. 2012, Boyer, et al. 2012). To adjust for these neurocognitive deficits, based on the literature and our clinical and research experience, our hypothesis was that questions have to be phrased in a non-leading and understandable way and preferably the questionnaire is relatively short. It may also be difficult for psychotic patients to distinguish between questions that appear to be similar, but actually differ in one detail, for instance if a questionnaire has more than one question per phase of sexual functioning. In comparison with questionnaires for the evaluation of sexual functioning in the general population or in depressed patients, questionnaires for patients using antipsychotics are shorter, have simpler formulations and contain less details, e.g. with only one question per stage of sexual functioning instead of several questions on the same stage (Rizvi, et al. 2011, Ohlsen, et al. 2008, Mahmoud, et al. 2011, McGahuey, et al. 2000, Byerly, et al. 2006, Clayton, et al. 1997, Garcia-Portilla, et al. 2011, Knegtering. 2003, Kikuchi, et al. 2011, Montejo & Rico-Villademoros. 2008). No studies among patients with a psychotic disorder are available in which general questionnaires and specific questionnaires for sexual functioning were compared. When validated and non-validated instruments were compared in studies among patients using antipsychotics, the differences are comparable with the differences described between questionnaires for the general population and patients using antipsychotics (Serretti & Chiesa. 2011, Rizvi, et al. 2011, Ohlsen, et al. 2008, Mahmoud, et al. 2011, McGahuey, et al. 2000, Byerly, et al. 2006, Clayton, et al. 1997, Garcia-Portilla, et al. 2011, Knegtering. 2003, Kikuchi, et al. 2011, Montejo & Rico-Villademoros. 2008).

Questionnaires can be clinician-administered or self-reported by the patient. Clinician-administration of a questionnaire requires a qualified person, but also entails more possibilities for standardization and clarification (Rizvi, et al. 2011, Keller, et al. 2006). A clinician-administered questionnaire may help to solve potential problems such as difficulty understanding the questions, interference with cognitive symptoms, and the discrimination of medication-related changes in sexual performance and sexual problems that are not medication related. On the other hand, some authors suggest that sensitive information, such as on sexual functioning, is more easily reported in self-report questionnaires (Keller, et al. 2006, Kurth, et al. 2004).

The interaction between psychotic symptoms and the evaluation of sexual symptoms may also lead to difficulties in evaluating sexual symptoms, and baseline assessment of sexual performance is hampered in patients with severe psychotic symptoms. Furthermore, if patients have been using antipsychotics for many years, they may be less able to judge whether reported sexual dysfunctions are related to their illness, to their medication or to social factors.

Several questionnaires on the sexual side effects of antipsychotics have been used in previous studies (Serretti & Chiesa. 2011), but psychometric properties have been reported for only a few instruments. Because of the scarcity of validation and standardization studies, a gold standard method to evaluate antipsychotic-induced changes in sexual functioning is lacking. This makes it difficult to compare studies on this issue and may partly explain why results vary considerably between studies.

This review provides an overview of validated instruments for the assessment of sexual functioning in patients using antipsychotics, and will help researchers and clinicians to make a purpose-oriented choice.

Methods

Search procedure

The following search terms were entered in the online databases PubMed, Embase, and PsycINFO: (("schizophrenia" OR "antipsychotic" OR "psychotic") AND ("sexual function" OR "sexual dysfunction" OR "sexual side effect") AND ("instrument" OR "rating scale" OR "questionnaire" OR "interview") AND ("psychometric" OR "reliability" OR "validation" OR "validity" OR "reproducibility")). The search was carried out in January 2013. All retrieved studies were checked for cross-references.

Titles and abstracts were screened on relevance for the defined topic, namely psychometric properties of instruments for the assessment of sexual functioning in patients using antipsychotics. If found eligible, the full paper was examined. Inclusion criteria were: 1) studies assessing psychometric properties of instruments measuring (change in) sexual functioning in patients using antipsychotics; 2) the availability of an English translation of the instrument.

Reliability

Reliability is generally estimated by internal consistency, inter-rater and test-retest reliability. For internal consistency, Cronbach's alpha values of 0.60-0.70 are considered acceptable and values > 0.70 as good

(Cicchetti. 1994). Inter-rater reliability represents the correlation between raters and can be assessed only in clinician-rated instruments.

Validity

Validity is often described in terms of face validity, content validity, construct validity, convergent validity, divergent validity and predictive validity. Correlations ≥ .70 are considered to be sufficient for convergent validity, and correlations ≤ .40 are considered to be sufficient for divergent validity (Cohen. 1988).

Results

Questionnaires

Searching the literature using the described search terms yielded 25 publications, of which 7 publications, describing 6 instruments, were found to be relevant, as these studies described the psychometric properties of instruments the assessment of sexual functioning in patients using antipsychotics:

- Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS) (Ohlsen, et al. 2008, Mahmoud, et al. 2011);
- Arizona Sexual Experience Scale (ASEX) (McGahuey, et al. 2000, Byerly, et al. 2006);
- Antipsychotics and Sexual Functioning Questionnaire (ASFQ) (Knegtering. 2003), De Boer et al., 2013);
- Changes in Sexual Function Questionnaire-14 (CSFQ-14) (Clayton, et al. 1997, Garcia-Portilla, et al. 2011);
- Nagoya Sexual Function Questionnaire (NSFQ) (Kikuchi, et al. 2011);
- Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo & Rico-Villademoros. 2008).

In these studies, all included patients were diagnosed with schizophrenia or a related psychotic disorder, except for a subgroup of patients in the study on the CSFQ-14, who were diagnosed with a bipolar disorder. All questionnaires are relatively short with 4 (ANNSERS) to 14 (CSFQ) questions, and use 4-6-point Likert scales. The ASFQ is clinician-administered, the NSFQ is self-administered, and the other questionnaires have a self-administered as well as a clinician-administered version. In the ANNSERS, ASFQ and NSFQ most of the questions ask about changes in sexual functioning, whereas the CSFQ-14 and PRSexDQ only inquire about a change in one question. The time frames across which changes are investigated, are mentioned in table 1. The ASFQ and PRSexDQ ask specifically for changes in sexual functioning that can be attributed to the patient's current medication. The ASFQ is the only questionnaire in which not only deterioration, but also improvement of sexual functioning can be indicated. Characteristics of the questionnaires are shown in table 1.

Table 1. Comparison of ASFQ, ASEX, PRSexDQ, ANNSERS, CSFQ-14 and NSFQ

	ANNSERS	ASEX	ASFQ	CSFQ-14	NSFQ	PRSexDQ
Number of items	4	5	Male 7; Female 9	14	7	7
Self- or clinician administered	Self or clinician	Self or clinician	Clinician	Self or clinician	Self	Clinician
Time frame	?	1 week	4-6 weeks	?	1 month	Since start of medication
Number of participants in validation study	26	147	30	171	60	45
Number of men (M) and women (F) in validation study	M = 15 F = 11	M = 125 F = 122	M = 21 F = 9	M = 97 F = 74	M = 30 F = 30	M = 37 F = 8
Diagnosis of patients in validation study	Schizophrenia and spectrum	Schizophrenia and schizoaffective disorder	Schizophrenia and spectrum	Schizophrenia (n = 89), bipolar disorder (n = 82)	Schizophrenia and spectrum	Schizophrenia and spectrum
Sexual desire	Loss of libido	Sex drive	Libido change	Frequency engaging in sexual activity Desire to engage in sexual activity Frequency engaging in sexual thoughts Enjoying books, movies, music or artwork with sexual content Pleasure from thinking and fantasizing about sex	Loss of sexual interest in the opposite sex Less interested in sexual matters	Loss of libido
Arousal: erection	Erectile problems	Obtain and maintain erection	Erection change	Erection: frequency Erection: getting erection Erection: maintenance Erection: priapism	More problems related to erection	Erectile dysfunction
Arousal: vaginal lubrication		Lubrication	Lubrication change	Vaginal lubrication		Vaginal lubrication dysfunction

Table 1. Comparison of ASFQ, ASEX, PRSexDQ, ANNSERS, CSFQ-14 and NSFQ (continued)

	ANNSERS	ASEX	ASFQ	CSFQ-14	NSFQ	PRSexDQ
Arousal: other	Arousal problems	How sexually aroused are you?	Dyspareunia change	Arousal: frequency Arousal: easiliy aroused Becoming aroused and then lose interest	Decreased sexual arousal	
Orgasm: orgasm	Orgasmic difficulties/ delayed ejaculation	Reach orgasm	Orgasm change	Orgasm: frequency Orgasm: ability to have orgasm Orgasm: painful		Delayed orgasm/ ejaculation
Orgasm: ejaculation	Reduced ejaculatory volume/intensity		Ejaculation change	Ejaculation: frequency Ejaculation: ability	More problems related to ejaculation	Lack of orgasm/ ejaculation
Orgasm: other		Orgasms satisfying?		Pleasure from orgasms		
Other questions about sexual functioning				Enjoyment/pleasure of sex life	Less sexually confident	Patients' tolerance to the sexual dysfunction Change in sexual functioning since current medication? Change spontaneously reported?
Menstrual disturbance	Change in menstruation		Menstrual disturbance		Menstrual cycle irregularities	
Gynaecomastia			Swelling breasts/nipples		Pulsating sensation in breast area	
Galactorrhoea			Milk from breasts/nipples		Milky discharge from nipples	

ANNSERS = Antipsychotic Non-Neurological Side Effects Rating Scale; ASEX = Arizona Sexual Experience Scale; ASFQ = Antipsychotics and Sexual Functioning Questionnaire; CSFQ-14 = Changes in Sexual Function Questionnaire-14; NSFQ = Nagoya Sexual Function Questionnaire; PRSexDQ = Psychotropic-Related Sexual Dysfunction Questionnaire.

Reliability

Internal consistency has not been determined in the ANNSERS, is modest in the PRSexDQ and is good in the other questionnaires. Only for the ASFQ and ANNSERS the inter-rater reliability was described, despite the fact that of the ASEX, CSFQ-14 and PRSexDQ, clinician-rated versions are also available. Only for the ASFQ and NSFQ the test-retest reliability was described. Data are shown in table 2.

Table 2. Reliability of questionnaires measuring sexual functioning in patients using antipsychotics

	Internal consistency (Crohnbach's alpha)*	Inter-rater reliability (correlation)	Test-retest reliability (correlation)
ANNSERS	-	0.84-1.00	-
ASEX	0.90	-	-
ASFQ	0.84	0.72-0.87	0.76
CSFQ-14	0.90	-	-
NSFQ	0.76-0.79	-	0.92
PRSexDQ	0.68	-	-

ANNSERS = Antipsychotic Non-neurological Side Effects Rating Scale; ASEX = Arizona Sexual Experience Scale; ASFQ = Antipsychotics and Sexual Functioning Questionnaire; CSFQ-14 = Changes in Sexual Function Questionnaire-14; NSFQ = Nagoya Sexual Function Questionnaire; PRSexDQ = Psychotropic-Related Sexual Dysfunction Questionnaire.
* Cronbach's alpha for the questionnaire as a whole.

Validity

Face validity was tested by comparing the content of the six questionnaires. Data are described in table 1. The CSFQ-14 is the most extensive questionnaire, with several questions per stage of sexual functioning. The ASFQ and PRSexDQ also cover all stages of sexual functioning. The ASEX does not specifically ask for ejaculation. The ANNSERS and NSFQ do not ask specifically about vaginal lubrication, but ask a general question about arousal in women. The NSFQ also does not include a question about orgasm.

The ASFQ and PRSexDQ ask specifically for attribution of sexual dysfunction to the use of the current medication, in an attempt to distinguish sexual side effects from other causes of sexual dysfunction. Both questionnaires have an introductory phrase that explains that in some people sexual functioning changes due to medication, which may help patients to report on aspects of their sexual functioning. Other instruments ask whether change in sexual functioning has occurred in one or more questions, but do not ask whether any change can be attributed to the use of medication (ANNSERS, CSFQ-14, NSFQ), while the ASEX does not ask for change, nor for attribution to medication. The characteristics of the questionnaires that cover all stages of sexual functioning (ASFQ, CSFQ-14, PRSexDQ) are described in table 3 and will help to make a purpose-oriented choice.

Table 3. Characteristics of questionnaires that cover all stages of sexual functioning (ASFQ, CSFQ-14, PRSexDQ)

Characteristics	ASFQ	CSFQ-14	PRSexDQ
Clinician-administered	Yes	No	Yes
Self-report	No	Yes	Yes
Time frame	Yes	No	Yes
Measuring change	Yes	No	Yes
Measuring sexual functioning related to medication	Yes	No	Yes
Measuring improvement and deterioration	Yes	No	No
Measuring symptoms of hyperprolactinemia	Yes	No	No
Measuring frequency of sexual activity (to a certain degree)	No	Yes	No
Short	Yes	No	Yes
Easy	Yes	No	Yes
Detailed	No	Yes	No

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; CSFQ-14 = Changes in Sexual Function Questionnaire-14; PRSexDQ = Psychotropic-Related Sexual Dysfunction Questionnaire.

Although, strictly spoken, symptoms of hyperprolactinemia (e.g. menstrual irregularities, galactorrhoea and gynaecomastia) are not disorders of sexual functioning, these can be relevant issues for patients using antipsychotics as these medications can cause hyperprolactinemia, which is thought to be a factor in antipsychotic-induced sexual dysfunction. Therefore, some of the questionnaires ask for these aspects. The ASFQ and NSFQ ask for all three aspects, while the ANNSERS only identifies a change in menstruation pattern.

Convergent validity has been determined in all questionnaires by comparison with another questionnaire. Unfortunately, only the ASFQ has been compared with one of the other validated questionnaires (ASEX), while all other validated questionnaires were compared with unvalidated questionnaires. Data about convergent and divergent validity are described in table 4. Some correlations are negative, because in some questionnaires a lower score reflects better sexual functioning, while in others higher scores are better.

Sensitivity, specificity, positive and negative predictive values have only been described in the study of the ASEX and CSFQ-14. In the study of the ASEX, sensitivity, specificity, and positive and negative predictive values were determined for the one-item screening question (85%, 64%, 83%, 76%, respectively). The one-item screening question was 'Have your prescribed drugs caused problems with your sexual functioning recently?', with answering options 'yes' or 'no'. This answer was compared with the ASEX cut-off scores for sexual dysfunction (total ASEX score ≥ 19, or any one item with an individual score ≥ 5 or any three items with individual scores ≥ 4). The study of the CSFQ-14 also compared a screening question (Clinical Global Impression with a cut-off score (cut-off score 43), leading to a sensitivity of 93%, a specificity of 63%, a positive predictive value of 74% and a negative predictive value of 87%.

Table 4. Convergent and divergent validity: mean correlations and range on item niveau

	Convergent validity							Divergent validity
	DISF-SR	**1-item screening**	**ASEX**	**SRA**	**CGI-SF**	**VAS-SFS**	**UKU**	**JESS**
ANNSERS	-0.64 *	-	-	-	-	-	-	-
ASEX	-	-0.41*	-	-	-	-	-	-
ASFQ	-	-	0.77 ** (0.54-0.98)	0.56 ** (0.16-0.88)	-	-	-	-
CSFQ-14	-	-	-	-	-0.71/-0.74	0.33-0.57	-	-
NSFQ	-	-	-	-	-	-	0.69-0.85	0.16-0.45
PRSexDQ	-	-	-	-	0.73 * (0.37-0.61)	-	-	-

ANNSERS = Antipsychotic Non-Neurological Side Effects Rating Scale; ASEX = Arizona Sexual Experience Scale; ASFQ = Antipsychotics and Sexual Functioning Questionnaire; CGI = Clinical Global Impression of sexual functioning; CSFQ-14 = Changes in Sexual Function Questionnaire-14; DISF-SR = Derogatis Interview for Sexual Functioning – self-report version; JESS = Japanese version of the Epworth Sleepiness Scale; NSFQ = Nagoya Sexual Function Questionnaire; PRSexDQ = Psychotropic-Related Sexual Dysfunction Questionnaire; SRA = Subjects' Response to Antipsychotics; VAS-SFQ = Visual Analog Scale for Sexual Functioning Satisfaction; UKU = Udvalg for Kliniske Undersøgelser Side Effect Rating Scale.
* = correlation of total scores; ** = based on mean of correlations of items.

Discussion

We identified six validated instruments for the assessment of sexual functioning in patients using antipsychotics, namely the ANNSERS, ASEX, ASFQ, CSFQ-14, NSFQ, and PRSexDQ.

The internal consistency of the questionnaires was found to be modest to good. Few data are available about inter-rater reliability (only for ANNSERS and ASFQ) and test-retest reliability (only for ASFQ and NSFQ). Only for the ASFQ all aspects of reliability have been described.

Convergent validity was modest to good in all of the six questionnaires, although it has to be noted that most questionnaires were compared with non-validated instruments and only one comparison was made between two of the six validated instruments that were identified in our search. Few data are available about divergent and predictive validity.

Especially for questionnaires measuring change in sexual functioning, it is important to mention a clear time frame and to have the ability to report deterioration as well as improvement. For instance, some patients using aripiprazole have reported an improvement in sexual functioning (de Boer, et al. 2011, Mir, et al. 2008). The ASFQ is the only questionnaire in which deterioration as well as improvement of sexual functioning can be assessed.

The ASFQ, CSFQ-14, and PRSexDQ cover all stages of sexual functioning. In the ASEX, ANNSERS, and NSFQ questions on some of the stages are lacking. This leads not only to a lack of information, but may also lead to increased concerns in patients who are experiencing a decreased or absent ejaculatory volume, lubrication problems, or orgasm problems. It might become more difficult for them to speak about these matters to their clinician and to discuss possible treatment strategies.

Although, strictly spoken, symptoms of hyperprolactinemia are not disorders of sexual functioning, it is important to ask for these symptoms in patients using antipsychotics. The ASFQ, NSFQ and ANNSERS ask for these symptoms, which is thought to be an advantage of these questionnaires.

Even though psychometric properties have been assessed for the six retrieved instruments, it is unfortunate that comparisons between these instruments are mostly lacking. Future research is needed to compare the psychometric properties of these instruments in more detail. The information in this review can help to formulate specific questions for research. Subsequently, a gold standard can be chosen for measuring sexual functioning in patients using antipsychotics and/or patients with schizophrenia.

Conclusions and recommendations

We described six instruments for the assessment of sexual functioning in patients using antipsychotics and/or patients with a psychotic disorder. For research as well as for clinical purposes it is preferable to use a short instrument which covers all stages of sexual functioning. The ASFQ, CSFQ-14, and PRSexDQ are meeting these criteria. Data in table 3 can be helpful to make a choice, depending on the clinician's purpose.

Because the ASFQ and PRSexDQ ask for changes in sexual functioning due to medication, these are the most appropriate instruments for intervention studies in which an antipsychotic is started or switched. Both questionnaires are clinician-administered. An advantage of the ASFQ is that improvement as well as deterioration can be scored and the fact that questions about symptoms of hyperprolactinemia are also included.

When a self-report questionnaire is desired for the assessment of sexual functioning, the CSFQ-14 is appropriate. The CSFQ-14 asks more about how often the patient has specific problems during sexual activity, while the other five described questionnaires ask more about the experienced severity of symptoms. If it is desired to measure a change in frequency of specific problems during sexual activity, the CSFQ-14 can be administered at baseline and at a later time. However, the CSFQ-14 is longer and more detailed than the other questionnaires. The ASEX, ANNSERS and NSFQ are shorter than the CSFQ-14, but do not cover all stages of sexual functioning and are therefore less appropriate for the evaluation of sexual functioning.

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Chapter 5

The Antipsychotics and Sexual Functioning Questionnaire (ASFQ): preliminary evidence for reliability and validity

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Abstract

The aim of this study is to describe the psychometric properties of the Antipsychotics and Sexual Functioning Questionnaire (ASFQ). Internal reliability, test-retest reliability, inter-rater reliability, validity and sensitivity to change were calculated in a sample of 30 patients with schizophrenia or a schizophrenia spectrum disorder using antipsychotics. The ASFQ is a semi-structured interview, with good face validity and content validity, that takes on average about 10 minutes to complete. The ASFQ has good internal reliability (Cronbach's alpha 0.84) and good test-retest reliability (mean Spearman's rho = .76). The inter-rater reliability is good for questions about libido, orgasm, erection and ejaculation. Correlation coefficients for calculating convergent validity were modest to good when comparing the ASFQ with the corresponding items on the Subject's Response to Antipsychotics questionnaire (SRA) and the Arizona Sexual Experience Scale (ASEX). Based on preliminary evidence, it can be concluded that the Antipsychotics and Sexual Functioning Questionnaire has reasonable reliability and is available for clinical use and research.

Introduction

Sexual dysfunction in patients with schizophrenia may be related to the disease itself, as well as to psychosocial factors, physical health and the use of psychotropic medications (Aizenberg, et al. 1995, Dickson & Glazer. 1999). Antipsychotics have been associated with sexual dysfunction, such as decreased libido, erectile dysfunction, anorgasmia, and decreased ejaculatory volume (Knegtering, et al. 2008, Smith. 2003). Besides postsynaptic dopamine antagonism, prolactin elevation may be a factor in the pathogenesis of antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008).

Sexual side effects have a considerable impact on quality of life and are a major factor in non-adherence to prescribed antipsychotic drugs (Olfson, et al. 2005). Sexual dysfunction is rarely reported spontaneously, leading to underestimation of its prevalence. In contrast, studies using structured interviews or questionnaires show that 16 to 60% of the patients experience sexual dysfunction (Knegtering, et al. 2008, Serretti & Chiesa. 2011).

Several questionnaires on the sexual side effects of antipsychotics have been developed but psychometric properties have been reported for only a few instruments, namely the Antipsychotic Non-neurological Side Effects Rating Scale (ANNSERS) (Mahmoud, et al. 2011, Ohlsen, et al. 2008), the Arizona Sexual Experience Scale (ASEX) (Byerly, et al. 2006), the Changes in Sexual Function Questionnaire-14 (CSFQ-14) (Garcia-Portilla, et al. 2011), the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo & Rico-Villademoros. 2008) and the Nagoya Sexual Function Questionnaire (NSFQ) (Kikuchi, et al. 2011). Because of the scarcity of validation and standardization, there is no gold standard to evaluate antipsychotic-induced changes in sexual functioning. This makes it difficult to compare studies and may partly explain why results vary.

At the start of our studies, no instruments on this topic had been validated. We felt that a new instrument was needed in order to evaluate antipsychotic-induced changes in sexual functioning. Therefore, the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) was developed (see appendix) (Knegtering. 2003). To increase reliability and to take account of the cognitive abilities of patients with a psychotic disorder, a semi-structured interview was constructed with questions phrased in a non-leading and easily understandable way. Items for men and women were included, covering the main areas of sexual functioning. Furthermore, both improvement and deterioration of sexual functioning could be scored. The interview was intended to help clinicians discuss sexual side effects with their patients more easily. The aim of this study is to describe the psychometric properties of the Antipsychotics and Sexual Functioning Questionnaire (ASFQ).

Methods

Participants

Inclusion criteria for patients in this methodological study about reliability and validity of the ASFQ were the use of an antipsychotic for at least four weeks, being between 18 and 50 years old, and having a clinical diagnosis of schizophrenia or a schizophrenia spectrum disorder (DSM-IV-TR). The majority of participants who participated in this study were inpatients. All patients gave oral and written informed

consent to participate. We used two different patient samples (with the same inclusion criteria), in line with the specific aims of the different elements of this study, namely the first sample for internal reliability, test-retest reliability and validity, and the second sample for inter-rater reliability. The characteristics of the population of the first part of this study will be described in more detail, as this sample was used for most calculations in this study.

Procedure for internal reliability, test-retest reliability and validity (sample 1)

The Antipsychotics and Sexual Functioning Questionnaire (ASFQ), the Arizona Sexual Experience Scale (ASEX) (Byerly, et al. 2006, McGahuey, et al. 2000) and the Subject's Response to Antipsychotics questionnaire (SRA) (Wolters, et al. 2006) were assessed in 30 patients. For test-retest reliability we assessed all patients on Day 1 and Day 3, which time frame was thought to be sufficient to limit recall bias without too much fluctuation in sexual performance. Internal reliability reflects the coherence between items within an instrument. Validity of the ASFQ was calculated by comparing the ASFQ with the corresponding items of the ASEX and the SRA. At the start of the study, the ASEX was the only available questionnaire for assessment of sexual functioning that had been validated in patients with schizophrenia or a related psychotic disorder. The SRA is a detailed questionnaire about the side effects of antipsychotics. The SRA has been validated as a whole questionnaire, but not specifically for its individual questions on sexual functioning.

Procedure for inter-rater reliability (sample 2)

Inter-rater reliability represents the correlation between raters. Thirty videos of ASFQ interviews were assessed by six raters. Of nine patients, two videos were available with a time interval of four to six weeks, leading to a total of 18 videos. The other 12 videos contained interviews of 12 separate patients. The videos were mixed in a random order to prevent that the raters recall on a specific patient.
The videos were assessed by the raters in two sessions. To prevent a possible drift in rating during the study, an instruction on the assessment of the ASFQ was given to the raters before both sessions. Also, all raters viewed the videos in the same order.

Description of assessment tools

The ASFQ contains seven items for men and nine for women on sexual functioning (see appendix). In order to ensure consistency in the structure of the ASFQ, each item offers scoring possibilities for the improvement or deterioration of symptoms. Each item can be scored as 0 (unknown); 1 (significantly decreased); 2 (mildly decreased); 3 (unchanged); 4 (mildly increased); 5 (significantly increased). Items on the ASFQ included sexual desire (libido), orgasm, erectile dysfunction, ejaculatory dysfunction, vaginal lubrication and pain during intercourse (dyspareunia). Also included, but not within the scope of this study on sexual functioning, were amenorrhoea, dysmenorrhoea, galactorrhoea and gynaecomastia. The ASFQ guides interviewers in introducing the subject of sexual side effects to the patient in a normalizing and non-directive way. At the beginning of the interview, some basic clinical and demographic information is solicited. After a general introduction, questions are provided for each item.

The interviewer is instructed to continue questioning, while probing for sexual performance related to (changes in) medication, until the answers are clear enough for scoring. The interview covers the past four to six weeks.

The ASEX is a five-item self-report questionnaire that has been validated in patients with psychotic disorders, in which each question has six possible answers. The first question is 'how strong is your sex drive?' (1= extremely strong, 2= very strong, 3= somewhat strong, 4=somewhat weak, 5= very weak, 6= no sex drive). The next questions are 'how are you sexually aroused?', 'can you easily get and keep an erection?' (question for males), 'how easily does your vagina become moist or wet during sex?' (question for females), 'how easily can you reach an orgasm?' and 'are your orgasms satisfying?'. (Byerly, et al. 2006).

The SRA is a 74-item self-report questionnaire on the side effects of antipsychotics (Wolters, et al. 2006). In this study, we used a 76-item version of this questionnaire to which two more items on sexual functioning have been added. Five questions are for men (decreased libido, decreased orgasm, decreased erection, decreased ejaculation, increased libido), and four for women (decreased libido, decreased orgasm, decreased lubrication, increased libido). These questions can be answered with 0 (no), 1 (yes, to a certain degree) or 2 (yes, to a high degree).

Statistical analysis

Information on analyses and desired correlation values for internal consistency, test-retest reliability and validity are mentioned in the results. As our questionnaire has one question per stage of sexual functioning, this makes a factor analysis less appropriate

Inter-rater reliability was calculated with weighted kappa and a latent variable model. Values of kappa 0.41-0.60 are considered as moderate agreement, 0.61-0.80 as substantial agreement and 0.81-1.00 as outstanding agreement (Landis & Koch. 1977). For each question on the ASFQ, we calculated a weighted kappa between any pair of observers, using the Fleiss-Cohen quadratic weight. Six observers form fifteen possible pairs of observers, resulting in fifteen kappa values. These fifteen kappa values were averaged to obtain a first overall measure of agreement and accompanied with the range to indicate the differences in agreement between pairs of observers. A more formal approach used a latent variable model to determine an intraclass correlation coefficient (ICC). The latent variable model was applied to the two general questions for males and females simultaneously, and to the two additional questions for males and females separately.

A bivariate latent variable was applied to generate a latent variable for subjects per question and an ICC value, with an approximate 95% confidence interval using the delta method, was calculated for each question separately, using its individual variance component. A systematic observer effect was tested with a likelihood ratio test, and for the two general questions, the model was corrected for gender.

Results

Demographic and clinical characteristics

The study consisted of 30 patients, of whom 21 were male (68%). All had been diagnosed with schizophrenia or a schizophrenia spectrum disorder. The mean age was 30.0 years (SD 10.7), with a range

of 18 to 50 years. The duration of use of the current antipsychotic was one to three months in seventeen patients (57%), three to twelve months in six patients (20%), one to two years in two patients (7%) and >2 years in five patients (17%). Seventeen patients (57%) were experiencing one or more types of sexual dysfunction, measured with the ASFQ. Demographic and clinical characteristics are shown in Table 1. The average time interviewers needed to complete the ASFQ was 10 minutes.

Table 1. Demographic and Clinical Characteristics

Characteristic/Variable	N = 30
Age (years), mean (SD)	30.0 (10.7)
Sex, n (%)	
Male	21 (70.0)
Female	9 (30.0)
DSM-IV diagnosis, n (%)	
Schizophrenia	11 (36.7)
Schizophreniform disorder	2 (6.7)
Schizoaffective disorder	8 (26.7)
Other psychotic disorder	8 (26.7)
Bipolar I disorder	1 (3.3)
Antipsychotic medication, n (%)	
Risperidone	8 (26.7)
Olanzapine	7 (23.3)
Clozapine	4 (13.3)
Aripiprazole	4 (13.3)
Quetiapine	3 (10.0)
Paliperidone	2 (6.7)
Sertindole	1 (3.3)
Pimozide	1 (3.3)
Duration use of current antipsychotic, n (%)	
<3 months	17 (56.7)
3-12 months	6 (20.0)
1-2 year	2 (6.7)
>2 years	5 (16.7)
Duration use of antipsychotics during life, n (%)	
<3 months	6 (20.0)
3-12 months	10 (33.3)
1-2 year	2 (6.7)
>2 years	12 (40.0)
Sexual dysfunction measured by ASFQ, n (%)	
One or more sexual dysfunctions	17 (56.7)

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; r = Spearman's rho.

Internal consistency

For our setting with only six items, Cronbach's alpha values larger than 0.70 are considered as "good" (Cicchetti. 1994, Ponterotto & Ruckdeschel. 2007). On the other hand, we believe that values larger than 0.90 are considered too large, since this may indicate that some of the items on sexual function are redundant (Streiner and Norman, 2008).

The Cronbach's alpha was calculated only for the items libido, orgasm, erection, and ejaculation, since we had too few women in our study to include the items lubrication and dyspareunia. Cronbach's alpha of the combined four items of the ASFQ for males was 0.84. Cronbach's alpha was 0.80 when the item on libido was deleted, 0.73 when the item on orgasm was deleted, 0.83 when the item on erection was deleted and 0.84 when the item on ejaculation was deleted.

Test-retest reliability

Test-retest reliability was assessed by calculating correlations of the ASFQ on Day 1 and Day 3 using Spearman's rho. Correlations of 0.30-0.70 are considered as moderate and 0.70-1.00 as strong.

The correlation coefficients of the items of the ASFQ on Day 1 and Day 3 are: libido r = .67, orgasm r = .85, erection r = .53, ejaculation r = .99, lubrication r = .89, sexual intercourse r = 1.00. The correlation coefficient for dyspareunia could not be calculated because of the small number of women who had sexual intercourse, and it should also be noted that the number of patients was low for the items on lubrication and sexual intercourse (n = 9). The mean correlation coefficient of the items with a sufficient number of patients (libido, orgasm, erection and ejaculation) is r = .76. Data on test-retest reliability are described in Table 2.

Table 2. Test-retest data of ASFQ: correlations per item

Item of ASFQ	r	p
Libido (♂♀, n=30, 100%)	.67	.00
Orgasm (♂♀, n=30, 100%)	.85	.00
Erection (♂, n=21, 70%)	.53	.01
Ejaculation (♂, n=21, 70%)	.99	.00
Lubrication (♀, n=9, 30%)	.89	.00
Sexual intercourse (♀, n=9, 30%)	1.00	.00
Dyspareunia (♀, n=5, 17%)	-	-

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; r = Spearman's rho.

Inter-rater reliability

The results of Fleiss-Cohen's weighted kappa's are presented in Table 3. A negative kappa is possible and would indicate that a pair of observers has an agreement that is less than a random allocation. It should be noted that the results for questions about lubrication and dyspareunia are based on only seven female subjects and are therefore not very reliable. On the other hand, the average kappa values

for questions about libido, orgasm, erection and ejaculation indicate that there is moderate to good agreement among all six observers.

The intraclass correlation coefficient (ICC) values based on the latent variable model applied to the questions are provided in Table 4. These values are slightly different from the weighted kappa values, but they paint a similar picture. There is reasonable to good agreement among observers for questions about libido, orgasm, erection and ejaculation. Lubrication seems to be more difficult to assess, probably because the estimate is based on only seven subjects. The question on dyspareunia deviates from the weighted kappa value, and is possibly more realistic considering the low number of subjects involved.

The likelihood ratio test indicated that a systematic observer effect was not significant (libido and orgasm: p=0.78; erection and ejaculation: p=0.09; lubrication and dyspareunia: p=0.11). A gender effect was observed for the questions on libido and orgasm (p=0.03), indicating that males and females answer these questions differently. If the (non-significant) systematic observer effects were added to the random observer effect, the ICC calculations would only be marginally lower (at most 0.4% in absolute sense). This indicates that the systematic differences in observers are statistically non-significant and clinically irrelevant.

Table 3. Average Fleiss-Cohen weighted Kappa's for pairs of observers per item on the ASFQ

Question	Target gender	Average Kappa	Minimum Kappa	Maximum Kappa
Libido	Both	84.1%	66.4%	100%
Orgasm	Both	61.9%	25.5%	91.3%
Erection	Males	71.4%	29.9%	94.1%
Ejaculation	Males	66.8%	21.5%	100%
Lubrication	Females	11.6%	-47.4%	100%
Dyspareunia	Females	100%	100%	100%

ASFQ = Antipsychotics and Sexual Functioning Questionnaire.

Table 4. ICC estimates based on a bivariate latent variable model applied to ASFQ questions 8 and 9, 12 and 13, and 17 and 19 separately

Question ASFQ	Target gender	ICC	Confidence Interval
8. Libido	Both	86.8%	[78.4% ; 95.1%]
9. Orgasm	Both	83.1%	[73.2% ; 92.9%]
12. Erection	Males	79.6%	[70.9% ; 88.2%]
13. Ejaculation	Males	71.6%	[58.6% ; 84.5%]
17. Lubrication	Females	0%	NA
19. Dyspareunia	Females	64.2%	[27.8% ; 100%]

ASFQ = Antipsychotics and Sexual Functioning Questionnaire ; ICC = intraclass correlation coefficient.

Validity

The face validity of the ASFQ appears to be good, based on the wording and content of the items. Interviewers and patients did not experience problems understanding or completing the questionnaire. Clinicians found the interview helpful in discussing sexual side effects with patients. The content validity also appears to be good, as the questionnaire covers all stages of sexual functioning.

Convergent validity of the ASFQ was assessed by performing correlations (using Spearman's rho) between ASFQ items and corresponding items on the ASEX and SRA. Table 5 shows which items are compared with each other, classified by phase in the sexual response cycle, and Table 6 provides the correlations of the ASFQ with items on the SRA and the ASEX.

When comparing the ASFQ with the SRA, the highest correlations were found for lubrication (r = .98), libido (r = .77) and orgasm (r = .76), and the lowest correlations for ejaculation (r = .58) and erection (r = .54).

A similar pattern emerged when comparing the ASFQ items for lubrication, orgasm and erection with the corresponding items of the ASEX (lubrication r = .88; orgasm r = .71; erection r = .50). However, the ASEX Question 1 ('how strong is your sex drive?') and 2 ('how are you sexually aroused?') did not correlate to any item of the ASFQ, and Question 5 ('are your orgasms satisfying?') correlates most (but not very convincingly) with the item on the ASFQ about libido (r = .38; p = .04). This could have been expected, because in terms of their content, these three questions (especially Questions 2 and 5) could not be properly linked to a corresponding question on the ASFQ, as described in Table 5.

Table 5. Corresponding items of ASFQ, ASEX and SRA

		Items ASFQ	Items ASEX	Items SRA
Libido		Libido change	Sex drive	Decreased libido Increased libido
Arousal				
-	**Erection**	Erection change	Get and keep erection	Decreased erection
-	**Lubrication**	Lubrication change	Lubrication	Decreased lubrication
-	**Other**	Dyspareunia	Sexual arousal	
Orgasm				
-	**Orgasm**	Orgasm change	Reach orgasm	Decreased orgasm
-	**Ejaculation**	Ejaculation change		Decreased ejaculation
-	**Other**		Satisfaction orgasms	

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; ASEX = Arizona Sexual Experience Scale; SRA = Subject's Response to Antipsychotics questionnaire.

Table 6. Correlations between ASFQ and SRA/ASEX

Items ASFQ	Items SRA	r	p
Libido change	Decreased libido	.77	.00
Orgasm change	Decreased orgasm	.76	.00
Erection change	Decreased erection	.54	.01
Ejaculation change	Decreased ejaculation	.58	.01
Lubrication change	Decreased lubrication	.98	.00
Items ASFQ	**Items ASEX**	**r**	**p**
Libido change	Sex drive (q. 1)	.16	.39
Erection change	Get and keep erection (q. 3.m)	.50	.02
Lubrication change	Lubrication (q. 3.f)	.88	.00
Orgasm change	Reach orgasm (q. 4)	.71	.00

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; SRA = Subject's Response to Antipsychotics questionnaire; ASEX = Arizona Sexual Experience Scale; r = Spearman's rho.

Discussion

Sexual dysfunction during antipsychotic use is rarely reported spontaneously, but occurs frequently, has a considerable impact on quality of life and is probably a major factor in non-adherence to prescribed antipsychotic drugs. For patients and clinicians, as well as for researchers, it is important to investigate these side effects adequately. Unfortunately, most questionnaires used in trials have not been validated in this patient category.

The ASFQ is one of six validated questionnaires on sexual functioning in patients with psychotic disorders, together with the ASEX (Byerly, et al. 2006), the ANNSERS (Mahmoud, et al. 2011, Ohlsen, et al. 2008), the CSFQ-14 (Garcia-Portilla, et al. 2011), the PRSexDQ (Montejo & Rico-Villademoros. 2008) and the NSFQ (Kikuchi, et al. 2011). For most questionnaires, internal reliability and convergent validity have been described, but the description of other psychometric properties is lacking. Also, the ASEX, ANNSERS and NSFQ do not cover all stages of sexual functioning.

The ASFQ can be used by clinicians or nurses. The questionnaire asks about the most important aspects of sexual functioning and is brief. This is an advantage for clinicians as well as for patients with psychotic disorders, who often experience problems with cognitive functioning and concentration.

This preliminary study suggests that the ASFQ has good test-retest reliability, which suggests that patients understand the questions well, and the structured manner of the instrument ensures that the interviewer asks the question in the same way each time. Only the item about erection had a relatively low correlation coefficient (r = .53, Table 2). An explanation may be that the reported erectile functioning may have changed because of recent experiences, within the time interval in which test-retest reliability was measured.

This study suggests that the inter-rater reliability is good. It should be noted that for this study, the interviewers had received prior instruction on how to use the ASFQ. If other researchers plan to use the ASFQ in the future, we would also advise them to instruct the interviewers in advance.

The limitations of this study are its relatively small sample size (except for inter-rater reliability) and the fact that the degree of psychotic symptoms was not assessed. Because the number of women was small (n=9), the results of the female items should be viewed with some caution. Also, the duration of the use of the antipsychotic differs between patients, but based on the literature, we think that the duration of use of antipsychotic medication does not affect the prevalence of sexual dysfunction (Malik, et al. 2011). In a previous study, the ASFQ has shown to be sensitive to change in patients who were switched from a prolactin-elevating antipsychotic to a prolactin-sparing antipsychotic (Knegtering. 2003). Also, the ASFQ has been used in three open-label randomized trials, which compared quetiapine and risperidone (Knegtering, et al. 2004), olanzapine and risperidone (Knegtering, et al. 2006) and aripiprazole and risperidone (de Boer, et al. 2011) and also in a cross-sectional study (Knegtering. 2003). In these four studies, highly comparable rates of sexual dysfunction were found for patients treated with risperidone, which further contributes to the reliability of the ASFQ. Different rates of sexual dysfunction were found for the different antipsychotics, corresponding with data in the literature (Serretti & Chiesa. 2011).
The ASFQ is available in the public domain for clinical use and research (see appendix). The questionnaire guides patients and clinicians in discussing sexual functioning. Not every clinician or patient feels comfortable talking about sexual functioning and this instrument may facilitate this exchange and lead to further questions from the patient. If a patient has sexual side effects, it is important to weigh the burden of these side effects and discuss alternative treatment options (Nunes, et al. 2012).

Conclusion

The Antipsychotics and Sexual Functioning Questionnaire (ASFQ) is a semi-structured interview that is designed to assess and discuss possible sexual side effects of antipsychotics in all phases of sexual functioning among patients with psychotic disorders, and is able to rate deterioration as well as improvement of sexual functioning. The assessment takes on average 10 minutes.
The ASFQ has good internal reliability (Cronbach's alpha 0.84) and good test-retest reliability (mean Spearman's rho = .76). The inter-rater reliability is good for questions about libido, orgasm, erection and ejaculation. Further, the questionnaire has a satisfying face validity, content validity and convergent validity. Based on preliminary evidence, it can be concluded that the ASFQ has reasonable reliability and is available for clinical use and research.

Appendix 1: English version of the ASFQ

Antipsychotics and Sexual Functioning Questionnaire (ASFQ)©

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H. Knegtering, S. Castelein and M.K. de Boer

Data of the patient:

- Name: ……

- Date of birth, sex: ……(dd/mm/yyyy), m/f

- Name of hospital, patient number: ……

- Date: ….…… (dd/mm/yyyy)

Instruction for interviewers:

Please read out the text or questions that are in bold to the patient. Continue questioning until the answer is clear or no further clarification can be obtained. Score changes in sexual functioning that may be related to the use of this antipsychotic. Compare current sexual functioning with previous sexual functioning during lifetime.

Interpretation of the following answering options:

0. Unknown will be scored if patients are not willing or unable to answer the question, or if no clear answer can be obtained despite thorough questioning.
1. Significantly decreased will be scored if the patient experiences an extreme decrease in sexual functioning and/or if the patient is suffering as a consequence of the decrease in sexual functioning.
2. Mildly decreased will be scored if the patient experiences a decrease in sexual functioning, but does not suffer severely as a consequence.
3. Unchanged will be scored if there is no change in sexual functioning caused by the use of antipsychotic medication. Please note the following: some patients acknowledge that they have never had sexual interests. If this is the case and this did not change, the patient scores unchanged.
4. Mildly increased will be scored if the patient experiences an increase in sexual functioning since the use of the current antipsychotic.
5. Significantly increased will be scored if the patient experiences a strong increase in sexual functioning since the use of the current antipsychotic.

Questions:

1. Indication for use of the current antipsychotic:

……

……

2. Please list all medication taken prior to the current antipsychotic (with dosage; including non-antipsychotics):

……

……

3. For how long did you use the previous antipsychotic?

1. No use of any other antipsychotic in the month before the current antipsychotic
2. < 1 week
3. 1-2 weeks
4. 2-6 weeks
5. 6 weeks – 3 months
6. > 3 months

4. What was the main reason for quitting the previous antipsychotic?

1. Another psychotic episode
2. Not effective
3. Side effects
4. Scientific research
5. Other, namely……

5. Current medication (antipsychotic and co-medication, including dosage):

……

……

……

6. Can you describe the experienced result(s) of treatment with the current antipsychotic medication?

(Score is based on the opinion of the patient and the general clinical impression on the interviewer.)

0. Unknown
1. Significant deterioration
2. Mild deterioration
3. Unchanged
4. Mild improvement
5. Significant improvement

7. Which side effects did you experience from the current antipsychotic?

(Describe side effects mentioned spontaneously by the patient that may be related to the antipsychotic used during the past four weeks. Please, do not describe side effects here that are mentioned by the patient in a later phase of the interview.)

……

……

……

Questions about sexual functioning:

Some patients notice changes in their sexual desires and functioning when using antipsychotics. Changes can be noticed during sexual intercourse with a partner or during sexual self-stimulation. Some patients notice an improvement in sexual functioning, others experience a deterioration. The following questions ask about your condition over the last 4-6 weeks.

♂♀ **8. Sexual desire:**

Have you noticed a change in sexual desire since using the current antipsychotic?

0. Unknown
1. Significantly decreased
2. Mildly decreased
3. Unchanged
4. Mildly increased
5. Significantly increased

♂♀ **9. Orgasm:**

Has your ability to achieve orgasm (come) changed since using the current antipsychotic?

0. Unknown
1. Significantly decreased
2. Mildly decreased
3. Unchanged
4. Mildly increased
5. Significantly increased

♂♀ **10. Galactorrhoea:**

In the past four to six weeks, did milk leak from your breasts/nipples?

0. Unknown
1. Yes
2. No

♂♀ **11. Swelling of breasts:**

In the last four to six weeks, did you notice a swelling of your breasts and/or nipples?

0. Unknown
1. Yes
2. No

Questions for men

For women, continue to question 15.

♂ **12. Erection:**

Has your ability to have an erection changed since using the current antipsychotic? (e.g. stiffness of the penis or the time required to obtain and maintain an erection)

(Instruction: priapism is an unwanted erection that is painful and lasts for over one hour without any stimulation. Priapism must be treated immediately.)

0. Unknown
1. Significantly decreased
2. Mildly decreased
3. Unchanged
4. Mildly increased
5. Significantly increased
6. Priapism

♂ **13. Ejaculation:**

Have you noticed a change in the volume of ejaculate (sperm) since using the current antipsychotic? (e.g. less or more ejaculate than normal, or was ejaculation absent?)

0. Unknown
1. Significantly decreased
2. Mildly decreased
3. Unchanged
4. Mildly increased
5. Significantly increased

♂ **14. Sexual intercourse:**

Did you have sexual intercourse with a partner in the last four to six weeks?

1. Yes
2. No

End of questionnaire for men

Questions for women

♀ **15. Contraception:**

Are you using hormonal contraception?

0. Unknown
1. Yes. Which method?
   (e.g. birth control pill, birth control hormonal injection, hormonal intrauterine device, intravaginal hormonal ring)……
2. No

♀ **16. Menstruation:**

Was your menstruation absent over the past four to six weeks?

0. Unknown
1. Yes. Date of last menstruation … /… /…
   Cause: pregnancy / menopause / other / unknown.
2. No

♀ **17. Lubrication:**

Have you noticed a change in the amount of vaginal lubrication (wetness) when you are sexually aroused (e.g. during sexual intercourse or during sexual self-stimulation) since using the current antipsychotic?

0. Unknown
1. Significantly decreased
2. Mildly decreased
3. Unchanged
4. Mildly increased
5. Significantly increased

♀ **18. Sexual intercourse:**

Did you have sexual intercourse with a partner in the last four to six weeks?

1. Yes, continue
2. No, end of questionnaire

♀ **19. Pain during sexual intercourse:**

Did you have pain during sexual intercourse and has this changed since you began to use the current antipsychotic?

0. Unknown
1. Deterioration
2. Unchanged
3. Improvement

End of questionnaire

Appendix 2: Dutch version of the ASFQ

Antipsychotics and Sexual Functioning Questionnaire (ASFQ)©

Universitair Centrum Psychiatrie, Universitair Medisch Centrum Groningen
H. Knegtering, S. Castelein en M.K. de Boer

Patiëntgegevens:

- **Naam:** .....
- **Geboortedatum, geslacht:** .....(dd/mm/jjjj), m/v
- **Naam ziekenhuis, patiëntnummer:** .....
- **Datum**: ..... (dd/mm/jjjj)

Instructie voor interviewers:

We willen u vragen om dikgedrukte tekst en vragen hardop voor te lezen aan de patiënt. Het is de bedoeling dat u doorgaat met vragen stellen tot het antwoord duidelijk is of het niet mogelijk is om verdere verduidelijking te verkrijgen. Noteer veranderingen die mogelijk gerelateerd zijn aan het gebruik van het huidige antipsychoticum. Vergelijk daarbij het huidige seksueel functioneren met seksueel functioneren ooit eerder in het leven.

Interpretatie van de volgende antwoordmogelijkheden:

0. Onbekend wordt gescoord indien de patiënt niet bereid of in staat is om deze vraag te beantwoorden, of indien ondanks voldoende doorvragen geen duidelijk antwoord kan worden verkregen.
1. Sterk verminderd wordt gescoord indien de patiënt een sterke afname ervaart in seksueel functioneren en/of de patiënt sterk lijdt onder de afname in seksueel functioneren.
2. Verminderd wordt gescoord indien de patiënt een afname in seksueel functioneren ervaart, zonder dat dit voor de patiënt erg hinderlijk is.
3. Onveranderd wordt gescoord indien de patiënt geen verandering ervaart in seksueel functioneren ten gevolge van het gebruik van antipsychotische medicatie. Het is belangrijk om op het volgende punt te letten: sommige patiënten geven aan dat ze nooit seksuele interesse hebben gehad. Als dit het geval is, en dit niet is veranderd, dan wordt 'onveranderd' gescoord.
4. Toegenomen wordt gescoord als de patiënt een toename in seksueel functioneren ervaart sinds het gebruik van het huidige antipsychoticum.
5. Sterk toegenomen wordt gescoord als de patiënt een sterke toename ervaart in seksueel functioneren sinds het gebruik van het huidige antipsychoticum.

Vragen:

1. **Indicatie voor het gebruik van het huidige antipsychoticum:**

   ……
   ……

2. **Noteer hier alle medicatie die voor het huidige antipsychoticum is gebruikt (met dosering; ook andere middelen dan antipsychotica):**

   ……
   ……

3. **Hoe lang heeft u het vorige antipsychoticum gebruikt?**
   1. Er werd de laatste maand voor het huidige antipsychoticum geen antipsychoticum gebruikt
   2. < 1 week
   3. 1-2 weken
   4. 2-6 weken
   5. 6 weken - 3 maanden
   6. > 3 maanden

4. **Wat was de reden om met het vorige antipsychoticum te stoppen?**
   1. Nieuwe psychotische episode
   2. Onvoldoende effect
   3. Bijwerkingen
   4. Wetenschappelijk onderzoek
   5. Anders, namelijk……

5. **Huidige medicatie (antipsychoticum en comedicatie, inclusief dosering):**

   ……
   ……
   ……

6. **Kunt u het effect beschrijven van de huidige antipsychotische medicatie? Hoe gaat het momenteel met u?**

   (De score is gebaseerd op de mening van de patiënt en de klinische impressie van de interviewer.)
   0. Onbekend
   1. Sterk verslechterd
   2. Verslechterd
   3. Onveranderd
   4. Verbeterd
   5. Sterk verbeterd

7. Welke ongewenste effecten heeft u ervaren van het huidige antipsychoticum?

(Noteer ongewenste effecten die spontaan worden genoemd door de patiënt, die gerelateerd kunnen zijn aan het antipsychoticum dat de afgelopen vier weken is gebruikt. Noteer hier geen bijwerkingen die later tijdens dit interview worden genoemd door de patiënt.)

.....

.....

.....

Vragen over seksueel functioneren

Sommige patiënten merken een verandering in hun seksuele verlangens of functioneren als ze medicijnen gebruiken. Veranderingen in seksueel functioneren kunnen gemerkt worden tijdens het vrijen met een ander of bij zelfbevrediging. Sommige patiënten melden een verbetering in het seksueel functioneren, anderen een verslechtering. De volgende vragen gaan over uw situatie in de laatste vier tot zes weken.

♂♀ **8. Seksueel verlangen:**

Heeft u een verandering gemerkt in seksueel verlangen sinds u het huidige antipsychoticum gebruikt?

0. Onbekend
1. Sterk afgenomen
2. Afgenomen
3. Onveranderd
4. Toegenomen
5. Sterk toegenomen

♂♀ **9. Orgasme:**

Heeft u een verandering gemerkt in het krijgen van een orgasme (klaarkomen) sinds u het huidige antipsychoticum gebruikt?

0. Onbekend
1. Sterk afgenomen
2. Afgenomen
3. Onveranderd
4. Toegenomen
5. Sterk toegenomen

♂♀ **10. Tepeluitvloed:**

Heeft u in de afgelopen vier tot zes weken uitvloed uit de tepels gehad?

0. Onbekend
1. Ja
2. Nee

♂♀ **11. Zwelling van borsten:**

Heeft u in de afgelopen vier tot zes weken een vergroting van de borsten en/of de tepels opgemerkt?

0. Onbekend
1. Ja
2. Nee

Vragen voor mannen

Voor vrouwen, ga naar vraag 15.

♂ **12. Erectie:**

Heeft u een verandering gemerkt in het kunnen krijgen van een erectie (stijve penis) sinds u het huidige antipsychoticum gebruikt? (bijv. de mate van stijfheid of de tijdsduur om een erectie te krijgen of te houden)

(Instructie: priapisme betreft een aanhoudende ongewenste erectie die pijnlijk is en langer dan een uur aanhoudt zonder seksuele stimulatie. Priapisme moet onmiddellijk worden behandeld.)

0. Onbekend
1. Sterk afgenomen
2. Afgenomen
3. Onveranderd
4. Toegenomen
5. Sterk toegenomen
6. Priapisme

♂ **13. Ejaculatie:**

Heeft u een verandering gemerkt in de hoeveelheid sperma (zaad) dat vrijkomt bij een orgasme sinds u het huidige antipsychoticum gebruikt? (bijv. minder of meer sperma dan normaal, of kwam er geen sperma vrij?)

0. Onbekend
1. Sterk afgenomen
2. Afgenomen
3. Onveranderd
4. Toegenomen
5. Sterk toegenomen

♂ **14. Seksueel contact:**

Heeft u in de afgelopen vier tot zes weken seksueel contact (gemeenschap) gehad met een partner?

1. Ja
2. Nee

Einde vragenlijst voor mannen

Vragen voor vrouwen

♀ **15. Anticonceptie:**

Gebruikt u hormonale anticonceptie?

0. Onbekend
1. Ja. Welke methode? (bijv. 'de pil', prikpil, spiraaltje, hormonale ring)……..
2. Nee

♀ **16. Menstruatie:**

Is de menstruatie (ongesteldheid) de afgelopen vier tot zes weken uitgebleven?

0. Onbekend
1. Ja. Datum laatste menstruatie … /… /…
   Oorzaak: zwangerschap / menopauze / anders / onbekend.
2. Nee

♀ **17. Lubricatie:**

Heeft u een verandering gemerkt in de vaginale vochtigheid (het 'nat' worden) wanneer u seksueel opgewonden was (bijvoorbeeld tijdens het vrijen met een partner of bij zelfbevrediging) sinds u het huidige antipsychoticum gebruikt?

0. Onbekend
1. Sterk afgenomen
2. Afgenomen
3. Onveranderd
4. Toegenomen
5. Sterk toegenomen

♀ **18. Seksueel contact**

Heeft u in de afgelopen vier tot zes weken seksueel contact (gemeenschap) gehad met een partner?

1. Ja, ga verder naar de volgende vraag
2. Nee, einde vragenlijst

♀ **19. Pijn bij seksueel contact (gemeenschap):**

Heeft u pijn bij het vrijen met een partner en is dit veranderd sinds u het huidige antipsychoticum gebruikt?

0. Onbekend
1. Verslechtering
2. Onveranderd
3. Verbetering

Einde vragenlijst

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Chapter 6

A randomized open-label comparison of the impact of aripiprazole versus risperidone on sexual functioning (RAS study)

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Abstract

This open–label trial included 36 patients randomized to either aripiprazole or risperidone for 6 weeks. Sexual dysfunction was assessed by the semi structured Antipsychotic and Sexual Functioning Questionnaire (ASFQ). The mean dose was 12.6 (SD 5.79) mg/day for aripiprazole and 3.2 (SD 1.15) mg/day for risperidone. Only one patient (6%) treated with aripiprazole (7,5-30 mg/day; N=18) reported sexual dysfunction attributed to the use of antipsychotics. In contrast, risperidone-treated patients (1-5 mg/day; N=18) reported frequently (61%) sexual dysfunctions (p=.001). The mean prolactin concentration was 214 (SD 148) mE/L in the aripiprazole group and 1181 (SD 673) mE/L in the risperidone group (p=0.000). In line with earlier studies, patients treated with risperidone frequently reported sexual side effects, significantly more than patients treated with aripiprazole. In contrast, patients treated with aripiprazole hardly reported sexual side effects, or reported improvement of sexual performance. Patients treated with risperidone showed a substantial prolactin elevation, while this was not found in patients treated with aripiprazole. Considering the small sample size, in view of possible important clinical consequences, a replication of this study in a larger clinical sample in a double blind study is warranted.

Introduction

Sexual dysfunction in patients with schizophrenia may be related to the disease itself, psychosocial factors, physical health, as well as to the use of psychotropic medication (Aizenberg, et al. 1995, Marques, et al. 2012). Antipsychotics have been associated with sexual dysfunction, such as decreased libido, erectile dysfunction, anorgasmia and decreased ejaculatory volume (Knegtering, et al. 2008, Baggaley. 2008). Sexual dysfunctions are rarely reported spontaneously, leading to underestimation of its prevalence. In contrast, studies using structured interviews or questionnaires result in 30 - 60% of the patients with schizophrenia reporting sexual dysfunctions (Serretti & Chiesa. 2011).

The pathogenetic mechanisms of antipsychotic-associated sexual dysfunction may involve post synaptic dopamine antagonism, α_1-antagonism and prolactin elevation (Knegtering, et al. 2008, Meston & Frohlich. 2000). Most antipsychotics are potent postsynaptic dopamine antagonists and can cause sustained elevation of prolactin (Knegtering, et al. 2008, Dickson & Glazer. 1999). Neuroleptic-induced hyperprolactinemia (NIHP) has been associated with a number of side effects including galactorrhea, menstrual disturbances, amenorrhea, and sexual dysfunction (Knegtering, et al. 2008, Hummer & Huber. 2004, Shim, et al. 2007). In line with a high (antagonistic) affinity for the dopamine receptor of risperidone, previous studies showed higher incidences of sexual dysfunctions and higher prolactin levels in patients treated with risperidone compared to patients treated with clozapine, olanzapine or quetiapine (Knegtering, et al. 2008, Shim, et al. 2007, Knegtering, et al. 2005, Knegtering, et al. 2004, Knegtering, et al. 2006). Aripiprazole is an antipsychotic with dopamine antagonistic and intrinsic agonistic properties, a partial agonist (Taylor. 2003). Aripiprazole usually acts as a dopamine antagonist with a high affinity for the dopamine receptor, working clinically as an antipsychotic agent. In brain regions which have a large receptor reserve for the D_2 dopamine receptor, for example in the anterior pituitary, aripiprazole can act as dopamine agonist (Meller, et al. 1991). As a consequence, aripiprazole doesn't induce hyperprolactinemia, it even may lower serum prolactin levels (Shim, et al. 2007, Haddad & Wieck. 2004). Aripiprazole's properties of being a dopamine antagonist with high affinity for postsynaptic dopamine receptors, may predict detrimental effects on sexual function, while, in contrast, its dopamine agonistic properties may predict no detrimental effects or even some beneficial effects on sexual performance. The net effects of aripiprazole on sexual performance were not known before the start of our study. In this open randomized study the effects of aripiprazole or risperidone on sexual performance and serum prolactin levels are investigated.

Methods

Study design

The study is an open-label trial in which patients are randomized to either aripiprazole or risperidone for 6 weeks. The starting dose of aripiprazole was 15 mg and the starting dose of risperidone 3 mg. For both groups, the dosage could be adjusted as deemed necessary on a weekly basis by the clinician (aripiprazole, 7.5-30 mg/day; risperidone, 1-6 mg/day). Patients were informed that effects of the medications would be assessed, but they were blinded with regard to any hypothesis to be tested.

Study participants

Study participants included inpatients and outpatients from the department of psychiatry of the University Medical Center in Groningen, The Netherlands, fulfilling the criteria for schizophrenia (DSM-IV-TR) or related psychotic disorders, who started with or were switched to a new antipsychotic for clinical reasons as determined by the attending psychiatrists. Patients' age had to be within 18 and 46 years old. Written and oral consent were given by patients in accordance with the local ethical committee for research.

Patients could be taking any antipsychotic before entering the study, except depot antipsychotics, aripiprazole or risperidone. Co-medication with known effects on sexual performance was not allowed, with the exception of oxazepam (maximum dose 30 mg/day).

Outcome measures

Primary outcome measures are the effect of risperidone and aripiprazole on sexual functioning and prolactin levels. Sexual dysfunction was assessed at 6 weeks post-randomization by a validated, semi-structured interview, the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) (de Boer, et al. 2013). Prolactin levels were measured after 6 weeks.

Secondary outcome measures are the efficacy of risperidone and aripiprazole on psychotic symptoms and levels of gonadal hormones. Psychotic symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay, et al. 1987) in week 1 and week 6 and the Clinical Global Impression-Improvement (GCI-I) in week 6.

Analysis

The Mann-Whitney U test was applied to ordinal outcomes. The Chi square test was applied to nominal outcomes (dichotomized sexual dysfunction evaluated with the ASFQ). The chi-square value was corrected for continuity because the sizes of the tables were all two by two. The Student t-test was used to analyze continuous outcomes including age and prolactin. Prolactin levels were normalized by converting to their natural logarithm. For all analyses, the effects were tested at the 2-sided α level of 0.05.

Results

Sociodemographic and clinical profile

50 patients fulfilled inclusion criteria of the study and were asked to participate, 44 patients agreed to enter the study. Three patients (of which one woman) treated with risperidone and five patients treated with aripiprazole discontinued in the first week of the study. Reasons for not completing the study were noncompliance (two patients) and unknown reason (one patient) in three patients treated with risperidone, and subjective restlessness in five patients treated with aripiprazole, in one patient accompanied by suicidal intentions. Although the study has not been designed to address the frequently

reported restlessness, lower dosages of aripiprazole and slower tapering of previous medication seemed to be associated with less reported inner restlessness.

Thirty-six patients (18 aripiprazole (13 men, 5 women)), 18 risperidone (15 men, 3 women)) completed the study and were included in the final analyses. Age ranged from 19 to 46 years old. At 6 weeks, the mean dosage of aripiprazole was 12.6 (SD 5.79) mg/day (range 7.5-30 mg/day) and risperidone 3.2 (SD 1.15) mg/day (range 1-5 mg/day). No significant differences were found in oxazepam and other co-medication use between the two groups. Additional demographic and clinical characteristics are provided in table 1.

Table 1. Demographic and clinical characteristics in patients using risperidone or aripiprazole

Variable	Risperidone (n=18)	Aripiprazole (n=18)	P-value
Age (mean ± SD)	29.0 (± 6.0)	29.2 (± 8.8)	NS
Gender (n male; % male)	15 (83)	13 (72)	NS
Diagnosis			
Delusional disorder (n; %)	1 (6)	2 (11)	NS
Schizophrenia (n; %)	14 (78)	15 (83)	NS
Schizoaffective disorder (n; %)	2 (11)	0 (0)	NS
Psychotic disorder NOS (n, %)	1 (6)	1 (6)	NS

NS = not significant, $p > 0.05$.

Primary outcome measures

Only one patient (6%) treated with aripiprazole reported sexual dysfunctions attributed to the use of antipsychotics. In contrast, risperidone-treated patients reported frequent (61%) sexual dysfunctions (p=.001). Three patients (17%) treated with aripiprazole reported improvement in sexual functioning versus one patient (6%) on risperidone.

Also for subtypes of sexual dysfunction (libido, orgasm, erection and ejaculation) a significant difference between both medication groups was demonstrated. Lubrication did not differ between both groups, but it has to be noted that the number of women in this study was very small.

Hormone levels could not be obtained in 6 patients (2 patients treated with aripiprazole and 4 patients with risperidone) because they refused blood sampling or for problems in organizing lab sampling at the desired time. The mean (±SD) prolactin concentration was 214 (SD 148) mE/L in the aripiprazole group and 1181 (SD 673) mE/L in the risperidone group (p=0.000). Prolactin levels in the aripiprazole group were on average a little below the normal values of the University Medical Center in Groningen laboratory. Details about sexual performance and prolactin levels at week 6 are presented in table 2.

Table 2. Prolactin levels and sexual dysfunction in patients using risperidone or aripiprazole in week 6

Variable	Risperidone (n=18)	Aripiprazole (n=18)	P-value
Prolactin (mE/L, mean ± SD)	1181 (± 673)	214 (± 148)	0.001
Prolactin in men	978 (± 453)	149 (± 83)	0.000
Prolactin in women	2399 (± 421)	356 (± 167)	0.000
Type of sexual dysfunction			
♂+♀ Decreased libido (n, %)	9 (50)	1 (6)	0.003
♂+♀ Decreased orgasm (n, %)	5 (28)	1 (6)	0.039
♂ Decreased erection (n, %)	4 (22)	0 (0)	0.044
♂ Decreased ejaculation (n, %)	5 (28)	0 (0)	0.012
♀ Decreased lubrication (n, %)	0 (0)	1 (20)	NS
♂+♀ Any sexual dysfunction (n, %)	11 (61)	1 (6)	0.001
Improvement of sexual functioning ♂+♀ (n, %)	1 (6)	3 (17)	NS

NS = not significant, p > 0.05.

Secondary outcome measures

The scores on the Positive and Negative Syndrome Scale (PANSS) at inclusion did not significantly differ between patients treated with aripiprazole or risperidone. Also at week six no major and statistically significant differences in treatment result could be identified between both treatment groups. Details are demonstrated in table 3.

Table 3. Scores on the Positive and Negative Syndrome Scale (PANSS) in patients using risperidone or aripiprazole at baseline and in week 6

	Risperidone (n=18)	Aripiprazole (n=18)	P-value
PANSS positive scale (mean ± SD)			
Baseline	12.9 (± 3.9)	14.9 (± 5.5)	NS
Week 6	11.3 (± 4.5)	12.6 (± 4.3)	NS
PANSS negative scale (mean ± SD)			
Baseline	15.1 (± 4.6)	15.5 (± 5.5)	NS
Week 6	15.5 (± 4.4)	13.6 (± 4.8)	NS
PANSS general scale (mean ± SD)			
Baseline	28.3 (± 5.9)	31.5 (± 8.3)	NS
Week 6	27.0 (± 6.3)	26.7 (± 6.0)	NS

NS = not significant, p > 0.05.

The Clinical Global Impression-Improvement (GCI-I) (rated as much worse, worse, unchanged, improved, or much improved) was used to assess treatment results by the attending physician. Both antipsychotics were considered effective: 72% of the patients were rated by their physician as being clinically significantly improved (improved and much improved) after 6 weeks without significant differences between the treatment groups (Mann-Whitney U 159.; z=-113; p=.910).

In contrast to prolactin, there was no signal that testosterone levels in men were influenced by the medication. There were not enough observations to analyze the levels of estrogen, progesterone or testosterone in women. In both genders no significant correlation was found between prolactin levels and other hormones.

Conclusion

In this randomized open label trial, sexual functioning is compared in patients with a psychotic disorder using aripiprazole (n=18) or risperidone (n=18). In line with earlier studies, patients treated with risperidone frequently (61%) reported sexual side effects, significantly more than patients treated with aripiprazole (6%). Patients treated with risperidone showed significant prolactin elevation, while this was not found in patients treated with aripiprazole.

Discussion

Although patients suffering from schizophrenia experience more often sexual dysfunction, with or without medication, the difference in the incidence of sexual side effects between patients treated with aripiprazole and risperidone is likely to be related to the pharmacological properties of medications used (Aizenberg, et al. 1995, Teusch, et al. 1995). In our study, the risperidone treated group reported frequent (61%) sexual side effects attributed to the use of risperidone, a significantly higher score than among patients treated with aripiprazole (5.6%). Only one patient treated with aripiprazole reported sexual dysfunctions and three patients reported improvement in sexual functioning. These three patients, all men, were switched from olanzapine to aripiprazole. Prolactin levels were higher in patients using risperidone compared to those using aripiprazole, and prolactine levels in patients on aripiprazole were a little below the normal laboratory reference values. Given the low number of female patients in each group, a separate analysis of female patients was not feasible.

The findings of this prospective open-label randomized study about aripiprazole and risperidone are consistent with prior studies of hyperprolactinemia in risperidone-treated patients and associating risperidone treatment with sexual dysfunction (Knegtering, et al. 2008, Baggaley. 2008, Serretti & Chiesa. 2011, Shim, et al. 2007, Knegtering, et al. 2007).

In patients treated with aripiprazole, the low prolactin levels may signal that dopamine agonism dominates the antagonistic effects in anterior pituitary. This may be an explanation for not finding sexual side effects, but even some improvement. These findings are of clinical importance as it may help to select medications with less detrimental effects on sexual performance.

The findings are also of theoretical importance as burst firing (phasic activity) of neurons in limbic areas is thought to be of importance in experiencing reward or in the context of this study sexual arousal and orgasm. However, other publications describe that dopamine does not have a prominent role in experiencing reward, but is specifically important in attention or motivation for reward (Pfaus. 2009).

Dahan et al. (Dahan, et al. 2009) studied the effect of aripripazole on tonic and phasic activity in the ventral striatum. Aripripazole displayed a stronger effect on the phasic than on the tonic firing. In other

words, aripripazole inhibits the dopamine release by burst firing stronger than the dopamine release by tonic firing. For the reward experience, however, the postsynaptic effect of the released dopamine may play a prominent role. Hamamura and Harada (Hamamura & Harada. 2007) proposed that aripripazole would suppress the phasic component of dopamine transmission relatively more than the tonic. This can be interpreted as relevant for the postsynaptic activity of the released dopamine. They describe the dopaminergic agonism of aripripazole as mimicking a tonic response and speculate that stimulation of tonic dopamine transmission may be related to impulsive behavior including hypersexuality in their case report (Kodama & Hamamura. 2010). This might support the idea that dopamine may be more important for motivation and attention to reward than experiencing reward. This aspect may also partly explain why suppression of the phasic component of dopaminergic activity by aripiprazole does not deteriorate sexual functioning.

A second hypothesis explaining the lack of detrimental effects on sexual performance of aripiprazole suggests that additional phasic dopaminergic activity will be imposed on an already by aripripazole partly activated/sensitized circuit. This aripripazole-induced tonic increased basic neuronal activity related to sexual activity may compensate the reduced additional phasic component resulting in an equal sexual performance as without aripripazole. The overall postsynaptic effects of the burst firing in this view is not affected by this partial agonist and may indicate that these dopaminergic pathways in the ventral striatum possess postsynaptically a large receptor reserve. This can explain that the partial agonist aripripazole will elicit a relatively pronounced agonistic effect which might contribute to a diminished postsynaptic antagonism of the dopamine burst and even a compensation for a diminished dopamine release by presynaptic inhibition of the burst firing. To support this idea, some clinical reports showed that aripiprazole can induce hypersexuality and it is hypothesized that the brain region which is responsible for sexual function may have large receptor reserve for D_2 dopamine receptor (Kodama & Hamamura. 2010, Schlachetzki & Langosch. 2008). On the other hand, studies showed that already low dosages of aripiprazole, starting from 2 mg a day, may result in a high D_2 receptor occupancy by aripiprazole in many different brain areas, leaving little receptor reserve left (Kegeles, et al. 2008).

Third, the fact that aripiprazole is not only a partial agonist for the D_2 receptor, but also a partial agonist for the 5-HT_{1A} receptor, may explain the lack of detrimental effects on sexual functioning. Other studies have shown that agonists for 5-HT_{1A} have a stimulation effect on sexual functioning (Moll & Brown. 2011). We do not know how much 5-HT_{1A} receptors should be occupied for this effect on sexual functioning, but we do know that in therapeutic dosages used in our study the 5-HT_{1A} receptor occupancy for aripiprazole is rather low (less than 20%) (Mamo, et al. 2007).

The high rates of sexual side effects in patients treated with risperidone may reflect its high affinity and antagonistic effects on postsynaptic dopamine receptors and may be potentiated by high prolactin levels. The high prolactin levels in patients treated with risperidone may not only reflect central dopamine antagonism but also the effects of its metabolite on the pituitary (Knegtering, et al. 2005). In addition α_1-antagonistic effects of risperidone may have contributed to sexual dysfunctions, especially ejaculatory dysfunction (Knegtering, et al. 2007).

As mentioned previously, five patients treated with aripiprazole did not complete the study because of side effects, best described as inner restlessness. In one patient this restlessness was accompanied by suicidal intentions. It is unclear whether these suicidal intentions may be attributed to the medication, the underlying mental illness or the experienced family stress. Although the study has not been designed to address the frequently reported restlessness in patients treated with aripiprazole, lower dosages of aripiprazole and slower tapering of previous medication seemed to be associated with less reported inner restlessness. It seems to be worthwhile to further investigate these clinical observations, especially in view of the possible advantages of lower dosages of aripiprazole in future studies.

The main limitations of this study are the small sample size, and the lack of baseline assessment of sexual functioning and serum prolactin levels. This lack of baseline sexual performance is partly compensated by the structure of the ASFQ scoring each dimension of sexual functioning in contrast to premorbid sexual functioning. Interestingly, this is the fourth published study using the ASFQ in the same way, including risperidone in one of the treatment arms (Knegtering, et al. 2008, Knegtering, et al. 2004, Knegtering, et al. 2006). Although the ASFQ has been applied by different research assistants in the different studies, all studies showed almost identical frequencies of sexual dysfunction in patients treated with risperidone 3-4mg/day, i.e. around 60%, validating the research procedures followed (Knegtering, et al. 2008). Significant differences between two medications in a study with a small sample size may signal important clinical differences. Future studies, taking the limitations of this study into consideration, should be randomized and double-blind in a larger patient sample.

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Chapter 7

Evaluation of sexual side effects in patients using long-acting depot antipsychotics in regular outpatient mental health care

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Submitted

Abstract

This cross-sectional study systematically assessed the nature and frequency of sexual dysfunction in a sample of 53 patients using depot antipsychotics in regular outpatient mental health care. The primary outcome measure was sexual performance as evaluated with the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), a semi-structured interview. The secondary outcome measure was sexual performance as evaluated with the Subjects' Response to Antipsychotics (SRA), a self-report questionnaire. Sexual dysfunction was reported by 47% of patients on the ASFQ, and by 57% on the SRA. These rates of sexual dysfunction are in the same range as the oral equivalents of the medication.

Introduction

Sexual dysfunction in patients with schizophrenia may be related to the disease itself, psychosocial factors, physical health and the use of psychotropic medications (Aizenberg, et al. 1995, Dickson & Glazer. 1999, De Boer et al. submitted). Antipsychotics have been associated with sexual dysfunction, such as decreased sexual desire, erectile dysfunction, anorgasmia, and reduced ejaculatory volume (Knegtering, et al. 2008, Smith. 2003). Besides postsynaptic dopamine antagonism, prolactin elevation may be a factor in the pathogenesis of antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008).

Sexual side effects have a considerable impact on quality of life and are a major factor in non-adherence to prescribed antipsychotic drugs (Finn, et al. 1990, Olfson, et al. 2005). Sexual dysfunction is rarely reported spontaneously, leading to underestimation of its prevalence. In contrast, studies using structured interviews or questionnaires show that 16% to 60% of patients using oral antipsychotics experience sexual dysfunction (Knegtering, et al. 2008, Serretti & Chiesa. 2011).

Besides oral antipsychotics, long-acting injectable (depot) antipsychotics are available. The use of depot antipsychotics is associated with previous non-adherence, poor attitudes toward medications, substance use and low illness awareness (Kelin, et al. 2010).

Studies about sexual dysfunction in patients using depot antipsychotics are rare (Aizenberg, et al. 1995, Montejo, et al. 2010, Novick, et al. 2009, Plevin, et al. 2007), and the number of patients using depot antipsychotics is small in most studies (n=51, n=13, n=119 and n=22, respectively). No randomized studies are available. In most research, patients using depot antipsychotics constitute a small proportion of a study sample in which the majority of subjects are using oral antipsychotics (Aizenberg, et al. 1995, Montejo, et al. 2010, Novick, et al. 2009). In the largest study, no specific questionnaire was used to investigate sexual functioning, and the type of sexual dysfunction was not mentioned (Novick, et al. 2009). The available studies suggest that the frequency of sexual dysfunction in patients using depot antipsychotics may be within the same range as in patients using oral antipsychotics.

The aim of this study is to systematically assess the nature and frequency of sexual dysfunction in a sample of patients being treated with depot antipsychotics in regular outpatient mental health care, using validated instruments, a semi-structured interview as well as a self-report questionnaire.

Methods

Inclusion and experimental design

Outpatients using depot antipsychotics were asked to evaluate desired and undesired effects of this treatment. They were treated in the Lentis Center of Mental Healthcare in the cities of Groningen and Winschoten, and the Department of Psychiatry of the University Medical Center in Groningen, The Netherlands. On the day of a new depot injection, two questionnaires were assessed to evaluate side effects. Afterwards, the patient's clinician was informed about the results (sexual side effects as well as other side effects), so that the possible burden of side effects could be discussed with the patient. All patients gave oral and written informed consent to participate in the study. The study was performed in keeping with the protocol of the Declaration of Helsinki. As the study did not include an experimental

intervention, and was part of the regular evaluation of treatment without appreciable burden to the patient, in line with national regulations, no approval by the medical ethics committee was required.

Description of assessment tools

The primary outcome measure is sexual performance as evaluated with the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), a semi-structured interview containing questions about changes in sexual desire, orgasm, erectile dysfunction, ejaculatory dysfunction, and vaginal lubrication. The ASFQ has been validated in patients using antipsychotics (de Boer, et al. 2013). Interviewers received training about the application of this semi-structured interview.

The secondary outcome measure is sexual performance as evaluated with the Subjects' Response to Antipsychotics (SRA) questionnaire. The SRA is a 74-item self-report questionnaire about desired and undesired treatment effects attributed to the use of antipsychotics (Wolters, et al. 2006). In this study we used a 76-item version of this questionnaire with two additional items on sexual functioning, resulting in 6 questions about sexual side effects. Of these questions, 5 apply to men (decreased sexual desire, decreased orgasm, decreased erection, decreased ejaculation, increased sexual desire), and 4 questions apply to women (decreased sexual desire, decreased orgasm, decreased lubrication, increased sexual desire). The ASFQ and the SRA both seek to establish whether any sexual dysfunction can be attributed to the antipsychotic being used.

Statistical analysis

Demographic and clinical characteristics were described using mean and standard deviation for continuous variables (e.g. age), and frequency and percentages for categorical variables (e.g. gender, diagnosis, type of sexual dysfunction).

Results

In total, 87 patients were asked to participate in this study, of whom 53 completed it. Of the 34 patients who did not participate, 10 patients refused participation, 13 patients did not meet the inclusion criteria and 10 did not participate due to other reasons (problems in planning the appointment (n=4), deceased (n=1), change of treatment department or institution (n=5)). One patient participated in the study, but was excluded because the degree of psychotic symptoms interfered with the ability to understand and reliably answer the questions.

Most patients were male (70%) and had a clinical DSM-IV diagnosis of schizophrenia (79%). Additional demographic and clinical characteristics are described in Table 1. Participants used the following depot antipsychotics: paliperidone (n=16), risperidone (n=6), flupenthixol (n=11), zuclopenthixol (n=8), fluphenazine (n=6), bromperidol (n=2), haloperidol (n=1), penfluridol (n=1), and olanzapine (n=1). In total, 30 patients (57%) were also using one or more oral psychotropic medications, like antipsychotics (n=20, including clozapine (n=13)), mood stabilizers, antidepressants and benzodiazepines.

Sexual dysfunction was reported by 47% of patients on the ASFQ, and 57% on the SRA.

Table 1. Demographic and clinical characteristics and frequency of sexual dysfunction

Demographic and clinical characteristics	
Demographic characteristics	
Number of patients	53
Age (mean ± SD)	40.0 (±10.0)
Gender (n male; % male)	37 (70)
Living together with a partner (n, %)	8 (15)
Diagnosis	
Schizophrenia (n; %)	42 (79)
Schizoaffective disorder (n; %)	7 (13)
Psychotic disorder NOS (n, %)	2 (4)
Bipolar disorder (n, %)	2 (4)
Duration of use of antipsychotics	
Use of current antipsychotic for more than 2 years (n, %)	32 (60)
Use of antipsychotics for more than 2 years during lifetime (n, %)	47 (89)
Type of sexual dysfunction (ASFQ)	
♂+♀ Decreased sexual desire (n, %)	14 (26)
♂+♀Decreased orgasm (n, %)	11 (21)
♂ Decreased erection (n, %)	10 (27)
♂ Decreased ejaculation (n, %)	13 (35)
♀ Decreased lubrication (n, %)	3 (19)
Any sexual dysfunction	
♂+♀ Any sexual dysfunction (ASFQ) (n, %)	25 (47)
♂+♀ Any sexual dysfunction (SRA) (n, %)	30 (57)
♂+♀ Any sexual dysfunction (ASFQ and/or SRA) (n, %)	32 (60)
Improvement of sexual functioning	
♂+♀ Improvement of sexual functioning (ASFQ) (n, %)	2 (4)
♂+♀ Improvement of sexual desire (SRA) (n, %)	5 (9)

ASFQ = Antipsychotics and Sexual Functioning Questionnaire; SRA = Subjects' Response to Antipsychotics.

Discussion

This study systematically assessed the nature and frequency of sexual dysfunction, using a semi-structured interview as well as a self-report questionnaire, in a sample of patients using depot antipsychotics in regular outpatient mental health care. Sexual dysfunction was reported by 47% of patients on the ASFQ, and 57% on the SRA. This is in the same range as the oral equivalents of the depot antipsychotics used (risperidone, paliperidone and classical antipsychotics) (Serretti & Chiesa. 2011). Antipsychotics that are supposed to have lower rates of sexual dysfunction (olanzapine, quetiapine, aripiprazole) (Knegtering, et al. 2008, Serretti & Chiesa. 2011, de Boer, et al. 2011), were scarcely used in this study, as of these, only a depot of olanzapine is available in the Netherlands. A few patients mentioned improved sexual functioning over time, possibly related to an improvement in the symptoms of the psychotic disorder.

Patients being treated with depot antipsychotics are frequently using co-medication and having somatic or psychiatric co-morbidity. Although this may limit our ability to reach firm conclusions about the attribution of the reported sexual dysfunction to the depot antipsychotic, the study population does reflect our population of patients with a severe mental illness using depot antipsychotics, as few patients were excluded from participation. Because of the study's cross-sectional design, and the variety of depot antipsychotics and psychotropic co-medication, it was not possible to compare groups within the study population in a reliable way. We explored whether patients using a depot of risperidone or paliperidone - antipsychotics known to induce relatively high prolactin levels - showed higher rates of sexual dysfunction (Knegtering, et al. 2008, Kapur, et al. 2002, Knegtering, et al. 2005). Rates of sexual dysfunction were similar in patients receiving risperidone or paliperidone (45%) or other antipsychotics (48%), while demographic and clinical characteristics were similar in both groups.

A strength of the present study is that we used different types of validated instruments to investigate side effects (semi-structured interview and self-report questionnaire). More sexual side effects were reported using the self-report questionnaire (SRA). Self-report questionnaires are known to detect higher frequencies of taboo related problems. Patients may feel more comfortable reporting sexual effects without an interviewer (Kurth, et al. 2004, Keller, et al. 2006). In contrast, a semi-structured interview may be better in order to disentangle whether sexual dysfunctions are related to the medication or other factors.

In contrast to earlier studies with patients using oral antipsychotics, many patients had difficulty understanding the questions in both the semi-structured interview and the self-report questionnaire. The population using depot antipsychotics had, in the opinion of the interviewers, more cognitive impairment, possibly related to the severity of the psychiatric disorder. However, cognitive functioning was not measured in this study.

Research can be helpful for treatment. In our study, we gave a summary of the results to the patient's clinician, with the aim that they could discuss the possible burden of the side effects with the patient, and consider possible treatment options. This concerned sexual side effects and other side effects, but the latter is beyond the scope of this article.

Despite both the limitations and the fact that sexual side effects can not with certainty be attributed to the depot antipsychotic only, we believe our study includes a representative sample of outpatients using depot antipsychotics and provides information about sexual functioning in this group. We hope that the challenges described concerning the subject and the population will be helpful in future research.

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Chapter 8

Efficacy of tadalafil on erectile dysfunction in male patients using antipsychotics: a double-blind placebo-controlled crossover pilot study

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Abstract

The objective of this study is to investigate the efficacy of tadalafil in antipsychotic-induced erectile dysfunction. The study design is a double blind placebo controlled randomized cross-over study with tadalafil and placebo treatment in male patients treated with an antipsychotic who experience erectile dysfunction. The primary outcome measure is the change in erectile functioning during a three weeks period of add-on treatment with either tadalafil or placebo, as measured with the International Index of Erectile Function Questionnaire (IIEF). Secondary outcome measures are the effects of tadalafil on erectile functioning as assessed with the Improvement Global Usefulness Question (IGUQ), effects on sexual functioning as assessed with the Antipsychotic and Sexual Functioning Questionnaire (ASFQ). For the numerical outcomes (sum scores) a linear mixed effects model was fitted to the data of the two periods, using a bivariate normal distribution. For the ordinal outcomes (items), general estimating equations (GEE) with the (cumulative) logit link function were used to estimate treatment effect. 16 patients were included in this study between October 2009 and November 2011. 15 patients completed the trial. Data of the IIEF are not consistent in outcome. The IGUQ and the question of the ASFQ about erection show a treatment effect of tadalafil on erectile functioning at significance level α=0.05. Tadalafil may improve antipsychotic-induced erectile dysfunction, but this double-blind placebo controlled cross-over pilot study was underpowered to make firm conclusions on the efficacy.

Introduction

Sexual dysfunction in patients with schizophrenia may be related to the disease itself, to psychosocial factors, medical conditions and to the use of psychotropic medications (Aizenberg, et al. 1995, Dickson & Glazer. 1999). Antipsychotics have been associated with sexual dysfunction, such as decreased libido, erectile dysfunction, anorgasmia, and decreased ejaculatory volume (Knegtering, et al. 2008, Smith. 2003). Besides postsynaptic dopamine antagonism, prolactin elevation may be an important factor in the pathogenesis of antipsychotic-induced sexual dysfunction (Knegtering, et al. 2008).

Sexual dysfunction is rarely reported spontaneously, leading to underestimation of its prevalence. In contrast, studies using structured interviews or questionnaires show that 16 to 60% of patients report sexual dysfunctions that do not subside over time (Knegtering, et al. 2008, de Boer, et al. 2011, Serretti & Chiesa. 2011, Montejo, et al. 2010). Sexual side effects have a considerable impact on quality of life (Olfson, et al. 2005). A large study among 243 patients diagnosed with schizophrenia or a related psychotic disorder showed that lack of compliance is present in 36% of male patients, and that 32% of the patients experiencing sexual side effects has a poor tolerance to these effects (Montejo, et al. 2010). Strategies to treat antipsychotic-induced sexual dysfunction often include lowering the dose, switching to a prolactin sparing antipsychotic or adding a dopamine agonist. This may lead to an increase in psychotic symptoms and therefore has clear clinical drawbacks (Nunes, et al. 2012). Treatment alternatives that would allow patients to continue their antipsychotic medication but at the same time restore sexual functioning are needed to address these concerns.

Phosphodiesterase-5 (PDE-5) inhibitors, like sildenafil, tadalafil, vardenafil and lodenafil, are registered for treatment of erectile dysfunction, and may also improve erectile dysfunction in patients treated with antipsychotics. Only a small amount of publications is available on this specific topic. One study about addition of lodenafil (a double blind placebo controlled cross-over trial, n = 48) (Nunes, et al. 2013) and three studies about addition of sildenafil were found in the literature: one double blind placebo controlled cross-over trial (n=32) (Gopalakrishnan, et al. 2006) and two open label non-controlled trials (n=12 and n=10) (Aviv, et al. 2004, Atmaca, et al. 2002). One open-label add-on study of vardenafil was found (n=25) (Mitsonis, et al. 2008). These five studies report improvement of erectile dysfunction. Furthermore, it has been suggested that sildenafil may be effective in the treatment of negative symptoms of schizophrenia (Akhondzadeh, et al. 2011).

The study described in this article is designed to investigate the influence of the PDE-5-inhibitor tadalafil on erectile dysfunction in patients diagnosed with schizophrenia or a schizophrenia spectrum disorder (DSM-IV-TR) treated with antipsychotics. The results of this study are relevant for clinical practice and may also be of theoretical importance in understanding sexual functioning. Lastly, the possible influence of PDE-5-inhibitors on negative symptoms deserves further exploration. The current study is the first to address these issues in a randomised controlled trial investigating the addition of tadalafil in antipsychotic-induced erectile dysfunction.

Methods

Study design

The study design is a double blind placebo controlled randomized 2x2 cross-over study with tadalafil and placebo treatment in male patients treated with an antipsychotic who experience erectile dysfunction. Patients were randomly assigned to the sequence placebo-tadalafil or the sequence tadalafil-placebo. Each period lasted three weeks and there was no washout period in between the two periods. Patients came for a weekly visit during the study, and received three pills a week (placebo or tadalafil 10 mg), to use on demand.

Study participants

Patients were recruited from the outpatient department of Mental Healthcare Center Parnassia in The Hague in The Netherlands between October 2009 and November 2011. The study was approved by the Medical Ethical Committee (METiGG) in Utrecht, in accordance to the Declaration of Helsinki. 29 patients were interested to participate in the study. Of those patients, 13 did not meet the in- or exclusion criteria. In total 16 patients were included in the study. One of the included patients did not take the study medication and was excluded from the study. Finally, 15 patients completed the study.

Originally, the design was based on sample size calculations of the study of Gopalakrishnan (Gopalakrishnan, et al. 2006), which has a similar study design, but other outcome measures. Therefore, an exact sample size calculation was not yet possible, leading to the decision to do a pilot study, which provides data about sample size calculation that can be used in future studies.

Inclusion and exclusion criteria

Inclusion criteria were: men, age between 18 and 45 years, with a clinical diagnosis of schizophrenia or a schizophrenia spectrum disorder (DSM-IV-TR), who developed erectile dysfunction subsequent to treatment with antipsychotics for at least three months (which implies that, most likely, the use of antipsychotics is the cause of erectile dysfunction in these patients), who had desire for sexual activity once a week during the month before inclusion of the study. Patients had to be able to understand the study objectives and to give oral and written consent, while agreeing not to use any other treatment for erectile dysfunction for at least 4 weeks before receiving the initial dose of the study drug. It was not necessary to have a sexual partner.

Exclusion criteria were: erectile dysfunction caused by other primary sexual disorders including premature ejaculation, erectile dysfunction caused by untreated endocrine disease (e.g. hypopituitarism, hypothyroidism, diabetes mellitus, or hypogonadism), history of pelvic surgery, treatment with anti-androgens, history of penile implant, presence of clinically significant penile deformity, clinically significant renal insufficiency within the last 6 months, active symptomatic hepatobiliary disease, chronic stable angina pectoris treated with long-acting nitrates, chronic stable angina pectoris who have short-acting nitrates in the last 90 days, angina pectoris occurring during sexual intercourse in the last 6 months, having met the criteria for unstable angina pectoris in the last 6 months, history of myocardial

infarction or coronary artery bypass graft in the last 90 days, percutaneous coronary intervention in the last 90 days, any supraventricular arrhythmia with an uncontrolled ventricular response at rest despite medical therapy, any history of spontaneous or induced sustained ventricular tachycardia despite medical therapy, the presence of an automatic internal cardioverter-defibrillator, a history of sudden cardiac arrest, any evidence of congestive heart failure class 2 or above in the last 6 months, a new significant conduction defect in the last 90 days, systolic blood pressure >170 or < 90 mmHg or diastolic blood pressure >100 or <50 mmHg, history of significant central nervous system injuries within the last 6 months, a history of HIV infection, a history of substance dependence in the last 6 months, having co-medication known to interact with tadalafil, blurred vision, loss of visual sight field and retinopathy.
Patients were asked about these inclusion and exclusion criteria and basic laboratory investigations were performed. In case of doubt about possible exclusion criteria, patients were asked to give consent to consult their physician.
Patients were instructed to call for medical assistance in case of the following emergent side effects: swelling of face, lips, tongue or throat (allergic reaction), changes in vision or sudden vision loss, tinnitus or sudden hearing loss, angina pectoris or myocardial infarction, cardiac arrhythmia, dyspnea, oedema of hands or feet, convulsion, fainting and priapism.

Outcome measures

The primary outcome measure was the change in erectile functioning during a three weeks period of add-on treatment with either tadalafil or placebo, as measured with the International Index of Erectile Function Questionnaire (IIEF) (Rosen, et al. 1997, Rosen, et al. 2002). Although the IIEF is considered internationally the gold standard method for measuring erection, it has not been validated for patients with a psychotic disorder. Before start of the study we were not sure if this was an appropriate instrument to measure erection in this population. Therefore, we added two other instruments to measure erection.
Secondary outcome measures were the effects of tadalafil on erectile functioning as assessed with the Improvement Global Usefulness Question (IGUQ), effects on sexual functioning as assessed with the Antipsychotic and Sexual Functioning Questionnaire (ASFQ) (Knegtering, et al. 2008, Knegtering. 2003), and effects on psychopathology, especially on negative symptoms, as evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay, et al. 1987). The ASFQ is a semi-structured interview. A recent validation study showed satisfactory internal reliability, test-retest reliability, inter-rater reliability and convergent validity of the ASFQ (de Boer, et al. 2013). The PANSS is a clinician-rated instrument that has been validated in patients with schizophrenia (Kay, et al. 1987) and is frequently used in clinical studies.
The IIEF consists of 15 questions with per question 4 or 5 answers that can be given. A problem with this questionnaire is that many questions ask about having sex with a partner, while not every patient has a partner. Therefore, calculating a sum score of all questions of the IIEF was not effective to compare the degree or change of erectile dysfunction. Furthermore, not all questions ask specifically about erection, but there are also questions about sexual functioning in general.
We chose to use the following parts of the IIEF, with only questions that did not ask about having sex with a partner:

- Sum scores of 3 questions about *erection*: question 1 (how often was the patient able to get an erection during sexual activity), 2 (how often were erections hard enough) and 15 (about confidence in getting and keeping an erection).
- Sum scores of 8 questions about *erection and sexual functioning in general*: question 1, 2, 9 (ejaculation), 10 (orgasm), 11 (how often sexual desire), 12 (level of sexual desire), 13 (level of satisfaction with sex life) and 15.
- Besides that, we looked at question 1, 2 and 15 on item level.

The ASFQ is a semi-structured interview, designed for measuring sexual functioning in patients with a psychotic disorder, which contains for men one question per following topic: sexual desire, erection, orgasm and ejaculation.

The IGUQ about erection has five options to answer, from no improvement to total improvement. It asks for the general conclusion of the patients about the effect of the treatment. This single question was assessed every week, providing information about the course of erectile functioning between the measurements of the IIEF and ASFQ, which were assessed every three weeks.

The PANSS is a questionnaire which measures symptoms of psychopathology in patients with psychotic disorders. Of the PANSS, sum scores were used of positive symptoms, negative symptoms, general psychopathology and the total sum of these three domains.

Finally, pills were counted during each visit, providing information about the amount of pills that were used.

Progress of patients during the trial is shown in Figure 1, and an overview of the measurements is given in Table 1.

Figure 1. Progress of patients during the trial

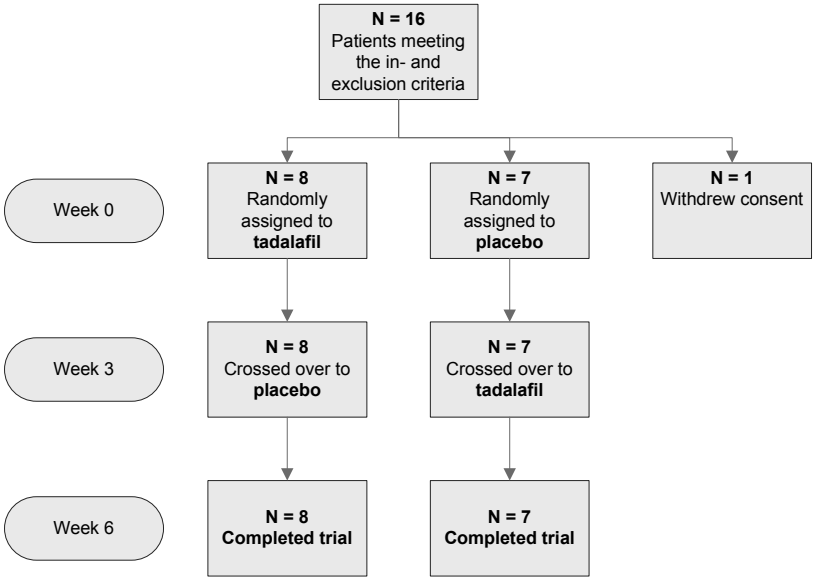

Table 1. Measurements during the trial

	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Laboratory investigations	x						
IIEF	x			x			x
ASFQ	x			x			x
PANSS	x			x			x
IGUQ		x	x	x	x	x	x
Somatic controls (blood pressure, side effects)	x	x	x	x	x	x	x
Pill count		x	x	x	x	x	x

ASFQ = Antipsychotic and Sexual Functioning Questionnaire; IGUQ = Improvement Global Usefulness Question; IIEF = International Index of Erectile Function Questionnaire (IIEF); PANSS = Positive and Negative Syndrome Scale.

Analysis

The outcome variables were determined by questionnaires: IIEF, ASFQ, IGUQ and PANSS. The questionnaires were conducted at the end of each period, but IGUQ was collected after each week. Before the study started a baseline measurement was conducted for the IIEF, the ASFQ and the PANSS (see Table 1).

For the numerical outcomes (sum scores) a linear mixed effects model was fitted to the data of the two periods, using a bivariate normal distribution. Type III tests were conducted for treatment effect, since this effect was corrected for age, baseline outcome, sequence and period effect. For the ordinal outcomes (items), general estimating equations (GEE) with the (cumulative) logit link function were used to estimate treatment effect. The independence working correlation matrix was taken together with the robust or emperical estimator. The type III generalized score statistic was applied to test treatment effect since it was again corrected for age, baseline outcome (except for IGUQ), sequence, and period effect. The baseline outcome was treated as numerical variable in this analysis. These corrections were applied to improve power.

A sample size calculation was conducted for the IIEF sum score on erection based on the formula of Diggle, Liang, and Zeger (Diggle, et al. 1994). Both the estimated treatment effect size and the variance-covariance estimates were taken as input, together with a type 1 error rate of 0.05 and a power of 0.80.

Results

Eight patients in were randomized in the treatment sequence tadalafil-placebo and seven patients in sequence placebo-tadalafil (n=15 in total).

Pills were counted to measure compliance. All patients used 2 to 3 pills a week. Tadalafil was well tolerated with no discontinuations due to adverse effects.

Sociodemographic and clinical profile

The mean age was 37.4 years (± 6.6). 10 patients were diagnosed with schizophrenia (n=8 paranoid type and n=2 undifferentiated type), and 5 patients were diagnosed with schizoaffective disorder. During the study, 9 out of 15 patients had a (sexual) partner. The fact that a substantial part of the patients had no partner is representative for the situation of patients with a schizophrenia spectrum disorder in The Netherlands.

The patients were using the following antipsychotics: olanzapine (n=4), clozapine (n=4), risperidone (n=1), flupentixol (n=4) or zuclopentixol (n=2). Of the total group, 8 patients used psychotropic comedication like another antipsychotic, a mood stabilizer, an antidepressant or a benzodiazepine.

No patients had thyroid problems, 3 had an elevated level of prolactin (probably due to the use of antipsychotics) and 5 patients had mild glucose intolerance. Glucose levels in these patients were just above the laboratory values.

Efficacy of treatment

The averages of the numerical and ordinal outcomes for the two treatments at the two periods are provided in Table 2. The ordinal outcomes are treated here as numerical values, to get an impression about the differences in periods and treatments, but in the statistical analysis for testing a possible treatment effect the ordinal outcomes were treated as such.

The statistical analysis demonstrated no significant treatment effect was measured with the IIEF. A significant treatment effect of tadalafil on erectile functioning was calculated for the ASFQ question about erection (p=0.032) and for IGUQ (p=0.016) at the significance level of α=0.05. For both outcomes the score increases with tadalafil compared to placebo.

A period effect was never detected at the level of significance of 0.05, but a sequence effect was detected for the IIEF sum score on erection, ASFQ question about orgasm, question IIEF1 and IGUQ. Since we corrected for baseline outcome (except for IGUQ), this effect may indicate some kind of carry-over effect. A more indepth analysis was conducted to explain these results.

The IIEF sum score on erection was 2.85 points lower for tadalafil than placebo in period 1 (p=0.023), but 3.15 higher at period 2 (p=0.057), when corrected for baseline and age. Interestingly, the effect of treatment for sequence tadalafil-placebo was estimated at zero (p=1.000), while the same effect was 1.57 points for sequence placebo-tadalafil (p=0.041), again all effects corrected for age and baseline. A similar pattern was seen for question IIEF1, which is not surprising since it is part of the sum score on erection of the IIEF, although a treatment effect for sequence placebo-tadalafil was not significant (p=0.093). For the ASFQ question about orgasm, there was no significant treatment effect at period 1 (p=0.204), but a positive treatment effect at period 2 (p=0.023), after correction of age and baseline. However, there was no treatment effect for either sequence (tadalafil-placebo: p=0.872; placebo-tadalafil: p=0.383). For IGUQ a similar pattern as the IIEF sum score on erection was seen. At period 1 there was no significant treatment effect (p=0.298), but a difference could be seen at the second period (p=0.006). For the sequence tadalafil-placebo, no effect was observed (p=0.689), but an effect was seen for the sequence placebo-tadalafil (p=0.026).

The correlation coefficient between the observations from the two periods for the IIEF sum score on erection was estimated at 0.51. The variation in sum scores was different for both periods. The variances were estimated at 3.713 and 8.679 for period 1 and period 2, respectively, after correction for age and baseline. The overall effect size was estimated at 0.79 points (although the effect size for sequence placebo-tadalafil was twice as large). To demonstrate a difference of at least one point on the sum score, the number of patients should have been in the range of 48 to 95. This is based on the IIEF, which is the primary outcome measure.
The number of unused pills did not differ significantly between both groups ($p = 0.378$).

Discussion

In conclusion, this double blind placebo controlled cross-over pilot study about the addition of tadalafil in antipsychotic-induced erectile dysfunction showed that no treatment effect could be demonstrated on the primary outcome of erectile functioning measured by the IIEF. However, the IGUQ and the question of the ASFQ about erection, showed a significant treatment effect of tadalafil on erectile functioning. There was no significant change in psychopathology measured by the PANSS.
This is the first study that investigates the addition of tadalafil in antipsychotic-induced erectile dysfunction. Tadalafil may improve antipsychotic-induced erectile dysfunction, but this double-blind placebo controlled cross-over pilot study was underpowered to make firm conclusions on the efficacy. A sample size of 48 to 95 patients is needed in a similar cross-over study, if the IIEF would be used as the primary outcome measure. On the basis of our study, it would be recommended though to change the set-up of the study and to choose another primary outcome measure, better adjusted to patients with schizophrenia, with or without a partner. Retrospectively, the ASFQ could have been the most appropriate primary outcome measure for this study, but we report our findings in line with the original study protocol. An article about the validation of the ASFQ has been submitted and shows satisfying psychometric properties (de Boer, et al. 2013). When an already published validated questionnaire is desired, the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) could be a good alternative, as this questionnaire also asks for medication-related changes and covers all stages of sexual functioning (like the ASFQ) (Montejo & Rico-Villademoros. 2008).
An advantage of a cross-over study is that each patient is his own control, and therefore the influence of confounding covariates is reduced. Second, most cross-over studies require less subjects than non-cross-over studies. Despite this, the small sample size (n=15) is an important limitation of this study.
A possible disadvantage of a cross-over design is a possible difference in 'carry-over effect' of the two treatments. Tadalafil reaches a maximum blood level in 2 hours and has a relatively short halflife of 17.5 hours. Therefore, and because of the fact that tadalafil was not taken every day, we expected that the carry over effect would be small or not present at all. Despite this, some calculations suggest that a carry-over effect was present for tadalafil (IIEF sum score on erection, question IIEF1, the AFSQ question about orgasm, and IGUQ (erection)).

Table 2: Averages (standard deviations) for the outcomes

Outcomes	Sequence	Period 1	Period 2
IIEF: sum score erection (question 1+ 2+ 15)	**tadalafil** - placebo	**9.38 (3.021)**	9.38 (2.937)
	placebo - **tadalafil**	10.57 (2.992)	**12.14 (2.610)**
IIEF: sum score total (question 1+ 2+ 9+ 10+ 11+ 12+ 13+ 15)	**tadalafil** - placebo	**26.88 (6.490)**	26.50 (7.278)
	placebo - **tadalafil**	29.57 (6.268)	**31.71 (6.921)**
IIEF1 (able to get erection)	**tadalafil** - placebo	**3.00 (1.309)**	3.25 (1.165)
	placebo - **tadalafil**	4.14 (0.900)	**4.71 (0.488)**
IIEF2 (erections hard enough)	**tadalafil** - placebo	**3.38 (1.408)**	3.38 (1.302)
	placebo - **tadalafil**	3.14 (1.574)	**4.00 (1.528)**
IIEF15 (confidence in erection)	**tadalafil** - placebo	**3.00 (1.069)**	2.75 (0.707)
	placebo - **tadalafil**	3.29 (1.113)	**3.43 (0.976)**
ASFQ libido	**tadalafil** - placebo	**1.38 (1.302)**	1.38 (1.302)
	placebo - **tadalafil**	2.43 (1.902)	**2.86 (1.864)**
ASFQ orgasm	**tadalafil** - placebo	**3.00 (0.926)**	3.00 (0.756)
	placebo - **tadalafil**	3.57 (0.787)	**3.86 (0.690)**
ASFQ erection	**tadalafil** - placebo	**3.50 (0.756)**	3.13 (0.835)
	placebo - **tadalafil**	3.43 (0.787)	**3.86 (0.690)**
ASFQ ejaculation	**tadalafil** - placebo	**2.50 (1.309)**	3.38 (0.916)
	placebo - **tadalafil**	2.86 (1.345)	**2.29 (1.604)**
IGUQ	**tadalafil** - placebo	**1.50 (0.978)**	0.96 (0.751)
	placebo - **tadalafil**	1.38 (1.071)	**2.19 (1.250)**
PANSS sum **positive** symptoms	**tadalafil** - placebo	**8.88 (2.800)**	10.63 (4.926)
	placebo - **tadalafil**	11.29 (4.030)	**10.57 (2.573)**
PANSS sum **negative** symptoms	**tadalafil** - placebo	**9.00 (2.726)**	9.50 (3.071)
	placebo - **tadalafil**	8.57 (0.787)	**8.00 (1.414)**
PANSS sum **general psychopathology**	**tadalafil** - placebo	**22.63 (5.630)**	22.50 (5.372)
	placebo - **tadalafil**	22.00 (1.732)	**21.00 (2.517)**
PANSS sum **total**	**tadalafil** - placebo	**40.50 (10.254)**	42.63 (12.118)
	placebo - **tadalafil**	41.86 (5.113)	**39.57 (3.994)**
Unused Pills	**tadalafil** - placebo	**0.63 (1.19)**	1.00 (1.20)
	placebo - **tadalafil**	1.57 (1.13)	**1.14 (1.21)**

ASFQ = Antipsychotic and Sexual Functioning Questionnaire; IGUQ = Improvement Global Usefulness Question; IIEF = International Index of Erectile Function Questionnaire (IIEF); PANSS = Positive and Negative Syndrome Scale.

Besides difference in outcome due to the used type of questionnaire, not every patient seemed to respond on tadalafil. Some factors that may have had influence on response are the dose of tadalafil, the frequency of use of tadalafil, the frequency of sexual activity, the degree of erectile dysfunction at baseline, the type of antipsychotic medication, the dose of antipsychotic medication and comedication. The level of initiative in general and the presence or absence of a sexual incentive (e.g. partner) may have influenced the frequency and quality of sexual functioning. The fact that in the study of Gopalakrishnan

(Gopalakrishnan, et al. 2006) all patients were married, may have contributed to finding significant effects of sildenafil in their study. It has to be mentioned that an important limitation of our study is that we did not ask how often patients had sexual activity. Besides that, compliance to tadalafil was only measured by pill count, but theoretically, this doesn't prove that patients used all the pills that they did not hand over to the investigator.

The pharmacological mechanism thought to be relevant for the treatment effects is that tadalafil increases the amount of nitric monoxide, which increases the amount of cGMP in smooth muscle cells, causing relaxation of those muscle cells. Relaxation of the smooth muscle cells in the penis induces erection. Tadalafil may also cross the blood-brain barrier and influence the second messenger system of glutaminergic neurotransmission. Effects of PDE-5-inhibitors on depression, memory, neuroproliferation and negative symptoms have been reported, mainly in animal studies, but also in some studies with patients (Akhondzadeh, et al. 2011, Reneerkens, et al. 2012, Baek, et al. 2011). It may be theorized whether possible effects of taladafil on sexual performance may be related to central as well as peripheral effects. In this study, there was no change in negative symptoms or overall symptoms measured with the PANSS. Because of the very low baseline level of psychopathology, in this study it was not possible to demonstrate if tadalafil has effect on these symptoms.

More studies on the effects of PDE-5-inhibitors on sexual dysfunctions induced by medications are warranted. The present study may contribute to the design of new studies.

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Lilly, The Netherlands, provided the investigational product (tadalafil and placebo) and partial funding of trial expenses incurred by the investigator for the trial.

Trial registry

This trial is registered by the Central Committee on Research Involving Human Subjects (CCMO) in The Netherlands, www.ccmo.nl, registration number NL26209.097.09.

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Chapter 9

Sexual dysfunction treated with addition of aripiprazole in a female patient with a schizoaffective disorder using risperidone and paroxetine

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Submitted

Case report

Introduction

Sexual dysfunction is a frequent side effect of antipsychotics experienced by 16-60% of patients (Baggaley. 2008, Knegtering, et al. 2008, Serretti & Chiesa. 2011) with a considerable impact on quality of life and medication non-adherence (Olfson, et al. 2005, Haddad & Sharma. 2007, Finn, et al. 1990). Besides postsynaptic dopamine antagonism, prolactin elevation may be a factor in its pathogenesis (Knegtering, et al. 2008). Sexual dysfunction is also frequently reported in antidepressants, e.g. SSRIs, probably due to the serotonergic effect (Serretti & Chiesa. 2009). Patients as well as clinicians may be reluctant to discuss sexual side effects in sufficient detail (Strauss & Gross. 1984).

Case report

We present a 53-year old female patient with a clinical diagnosis of schizoaffective disorder (DSM-IV-TR). Her clinical condition stabilized with treatment with risperidone 3 mg and paroxetine 20 mg daily. She has four children from a previous relationship and is living together with a male partner.

In our yearly routine outcome monitoring in 2010, she reported decreased sexual desire and a decreased ability to reach orgasm (Manchester Short Assessment of Quality of Life, MANSA (Priebe, et al. 1999) and Subjects' Response to Antipsychotics, SRA (Wolters, et al. 2006)), while no depressive or psychotic symptoms were present.

As the patient found sexual side effects troublesome, her clinician discussed possible treatment options with her. Reducing the risperidone dosage led to an increase of psychotic symptoms, and the dose was again increased to the original level. As a second step, aripiprazole 5 mg daily was added and her sexual dysfunction disappeared. This was confirmed in the following MANSA and SRA routine outcome assessment. There was no increase of psychotic symptoms.

Discussion

Sexual dysfunction may have been caused by the pharmacological characteristics of risperidone, a potent postsynaptic dopamine antagonist for the dopamine 2 (D_2) receptor that often increases prolactin levels (Knegtering, et al. 2008). Also, the serotonergic effect of paroxetine may have impaired sexual functioning.

To treat antipsychotic-induced sexual dysfunction, most of the available evidence suggests lowering the dose or switching to an antipsychotic with less effects on sexual functioning. Also, addition strategies have been studied, e.g. aripiprazole, a dopamine agonist, or a phosphodiesterase-5-inhibitor (Nunes, et al. 2012).

In this patient, a low dose of aripiprazole was added to treatment with risperidone and paroxetine. Aripiprazole, a partial agonist, shows a higher affinity to the D_2 receptor than most antipsychotics (including risperidone) (Taylor. 2003). Aripiprazole usually acts as a dopamine antagonist, in line with its antipsychotic properties. In brain regions with a large receptor reserve for the D_2 dopamine receptor,

for example the anterior pituitary, aripiprazole can act as dopamine agonist (Meller, et al. 1991). As a consequence, aripiprazole does not induce hyperprolactinemia, and may lower serum prolactin levels (Shim, et al. 2007, Haddad & Wieck. 2004, de Boer, et al. 2011). In contrast to most antipsychotics, treatment with aripiprazole has been associated with beneficial effects on sexual performance (Nunes, et al. 2012, de Boer, et al. 2011).

Different pharmacological mechanisms may explain the successful treatment of sexual dysfunction. First, aripiprazole may compensate the antagonistic effects of risperidone on the D_2 receptor, including lowering prolactin levels. Second, antagonistic effects on the 5-HT_2 receptor and agonism of the 5-HT_{1A} receptor are associated with improvement of sexual functioning (Moll & Brown. 2011). The serotonergic effects of paroxetine on sexual functioning may have been decreased by the antagonistic effects of risperidone and aripiprazole on the 5-HT_{2A} and 5-HT_{2C} receptor (Mamo, et al. 2007, Leysen & Gommeren. 1984, Richtand, et al. 2008). It has to be noted that aripiprazole is a partial agonist for the 5-HT_{2C} receptor, but there are indications that it acts as an antagonist for the 5-HT_{2C} receptor in the presence of antidepressants with high serotonergic activity (like paroxetine) (Nguyen, et al. 2012). Also, aripiprazole is a weak partial agonist for the 5-HT_{1A} receptor, but this effect is probably small (Mamo, et al. 2007).

This case report illustrates how different pharmacological mechanisms of antipsychotics and antidepressants could have influenced sexual functioning. Insight in these mechanisms may help clinicians to design tailor made treatment strategies to reduce undesired effects of medication on sexual performance. The frequently occurring sexual side effects of antipsychotics and antidepressants should be actively addressed by clinicians. Routine outcome monitoring, or other forms of systematic assessment of medication effects on sexual functioning, is helpful to address these adverse effects in regular treatment of patients using psychotropic medication (de Boer, et al. 2014).

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Chapter 10

Summary and General Discussion

Summary and General Discussion

In this chapter, the major findings of this thesis will be presented by answering the research questions formulated in the introduction of this thesis. In addition, the most important limitations and strengths of the design and implementation of the studies will be discussed. The general discussion includes the relevance of these findings from a clinical, neurobiological and public health standpoint, leading to the formulation of recommendations for future research.

Summary

Which factors influence sexual functioning in patients with schizophrenia?

Most patients with schizophrenia show an interest in sex that differs little from the general population. In contrast, psychiatric symptoms, institutionalization, somatic diseases and psychotropic medication contribute to frequently occurring impairments in sexual functioning. In general, women with schizophrenia have a better social outcome, longer lasting (sexual) relationships and more offspring than men with schizophrenia. Nevertheless, in both sexes social and interpersonal impairments limit the development of stable relationships, including sexual relationships. It is suggested that decreased sexual desire in patients with schizophrenia may be linked to the general reduction of initiative they experience, often referred to as negative symptoms. However, antipsychotic medication may be the most prominent cause of sexual problems, including reduced sexual desire (Chapter 2).

How often do antipsychotics cause sexual side effects?

Patients using antipsychotics report antipsychotic-induced sexual dysfunction in 16% to 60% of cases, which differs between antipsychotics. Although individual patients may differ in their susceptibility for sexual dysfunctions, pharmacological differences between antipsychotics, especially the affinity for postsynaptic dopamine receptors, seem to determine the impact on sexual performance (Chapter 2, 6). These percentages are much higher than those provided in the official pharmacological information (Farmacotherapeutisch Kompas).

Which sexual side effects of antipsychotics do patients report?

A decrease in sexual desire is the most reported sexual side effect in patients treated with antipsychotics. Other reported side effects are decreased arousal (i.e. erection problems in men and lubrication problems in women), orgasm problems and decreased ejaculatory volume (Chapter 2, 6, 7). Rarely reported side effects are priapism (prolonged and painful erection) and painful orgasm. Although menstrual disturbance, gynecomastia and galactorrhea are not considered to be sexual dysfunctions, they tend to coincide with some of the sexual dysfunctions since they may originate, at least partly, from the same source: high serum prolactin levels (Chapter 2).

Why is it important for clinicians to explicitly ask for sexual side effects?

Undesired treatment effects (side effects), in particular sexual side effects, are infrequently studied. This leads to an underestimation of undesired treatment effects in general, which is especially important when shame and reluctance to discuss them may be involved. Although studies show that patients consider sexual problems to be highly relevant, both patients and clinicians not always discuss these spontaneously. An underestimation of the prevalence of sexual problems related to the use of antipsychotics also leads to more treatment dissatisfaction and non-adherence. Studies using structured interviews or questionnaires report much higher frequencies of sexual dysfunction in comparison to studies based on spontaneous reports. The introduction of questionnaires in the clinical evaluation of (sexual) side effects may be helpful in identifying these effects. Clearly, this should lead to an open discussion with the clinician on both the background and the implications of these undesired effects of medication, including a 'shared decision' on what to do about it (Chapter 2).

Which instruments are available to evaluate antipsychotic-induced sexual dysfunction?

In 2013, six validated instruments were available for assessment of sexual functioning in patients using antipsychotics: Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS), Arizona Sexual Experience Scale (ASEX), Antipsychotics and Sexual Functioning Questionnaire (ASFQ), Changes in Sexual Function Questionnaire-14 (CSFQ-14), Nagoya Sexual Function Questionnaire (NSFQ) and Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ).

The ASFQ, CSFQ-14 and PRSexDQ cover all stages of sexual functioning, which makes these questionnaires preferable above the other three described questionnaires. The ASEX does not specifically ask about ejaculation, the ANNSERS and NSFQ do not ask about vaginal lubrication, and the NSFQ does not include a question about orgasm.

The ASFQ and PRSexDQ are clinician-administered and ask for a change in sexual functioning related to medication, which is helpful when such effects need to be objectivated. The ASFQ assesses improvement as well as deterioration of sexual functioning, which was for instance useful in the risperidone-aripiprazole study in Chapter 6, as some patients with aripiprazole reported improvement of sexual functioning. The ASFQ, NSFQ and ANNSERS include items about hyperprolactinemia which are relevant in patients using antipsychotics. The CSFQ-14 is useful when self-report is desired, but contains more items making it somewhat less feasible for use in patients in the acute phase of the illness, or with cognitive problems (Chapter 4).

In Chapter 5, the psychometric properties of the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) were studied in a sample of 30 patients with schizophrenia or a schizophrenia spectrum disorder using antipsychotics. The ASFQ is a semi-structured interview that takes on average about 10 minutes to complete. In studies about antipsychotic-induced sexual dysfunction, a semi-structured interview such as the ASFQ may be better than a self-report questionnaire, especially for patients with cognitive dysfunction, to distinguish medication-related sexual dysfunction from other causes of sexual dysfunction.

The ASFQ has good face validity, content validity, internal reliability (Cronbach's alpha 0.84) and test-retest reliability (mean Spearman's rho = .76). The inter-rater reliability is good for questions about sexual desire, orgasm, erection and ejaculation. Correlation coefficients for calculating convergent validity were modest to good when comparing the ASFQ with the corresponding items on the Subject's Response to Antipsychotics questionnaire (SRA) and the Arizona Sexual Experience Scale (ASEX).
Of the available validated questionnaires which measure a change in sexual functioning, the ASFQ is the only questionnaire measuring deterioration as well as improvement. Of all validated questionnaires for the assessment of sexual functioning in patients using antipsychotics, the ASFQ is the only questionnaire which includes all stages of sexual functioning in combination with all symptoms of hyperprolactinemia, the only questionnaire for which all aspects of reliability have been investigated (internal consistency, inter-rater reliability and test-retest reliability), and which has been compared with another validated instrument (ASEX) for the determination of convergent validity.
It is concluded that the Antipsychotics and Sexual Functioning Questionnaire is a reliable instrument that can be used in the evaluation of sexual functioning in relation to the use of antipsychotics.

What are the differences between antipsychotics in their influence on sexual functioning?

The effects of different antipsychotics on sexual behavior are discussed in Chapter 2. A high prevalence of sexual dysfunction is reported by patients treated with risperidone and classical antipsychotics, while a lower prevalence of sexual dysfunction is found for clozapine, olanzapine, quetiapine and aripiprazole. A randomized open–label trial in Chapter 6 compared the effects of aripiprazole versus risperidone on sexual functioning for 6 weeks in 36 patients. Sexual dysfunction was assessed by the semi-structured Antipsychotic and Sexual Functioning Questionnaire (ASFQ). The mean dose was 12.6 (SD 5.79) mg/day for aripiprazole and 3.2 (SD 1.15) mg/day for risperidone. Only one patient (6%) treated with aripiprazole (7,5-30 mg/day; N=18) reported sexual dysfunction attributed to the use of antipsychotics. In contrast, risperidone-treated patients (1-5 mg/day; N=18) very frequently (61%) reported sexual dysfunctions (p=.001). The mean prolactin concentration was 214 (SD 148) mE/L in the aripiprazole group and 1181 (SD 673) mE/L in the risperidone group (p=0.000). In line with earlier studies, patients treated with risperidone experienced sexual side effects much more often than patients treated with aripiprazole. Patients treated with aripiprazole hardly reported sexual side effects, or reported improvement of sexual performance. Patients treated with risperidone showed a substantial prolactin elevation, while this was not found in patients treated with aripiprazole (Chapter 6).
To study the influence of depot antipsychotics on sexual functioning, the nature and frequency of sexual dysfunction was systematically assessed in a sample of 53 patients in regular outpatient mental health care. At the day of a new depot injection, two questionnaires were assessed to evaluate sexual side effects. Sexual dysfunction was reported by 47% of patients on the ASFQ, and 57% on the Subjects' Response to Antipsychotics (SRA). The rates of sexual dysfunction for depot antipsychotics are in the same range as the oral equivalents of the used depot antipsychotics (Chapter 7).

Taken together, this shows that sexual side effects are frequently occurring in oral and depot antipsychotics, but that the prevalence of sexual dysfunction differs between antipsychotics.

Can differences in antipsychotic-induced effects on sexual performance be understood from their pharmacological profile?

Literature review combined with studies from this thesis leads to the conclusion that the degree of dopamine antagonism, prolactin elevation, and α_1 antagonism are important factors which explain differential effects of antipsychotics on sexual functioning. Dopamine antagonism leads to higher levels of prolactin and possibly also vice versa. Serotonergic effects often result in a decreased ability to achieve an orgasm, except for agonism of the 5-HT_{1A} receptor. Antagonism of the 5-HT_2 receptor appears to have a stimulating effect, especially the 5-HT_{2C} receptor (Chapter 2, 3, 6, 9).

The differential effects of risperidone versus aripiprazole on sexual functioning are probably related to their contrasting effects on the dopamine system of the brain. Risperidone is a potent postsynaptic dopamine antagonist (which also increases prolactin levels), while aripiprazole is a partial dopamine agonist (Chapter 6).

Some antipsychotics cause more sexual side effects than would be expected based on the degree of dopamine antagonism alone. Probably, the passage through the blood brain barrier is an additional influencing factor. Antipsychotics with a poor passage of the blood brain barrier (e.g. risperidone and its metabolite 9-OH-risperidone, also known as paliperidone), have to be dosed relatively high to accomplish a central effect, leading to a high peripheral level. The pituitary gland produces prolactin that is regulated by dopamine. The location of the pituitary gland outside the blood brain barrier leads to a considerable rise of prolactin levels for antipsychotics with a poor passage through the blood brain barrier. Prolactin elevation may contribute to sexual dysfunction by increasing (sexual) satiety (Chapter 2, 3).

In conclusion, this suggests that the degree of dopamine antagonism is a major factor in antipsychotic-induced sexual dysfunction. Prolactin elevation is another factor, which depends on the degree of dopamine antagonism and the degree in which an antipsychotic passes the blood brain barrier. This explains why potent postsynaptic D_2 antagonists, like risperidone and haloperidol, frequently cause sexual dysfunction and prolactin elevation, while antipsychotics with a weaker affinity for the D_2 receptor, like olanzapine, quetiapine and clozapine show lower frequencies of sexual dysfunction and prolactin elevation. Aripiprazole has a high affinity for the D_2 receptor, but is a partial agonist, which explains low frequencies of sexual dysfunction and the absence of prolactin elevation.

What is the effect of the phosphodiesterase-5-inhibitor tadalafil on antipsychotic-induced erectile dysfunction?

In Chapter 8, a double-blind placebo-controlled randomized cross-over pilot study investigated adjunctive treatment with tadalafil or placebo in 15 male patients treated with an antipsychotic who experienced erectile dysfunction. The primary outcome measure was the change in erectile functioning

during a three weeks period of add-on treatment with either tadalafil or placebo, as measured with the International Index of Erectile Function Questionnaire (IIEF). Secondary outcome measures were the effects of tadalafil on erectile functioning as assessed with the Improvement Global Usefulness Question (IGUQ), effects on sexual functioning as assessed with the Antipsychotic and Sexual Functioning Questionnaire (ASFQ). Tadalafil may improve antipsychotic-induced erectile dysfunction, but this double-blind placebo controlled cross-over pilot study was underpowered to make firm conclusions on the efficacy. This study adds up with other recently published studies suggesting that phosphodiesterase-5-inhibitors may improve antipsychotic-induced erectile dysfunction.

Which treatment strategies are available for antipsychotic-induced sexual dysfunction?

It is clear that it is important to actively address sexual side effects with the patient, preferably using a validated instrument. Knowledge of the underlying pharmacological mechanisms of antipsychotic-induced sexual dysfunction is important as insight into these mechanisms helps clinicians and patients to design tailor made treatment strategies to reduce undesired effects of medications, especially undesired effects on sexual performance. Strategies to treat antipsychotic-induced sexual dysfunction include lowering the dose or switching to an antipsychotic with a lower prevalence of sexual dysfunction. If this is not effective, the addition of a dopamine agonist, aripiprazole or a phosphodiesterase-5 inhibitor has shown some promising results, but evidence is currently limited (Chapter 2, 8).

General Discussion

Clinical relevance

Antipsychotic-induced sexual dysfunction is frequently occurring in patients with schizophrenia or a related psychotic disorder, and often leads to decreased treatment-adherence and quality of life (Finn, et al. 1990, Olfson, et al. 2005). Mostly, sexual side effects of antipsychotics do not subside over time (Malik, et al. 2011).

Clinicians as well as patients may be reluctant to discuss sexual functioning, although patients do consider this topic to be important (Strauss & Gross. 1984). Using a short, validated questionnaire to assess sexual functioning may be helpful to make sexual functioning open to discussion. It is important to discuss the burden of sexual dysfunction with the patient to determine whether sexual dysfunction may be related to medication, social factors or somatic health, with the aim to consider appropriate treatment strategies.

It remains difficult to determine to which degree sexual dysfunction is caused by the symptoms of the psychotic disorder. Aizenberg et al. (Aizenberg, et al. 1995) showed that sexual dysfunction is prevalent in patients using antipsychotics as well as in patients who are not using medication. Marques et al. (Marques, et al. 2012) assessed sexual functioning in patients with a first psychotic episode, individuals at ultra-high risk (UHR) of psychosis, and healthy controls. Sexual dysfunction was evident in 50% of the UHR group, 65% of the first-episode patients and 21% of controls. Across all groups, the severity of sexual

dysfunction was correlated with the severity of psychotic symptoms. Based on these results it could be hypothesized that the psychotic disorder is the main cause of sexual dysfunction and that the influence of antipsychotics is a minor factor. An alternative hypothesis may be that in patients with severe psychotic symptoms, these symptoms as well as the use of antipsychotics could be the cause of sexual dysfunction. By contrast, in patients who are symptomatically stabilized under use of antipsychotics, sexual dysfunction is more likely to be caused by the use of antipsychotics. Differences in the prevalence of sexual dysfunction between different antipsychotics (Serretti & Chiesa. 2011, Knegtering, et al. 2008, Baggaley. 2008) suggest an important role of pharmacological factors in sexual dysfunction.

Although the clinical condition of patients with a psychotic disorder is often stabilized by the use of antipsychotics, many of them continue to experience a reduction of initiative, often referred to as negative symptoms. Negative symptoms may also be linked to a reduction of sexual initiative. Interestingly, after completing the study which compared effects of aripiprazole and risperidone on sexual functioning (Chapter 6), we analyzed data of this study on subjective well-being, anhedonia and negative symptoms (initiative, social interaction) (Liemburg, et al. 2011). Risperidone and aripiprazole did not seem to have a significant beneficial influence on negative symptoms. In contrast, subjective well-being and anhedonia as evaluated with two different self-rating questionnaires showed that aripiprazole in comparison with risperidone reduced anhedonia and improved subjective wellbeing.

In line with the study of Liemburg et al., other studies demonstrated an association between high dopamine receptor occupancy by antipsychotics and decreased subjective well-being (de Haan, et al. 2005). In conclusion, a higher dopamine receptor occupancy by antipsychotics with dopamine antagonistic properties may lead to a deterioration in different outcomes such as subjective well-being, anhedonia and sexual performance.

Neurobiology and pharmacology

An overview has been provided of the pharmacological mechanisms by which frequently prescribed psychotropic medications such as antidepressants, antipsychotics, and anti-parkinsonian medications may influence sexual performance by discussing findings from animal as well as human studies (Chapter 2, 3). The main mechanisms are mentioned in the summary. A remarkable finding from clinical and preclinical studies is the central role of dopamine in the anticipation of reward and motivation for sexual activity, and its interaction with many other neurotransmitters. In treatment of sexual dysfunction, it is important to check for medications or diseases influencing dopaminergic systems and to restore these first if possible. It has to be noted that both dopamine antagonists and dopamine agonists may lead to sexual problems such as decreased sexual functioning and hypersexuality, respectively. Second, influencing other neurotransmitter systems may be considered in an attempt to treat sexual dysfunction, like serotonin or nitric oxide.

When interpreting the literature it should be noted that, although many findings in animal and human studies appear to support each other, the translational nature of the findings is not always proven. Medication in rats is often administered in a specific area in the brain, while in humans medication is

administered systemically which may give different effects. Also, brains of rats and humans are different in many aspects, although using the model of 'wanting, liking, inhibition' to describe stages of sexual functioning make it easier to compare preclinical and clinical research.
Another complexity in the investigation of the effects of neurotransmitters is that there are differences between acute and chronic administration, probably related to downregulation of receptors in chronic use. Also, the available amount of a neurotransmitter is important. For some neurotransmitters an optimal stimulating or rewarding effect has been described for intermediate levels (e.g. opioids, noradrenalin), while low or high levels impair (or do not stimulate) sexual functioning.
Interestingly, a comparable mechanism is found in the effects of rewards. Low rewards do not induce the continuation of behavior; moderate levels induce the reinforcement of behavior, while higher reward levels tend to induce inhibitory feedback that characterizes satiety.

Limitations and strengths

This thesis contains different study types addressing the research questions, of which we will discuss the most important limitations and strengths.
Chapter 2 and 3 provide practical and theoretical overviews which could be useful for clinicians as well as researchers. These chapters describe factors involved in sexual functioning in patients with schizophrenia using antipsychotics, treatment strategies for antipsychotic-induced sexual dysfunction, and pharmacological mechanisms involved in sexual functioning in general. As mentioned earlier, results from animal studies should be interpreted with caution when looking at the possible effects in humans. This is especially the case when in animal research medication is administered in a specific brain area, while in humans it is administered systemically.
Especially for Chapter 3, it should be noted that there was an overwhelming amount of data referring to different aspects of the research question. We selected contemporary reviews, completed with additional articles where needed to further elucidate the role of complex mechanisms in sexual (dys) function. As we wanted to provide a comprehensive, clinically oriented and concise overview of the different mechanisms, it was not possible to describe all aspects in detail. Particularly for animal studies it was not possible to mention all original studies, including the differences in the circumstances in which these studies have been performed, which may have influenced the results. On the other hand, no other recent overviews are available that describe all of the neurotransmitters involved in sexual functioning in both animals and humans. Despite the complexity of this endeavour, we hope we managed to provide an overall image of this field, which may encourage the interested reader to search for more details in the original articles.
The systematic review about validated instruments for the assessment of sexual functioning in patients using antipsychotics (Chapter 4) may be helpful for clinicians and researchers to make an informed choice, depending on purpose. Although this chapter provides an accurate overview of the currently known characteristics of the available instruments, few data are available about inter-rater reliability (only for ANNSERS and ASFQ) and test-retest reliability (only for ASFQ and NSFQ). For convergent validity,

most validated instruments (except the ASFQ) have been compared with non-validated instruments. It follows that in future validation research, new as well as existing questionnaires should preferably be compared with already validated questionnaires to gain a better insight into the pros and cons of the different instruments.

In the study about the validation of the ASFQ (Chapter 5), the sample size is relatively small. Especially women were underrepresented, and the results on items about female sexual dysfunction should be viewed with caution. Also, the fact that the degree of psychotic symptoms was not assessed in this study is a limitation. On the other hand, the ASFQ is relatively short and contains simply formulated questions, taking into account the cognitive problems many patients experience. In contrast to other validated instruments, all aspects of reliability have now been described for the ASFQ. Also, the ASFQ is the only questionnaire which includes all stages of sexual functioning in combination with all symptoms of hyperprolactinemia, the only questionnaire for which all aspects of reliability have been investigated (internal consistency, inter-rater reliability and test-retest reliability), and which has been compared with another validated instrument (ASEX) for the determination of convergent validity. Of the available validated questionnaires which measure a change in sexual functioning, the ASFQ is the only questionnaire measuring deterioration as well as improvement.

In the clinical studies (Chapter 6, 7, 8), the sample sizes are relatively small, especially in the pilot study about adjunctive treatment with tadalafil for antipsychotic-induced sexual dysfunction (Chapter 8). Further studies in larger patient samples are needed to enlarge the evidence base for future adaptations of treatment concerning sexual functioning. Still, the results are mostly in line with other available studies.

A strength of this thesis is that the same instrument to assess sexual functioning (ASFQ) has been used in all clinical studies, also taking note of the fact that the ASFQ is a semi-structured interview assessed by trained interviewers.

Chapter 6 describes the open–label randomized trial assessing sexual functioning in patients treated with aripiprazole or risperidone for 6 weeks. A limitation in this study is the lack of baseline assessment of sexual functioning and serum prolactin levels. This is partly compensated by the structure of the ASFQ scoring each dimension of sexual functioning in contrast to premorbid sexual functioning. A baseline assessment based on other instruments than the ASFQ would have had the disadvantage that 1) more severely psychotic patients may not have been able to provide detailed and accurate information on recent sexual functioning, and 2) patients that used another antipsychotic until a week before the start of the study, would not have been able to provide adequate baseline information on sexual functioning, because they would have reported sexual functioning related to the use of the previous antipsychotic. A strength of the current study design is that it makes it possible to specifically investigate sexual dysfunction related to the use risperidone or aripiprazole, and to distinguish this from other causes of sexual dysfunction. This randomized trial shows differential effects on sexual functioning, which can be explained by the pharmacological characteristics of aripiprazole and risperidone.

The main limitations of the study about depot antipsychotics (Chapter 7) are the cross sectional study design and the frequent use of co-medication. Although this study has a lower level of evidence than

a randomized controlled trial, it was a first step in the assessment of sexual functioning in this hardly studied patient group that is representative for regular clinical practice. It is clear that larger studies and also intervention studies are needed to determine whether these levels of sexual dysfunction are amenable to treatment in this group of chronic patients.

The double-blind placebo-controlled randomized cross-over pilot study in Chapter 8 focused on tadalafil and placebo treatment in male patients treated with an antipsychotic who experienced erectile dysfunction. It would have been preferable to use the ASFQ as the primary outcome measure instead of the International Index of Erectile Function (IIEF), because the IIEF contains many questions about sexual activity with a partner while a significant part of the population did not have a sexual partner. However, the IIEF was chosen because this instrument is internationally considered to be the gold standard for the assessment of erectile functioning. Also, at the time this study was started, the ASFQ was not yet completely validated. Another issue to be discussed is that we used a cross-over study rather than a regular double-blind placebo-controlled randomized study design. A cross-over study is often used when the addition of a treatment strategy is examined, while it is desired that the other conditions remain stable. Advantages of a cross-over study are that this design the guarantees that participants will receive the real treatment in one period, and that each patient serves as his own control, which reduces the influence of confounders in the comparison of both groups. If medication effects would induce more permanent changes affecting the primary outcome, cross-over designs are considered to be less appropriate, but this does not seem to be the case in this study. On the other hand, all other available randomized studies investigating the effects of phosphodiesterase-5-inhibitors (sildenafil, lodenafil) in patients using antipsychotics also used cross-over designs (Gopalakrishnan, et al. 2006, Nunes, et al. 2013). Strengths are the double-blind placebo-controlled study design and the use of different questionnaires for the assessment of sexual functioning.

In Chapter 9 a case study is described of a female patient using risperidone and paroxetine experiencing sexual dysfunction, treated with the addition of aripiprazole. This case report illustrates sexual dysfunction in clinical practice, and how insight in pharmacological mechanisms may help to design tailor made treatment strategies to reduce undesired effects of medication on sexual performance.

Public health implications

A recent population-based study in Britain showed that sexual response problems lasting at least 3 months in the preceding year were common, also in young people. More than 40% of men and 50% of women reported one or more problems, but the proportion of sexually active individuals reporting distress about their sex life was much lower, about 10% (Mitchell, et al. 2013). The severity of symptoms and the context (e.g. whether an individual has the desire for sexual activity, or if a sexual partner considers the sexual dysfunction as a problem) are often decisive to experience sexual dysfunction as a problem. Opinions in society also contribute to what people consider to be normal (Gijs et al., 2009). In recent years, research of sexual dysfunction has focused on physiological aspects of sexual response and clinical diagnoses of dysfunction, e.g. by the development of phosphodiesterase-5 inhibitors for men with erectile dysfunction, and female-desire drugs (Poels, et al. 2013, van Rooij, et al. 2013). Critics state

that the marketing of these drugs will pathologize a normal decrease in desire and make people feel as though they need a pill to please their partners or to meet demands of society, while low desire may be a normal reaction to stress or relationship problems, as well as normal part of physical variation, which should be addressed in other ways. Because these can indeed be relevant aspects for part of the people with sexual dysfunction, it is important for doctors to weigh the burden of sexual dysfunction in an open discussion with the patient, including giving attention to possible causal and influencing factors. Second, it is important to provide information about sexual functioning. In the Netherlands, brochures supplying simple but adequate information can be obtained from the websites of RutgersWPF (www.rutgerswpf.nl) and the Dutch Association of Sexology (www.nvvs.info). These can be handed to the patient to be read and discussed with the clinician. When sexual dysfunction is considered to be a problem and treatment is desired, psychological as well as medication options can be considered, depending on which factors are thought to influence sexual dysfunction in the individual patient. It is clear from this thesis that treatment of sexual dysfunction often concerns stimulation of sexual functioning. However, in some cases the inhibition of sexual functioning that we discussed could be the preferred outcome, e.g. in case of premature ejaculation or sexual disinhibition.

It is important to train clinicians how to discuss sexual functioning with patients. Special attention has to be paid to sexuality in people with a disease or handicap. This combination seems to be contradictory to some people, as sexuality often is associated with pleasure, while on the other hand in the context of disease or handicap, the body is often associated with discomfort. This may also play a role for the clinician, who may be less inclined to discuss these issues with patients who have chronic diseases. Likewise, patients with a disease or handicap, including psychiatric diseases, consider sexual functioning in general as important, but are often reluctant to discuss it with their clinician (Gijs et al., 2009). In patients with psychiatric problems, sexual functioning may also be negatively influenced by stigma, problems in social contact and negative cognitions (e.g. related to decreased self-esteem). Also financial and housing problems can decrease the possibility to engage in intimate relationships. Evidence shows that psychiatric patients and their partners have a need to discuss sexual problems with a clinician, even though they may feel uneasy to start the subject (Ostman & Bjorkman. 2013).

A different but also important aspect is that of providing information on sexual health and sexual behavior in patients with chronic (mental) illnesses. This should include information about regular sexual relationships, but also about (sexual) victimization. Especially in women with schizophrenia, it is important that clinicians provide adequate information about contraception, pregnancy, as well as (in a later phase) postpartum issues and safe and effective parenting (Seeman. 2013).

It is clear that clinicians should be trained to ask about all stages of sexual functioning. They have to know the correct medical definitions and have to be able to translate these toward the needs of individual patients. To illustrate the importance of understanding, the definition of the term 'ejaculation disorder' often leads to confusion. In male animals, ejaculation is the only objective measurement of orgasm. The 'ejaculation latency time' could be interpreted as the time for a male animal to reach orgasm. In humans, orgasm in men is normally accompanied by ejaculation. However, during the use of antipsychotics with α_1 antagonistic properties, the ejaculatory volume can be decreased or completely absent, while orgasm is intact. Therefore, the advice for clinical practice is to distinguish a decreased ability to reach

orgasm (including ejaculation) from a decreased ejaculatory volume by mentioning the first orgasm disorders and the second ejaculation disorders. Thereby, it is also possible to compare orgasm disorders in men and women.

In general, research on side effects, including sexual side effects, is not very popular in clinical research. Strikingly, despite the growing body of literature, the official (registration) information about most antipsychotics only rarely reports on sexual side effects (Farmacotherapeutisch Kompas). Probably, this information still originates from the testing phase of the medication and is based on spontaneous reports. Although more studies have become available which show a high prevalence of sexual side effects, these findings apparently do not find their way to the official information on medications. This may lead to a continued underestimation of undesired treatment effects, keeping patients as well as their clinicians insufficiently informed.

Future research

The fact that antipsychotic-induced sexual side effects may not subside over time emphasizes the importance of effective treatment strategies for these side effects. As research on treatment strategies in medication-induced sexual dysfunction is limited, this should be a focus of future research. Interesting research options include combination strategies, like a combination of a low dose of testosterone with a 5-HT_{1A} receptor agonist or a low dose of testosterone with a phosphodiesterase-5-inhibitor. These strategies have been investigated in women with hyposexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) (Poels, et al. 2013, van Rooij, et al. 2013, Bloemers, et al. 2013). Still, despite a lot of media attention, these approaches currently have little scientific basis and should be further explored, in healthy persons and possibly (if proven effective) also in the group of patients using psychotropic medication.

Second, the number of women in studies about antipsychotic-induced sexual side effects is small. Larger studies of women are needed to further explore possible gender specific effects. Also, studies in female animals are limited because of cyclic changes in hormones. In recent years, more evidence about female animals has become available and this trend should be continued.

Third, more research is needed on the possible interaction between sexual side effects and the symptoms of schizophrenia, e.g. negative symptoms, lack of motivation and initiative. There may be an overlap in underlying neurobiological mechanisms. This may also be relevant for other psychiatric disorders such as depression, in which an underlying mechanism of anhedonia may be associated with sexual dysfunction. Using the pleasure cycle of 'wanting', 'liking' and 'inhibition' makes it possible to link aspects of sexual functioning to comparable aspects of negative symptoms and anhedonia. Patients with schizophrenia report similar levels of positive emotions as healthy controls when reporting current feelings, but lower levels of positive emotion when reporting noncurrent feelings (i.e. decreased anticipatory pleasure or decreased pleasurable memory). As a result, the decision making process of whether to participate in pleasurable activities is impaired ('wanting'), while if they would actually participate, the actual experience ('liking') is intact (Strauss & Gold. 2012). For anhedonia in patients with depression, results are inconsistent on which aspects may be impaired (Ho & Sommers. 2013). Studies

that investigate an association between anhedonia and sexual functioning are scarce and did not investigate patients with schizophrenia or depression. To develop a better understanding of the relation between the anhedonia concept in mood disorders and the mechanisms involved in sexuality, it is very interesting to compare different aspects of anhedonia with different aspects of sexual functioning using the model of 'wanting, liking, inhibition' or the alternative version of 'wanting, liking, learning' in which 'learning' refers to the effects of pleasurable memories on future behavior. This would be an interesting subject for future research, as for instance in anhedonia related to impaired 'wanting', also 'wanting' in sexual functioning may be impaired. In the context of treatment, patients who only experience impaired 'wanting', while 'liking' is intact, may benefit from cognitive behavioral therapy, in which the cognitive part of the therapy aims to disconfirm the belief that nothing is pleasurable, while the behavioral strategies help patients to bring themselves in pleasurable situations more often (Grant, et al. 2012).

Fourth, the variation in outcome on sexual functioning between different studies in the literature could be the result of the study design and the instruments used. Future studies should use instruments that are validated for patients using antipsychotics. These questionnaires should be relatively short and simply formulated, thereby taking into account the cognitive symptoms that many patients with a psychotic disorder experience. A recent option is to use ecological momentary assessment, a method to measure different aspects of mood such as positive and negative affect, in relation to context several times a day (aan het Rot, et al. 2012). This could be a useful method to assess how patterns of anhedonia relate to different aspects of sexual (dys)function such as impaired anticipatory pleasure, actual pleasure or pleasurable memory. Likewise, the effect of treatment with medication to improve sexual functioning on psychological symptoms can be determined in more detail with this research method.

This leads to the fifth recommendation for further research. It would be interesting to further investigate the possible central effects of PDE-5 inhibitors on anhedonia or negative symptoms. One study has shown a positive effect of adjunctive treatment with sildenafil on negative symptoms in patients with schizophrenia (Akhondzadeh, et al. 2011). In the tadalafil study in this thesis however, no changes in negative symptoms were found, but it has to be noted that the level of negative symptoms in the study population was low. The central mechanism by which PDE-5 inhibitors may act, could be on nitric oxide and second messenger systems, thereby increasing central dopamine. When studying the effects of PDE-5 inhibitors on anhedonia, it would be important to include patients with relatively high levels of anhedonia (for instance patients with a depressive disorder), to prescribe the PDE-5 inhibitor daily (in contrast with studies about sexual functioning, in which PDE-5 inhibitors are mostly used on demand), and to choose a PDE-5 inhibitor with a halflife that is long enough to maintain an effective blood level during daily administration.

Finally, it would be important to investigate to which degree knowledge about antipsychotic treatment and sexual functioning is implemented in clinical care. For instance, to determine whether clinicians adequately ask for sexual side effects, consider the burden and possible treatment options with the patient and have sufficient knowledge about pharmacological mechanisms to design tailor made treatment strategies to reduce undesired effects of antipsychotics. If the implementation of these aspects in clinical care may be suboptimal, this might be a reason to improve knowledge as well as skills. I hope this thesis may be of help in this regard.

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Nederlandse samenvatting

Introductie in het onderwerp van dit proefschrift

Schizofrenie is een ernstige psychiatrische aandoening die gekenmerkt wordt door een combinatie van verstoorde waarneming, zoals het horen van stemmen, en verstoord denken, zoals wantrouwend zijn of verward denken (psychotische symptomen). De symptomen worden vaak onderverdeeld in positieve symptomen, negatieve symptomen en cognitieve symptomen. Positieve symptomen zijn verstoringen in het waarnemen, zoals hallucinaties, en verstoringen van het denken, zoals wanen. Hallucinaties zijn waarnemingen die anderen niet waarnemen, zoals het horen van stemmen of het zien van beelden. Wanen zijn stellige denkbeelden (overtuigingen) die niet overeenkomen met de realiteit. Veel mensen met schizofrenie hebben ook een verlies aan energie en nemen minder initiatieven. Deze kenmerken worden veelal negatieve symptomen genoemd. Cognitieve symptomen zijn problemen met het oplossen van problemen, geheugen, plannen en organiseren.

Mensen met schizofrenie maken vaak meerdere psychotische perioden mee, waarin ze tijdelijk het contact met de werkelijkheid kunnen kwijtraken door de eerder genoemde wanen en/of hallucinaties. Ook tussen de psychotische episoden ervaren patiënten vaak veel beperkingen in hun dagelijks functioneren, waarbij de negatieve en cognitieve symptomen een belangrijke rol spelen.

In de behandeling van schizofrenie speelt behandeling met antipsychotische medicatie (antipsychotica) een belangrijke rol. Door antipsychotica nemen onrust, angst, verwardheid, wanen en hallucinaties af, maar deze middelen hebben ook ongewenste effecten, waaronder seksuele bijwerkingen.

Seksualiteit is voor veel mensen belangrijk en plezierig. Problemen in de seksualiteit komen regelmatig voor, en hangen samen met een verminderde kwaliteit van leven, ook binnen de algemene bevolking. Veel mensen, zowel patiënten als artsen, praten niet gemakkelijk over seksualiteit. Zeker wanneer seksuele problemen worden ervaren, is het onderwerp vaak met schaamte beladen. Dit speelt ook bij patiënten met schizofrenie.

In dit proefschrift wordt beschreven welke factoren betrokken zijn bij seksueel functioneren bij patiënten met schizofrenie, de invloed van schizofrenie op seksueel functioneren en de invloed van antipsychotica. Het blijkt dat antipsychotica veel invloed kunnen hebben op seksueel functioneren. Dit proefschrift probeert inzicht te geven over hoe antipsychotica seksueel functioneren beïnvloeden. Dit geeft tevens inzicht hoe seksueel functioneren is geregeld in het lichaam. Daarnaast geeft het onderzoek informatie over hoe mensen die antipsychotica gebruiken en seksuele problemen ervaren via speciale behandelingsstrategieën geholpen kunnen worden.

Welke factoren hebben invloed op het seksueel functioneren van patiënten met schizofrenie?

De interesse in seks verschilt bij de meeste patiënten met schizofrenie weinig van mensen in de algemene bevolking. Het seksueel functioneren van patiënten met schizofrenie wordt echter vaak belemmerd door een aantal factoren, zoals de symptomen van de ziekte, antipsychotica, lichamelijke ziekten of institutionalisering. In het algemeen geldt dat bij vrouwen met schizofrenie het sociaal functioneren beter is, zij langer durende (seksuele) relaties hebben en dat ze vaker kinderen hebben dan mannen met

schizofrenie. Desondanks zijn sociale en interpersoonlijke beperkingen bij zowel mannen als vrouwen belemmerend bij het ontwikkelen van stabiele (seksuele) relaties. Mogelijk is er bij patiënten met schizofrenie een verband tussen verminderd seksueel verlangen en de algemene afname van initiatief die zij vaak ervaren (negatieve symptomen). Er wordt echter gedacht dat antipsychotica de belangrijkste oorzaak zijn van seksuele problemen, inclusief afgenomen seksueel verlangen (Hoofdstuk 2).

Hoe vaak veroorzaken antipsychotica seksuele bijwerkingen?

Patiënten rapporteren in 16% tot 60% van de gevallen problemen in het seksueel functioneren die gerelateerd zijn aan het gebruik van antipsychotica. De kans op seksuele bijwerkingen verschilt per antipsychoticum. Hoewel de gevoeligheid voor seksuele bijwerkingen per individuele patiënt kan verschillen, spelen de farmacologische verschillen tussen antipsychotica een belangrijke rol, vooral de mate waarin deze middelen het dopamine systeem in de hersenen remmen (Hoofdstuk 2, 6).

Welke seksuele bijwerkingen van antipsychotica worden door patiënten gemeld?

De meeste gemelde seksuele bijwerking is afgenomen seksueel verlangen. Andere bijwerkingen zijn opwindingsproblemen (erectieproblemen bij mannen en afgenomen vaginale vochtigheid bij vrouwen), orgasmeproblemen en een afgenomen hoeveelheid sperma bij de ejaculatie (Hoofdstuk 2, 6, 7). Zeldzame bijwerkingen zijn priapisme (langdurige en pijnlijke erectie) en pijn bij het orgasme. Verder kunnen bij het gebruik van antipsychotica menstruatiestoornissen, borstvorming (gynaecomastie) en uitvloed uit de tepels (galactorroe) voorkomen, samenhangend met een verhoging van het prolactine. Hoewel dit geen seksuele bijwerkingen zijn, komen ze vaak samen voor met seksuele bijwerkingen, aangezien prolactineverhoging vermoedelijk ook een van de factoren is bij het ontstaan van seksuele bijwerkingen (Hoofdstuk 2).

Waarom is het belangrijk dat artsen gericht vragen naar seksuele bijwerkingen?

Bijwerkingen, en in het bijzonder seksuele bijwerkingen, worden relatief weinig onderzocht. Dit leidt tot een onderschatting van ongewenste effecten in het algemeen, wat nog meer kan optreden wanneer het onderwerp met schaamte beladen is. Hoewel onderzoeken laten zien dat patiënten seksuele problemen erg belangrijk vinden, aarzelen zowel artsen als patiënten om hier spontaan over te beginnen. De onderschatting van seksuele problemen door het gebruik van antipsychotica leidt vaak tot ontevredenheid over de behandeling en afgenomen therapietrouw. Studies die gestructureerde interviews of vragenlijsten gebruiken rapporteren veel vaker seksuele disfunctie in vergelijking met studies die gebaseerd zijn op wat patiënten spontaan rapporteren. Het gebruik van vragenlijsten voor het evalueren van (seksuele) bijwerkingen kan behulpzaam zijn om deze bijwerkingen te achterhalen. Daarnaast is het echter noodzakelijk dat er een gesprek plaatsvindt tussen arts en patiënt, waarbij zij samen afwegen wat voor de patiënt de last is en welke mogelijkheden er zijn om seksuele bijwerkingen te verminderen (Hoofdstuk 2).

Welke meetinstrumenten zijn beschikbaar voor het evalueren van seksuele disfunctie bij het gebruik van antipsychotica?

In 2013 waren er zes goed onderzochte (gevalideerde) meetinstrumenten beschikbaar om seksueel functioneren in kaart te brengen bij patiënten die antipsychotica gebruiken: Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS), Arizona Sexual Experience Scale (ASEX), Antipsychotics and Sexual Functioning Questionnaire (ASFQ), Changes in Sexual Function Questionnaire-14 (CSFQ-14), Nagoya Sexual Function Questionnaire (NSFQ) en Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ).

De ASFQ, CSFQ-14 en PRSexDQ vragen naar alle fasen van seksueel functioneren, waardoor deze vragenlijsten de voorkeur hebben boven de andere drie vragenlijsten. De ASEX vraagt niet specifiek naar ejaculatie, de ANNSERS en NSFQ vragen niet naar vaginale vochtigheid en de NSFQ bevat geen vraag over orgasme.

De ASFQ en PRSexDQ worden afgenomen door een interviewer (bijvoorbeeld de behandelend arts) en vragen naar een verandering in seksueel functioneren die gerelateerd is aan het gebruik van medicatie. De ASFQ vraagt zowel naar verbetering als verslechtering van seksueel functioneren, wat zinvol bleek in de risperidon-aripiprazol studie in hoofdstuk 6, aangezien enkele patiënten onder gebruik van aripiprazol een verbetering van seksueel functioneren rapporteerden. De ASFQ, NSFQ en ANNSERS bevatten vragen over een verhoging van het prolactine, wat relevant is bij patiënten die antipsychotica gebruiken. De CSFQ-14 kan gebruikt worden wanneer een zelfrapportage vragenlijst gewenst is, maar deze vragenlijst bevat meer vragen dan de andere vragenlijsten, wat minder geschikt kan zijn wanneer patiënten psychotische symptomen of cognitieve problemen hebben (Hoofdstuk 4).

Hoofdstuk 5 betreft een onderzoek naar de psychometrische eigenschappen van de Antipsychotics and Sexual Functioning Questionnaire (ASFQ) in 30 patiënten met schizofrenie of andere psychotische stoornis die antipsychotica gebruiken. De ASFQ is een semigestructureerd interview dat in ongeveer 10 minuten kan worden afgenomen. In studies naar seksuele disfunctie bij gebruik van antipsychotica zou een semigestructureerd interview beter kunnen zijn dan een zelfrapportage vragenlijst voor het onderscheiden van medicatie gerelateerde seksuele disfunctie van andere oorzaken van seksuele disfunctie, vooral bij patiënten met cognitieve problemen.

De ASFQ heeft een goede indruksvaliditeit, inhoudsvaliditeit, interne consistentie (Cronbach's alpha 0.84) en test-hertest betrouwbaarheid (mean Spearman's rho = .76). De interbeoordelaarsbetrouwbaarheid is goed voor vragen over seksueel verlangen, orgasme, erectie en ejaculatie. Correlatie coëfficiënten voor het berekenen van convergente validiteit waren gemiddeld tot goed bij vergelijking van de ASFQ met de corresponderende items van de Subject's Response to Antipsychotics questionnaire (SRA) en de Arizona Sexual Experience Scale (ASEX).

Van de beschikbare gevalideerde meetinstrumenten die een verandering in seksueel functioneren meten is de ASFQ de enige die zowel verslechtering als verbetering meet. Van alle gevalideerde vragenlijsten voor seksueel functioneren bij patiënten die antipsychotica gebruiken is de ASFQ de enige vragenlijst die vraagt naar zowel alle fasen van seksueel functioneren in combinatie met alle

symptomen van een verhoogd prolactine, als de enige gevalideerde vragenlijst waarbij alle aspecten van betrouwbaarheid zijn onderzocht (interne consistentie, interbeoordelaarsbetrouwbaarheid en test-hertest betrouwbaarheid) en voor het bepalen van de convergente validiteit is vergeleken met een andere vragenlijst (ASEX) die voor deze doelgroep is gevalideerd.
Concluderend is de Antipsychotics and Sexual Functioning Questionnaire (ASFQ) een betrouwbaar instrument dat kan worden gebruikt voor het evalueren van seksueel functioneren in relatie tot het gebruik van antipsychotica.

Wat zijn de verschillen tussen antipsychotica wat betreft het effect op seksueel functioneren?

Het effect van verschillende antipsychotica op seksueel functioneren is besproken in hoofdstuk 2. Seksuele disfunctie komt frequent voor bij patiënten die risperidon en klassieke antipsychotica gebruiken, terwijl het minder vaak voorkomt bij gebruik van clozapine, olanzapine, quetiapine en aripiprazol.
De gerandomiseerde open-label studie in hoofdstuk 6 vergeleek de effecten van aripiprazol en risperidon op seksueel functioneren bij 36 patiënten gedurende 6 weken. Seksuele disfunctie werd in kaart gebracht met behulp van de Antipsychotics and Sexual Functioning Questionnaire (ASFQ). De gemiddelde dosis was 12.6 (SD 5.79) mg/dag voor aripiprazol and 3.2 (SD 1.15) mg/dag voor risperidon. Slechts één patiënt (6%) die werd behandeld met aripiprazol (7,5-30 mg/dag; N=18) rapporteerde seksuele disfunctie gerelateerd aan het gebruik van dat middel. Patiënten die werden behandeld met risperidon (1-5 mg/dag; N=18) rapporteerden echter zeer frequent (61%) seksuele disfunctie (p=.001). De gemiddelde prolactine concentratie was 214 (SD 148) mE/L in de aripiprazol groep and 1181 (SD 673) mE/L in the risperidon groep (p=0.000).
In overeenstemming met andere studies ervoeren patiënten die behandeld werden met risperidon veel vaker seksuele disfunctie dan bij behandeling met aripiprazol. Patiënten die aripiprazol gebruikten rapporteerden nauwelijks seksuele bijwerkingen, of rapporteerden een verbetering van seksueel functioneren. Bij patiënten die behandeld werden met risperidon was ook duidelijk sprake van prolactine verhoging, terwijl dit niet werd gevonden bij gebruik van aripiprazol (Hoofdstuk 6).
Verder werd de invloed van depot antipsychotica op seksueel functioneren onderzocht bij 53 ambulante patiënten. Op de dag van een nieuwe depot injectie werden twee vragenlijsten afgenomen om seksuele bijwerkingen in kaart te brengen. Seksuele disfunctie werd gerapporteerd door 47% van de patiënten op de ASFQ en 57% op de Subjects' Response to Antipsychotics (SRA). Hieruit bleek dat seksuele disfunctie bij depot antipsychotica ongeveer evenveel voorkomt als bij orale antipsychotica die dezelfde werkzame stof bevatten (Hoofdstuk 7).
Samengevat komen seksuele bijwerkingen frequent voor bij zowel orale als depot antipsychotica, maar verschilt de kans op seksuele disfunctie tussen antipsychotica.

Kunnen verschillende effecten van antipsychotica op seksueel functioneren verklaard worden op basis van hun farmacologische profielen?

Uit de literatuur en de studies in dit proefschrift blijkt dat bij geneesmiddelen zoals antipsychotica de mate van dopamine blokkade, prolactine verhoging en α_1 blokkade belangrijke factoren zijn in het effect van medicatie op seksueel functioneren. Dopamine blokkade leidt tot verminderd seksueel functioneren, maar leidt tevens tot een verhoging van de hoeveelheid prolactine in het bloed, wat zeer waarschijnlijk een aanvullende remmende factor op seksueel functioneren is. Een verhoging van het serotonine, bijvoorbeeld door het gebruik van bepaalde antidepressiva, leidt vaak tot een verminderd vermogen om een orgasme te bereiken. Beïnvloeding van bepaalde subtypen serotoninereceptoren heeft een gunstig effect op seksueel functioneren, namelijk stimulatie van de (presynaptische) 5-HT_{1A} receptor en blokkade van de (postsynaptische) 5-HT_2 receptor, in het bijzonder de 5-HT_{2C} receptor (Hoofdstuk 2, 3, 6, 9).

De verschillende effecten van risperidon en aripiprazol op seksueel functioneren worden zeer waarschijnlijk verklaard door hun verschillende effecten op het dopamine systeem in de hersenen. Risperidon blokkeert het dopamine in sterke mate (wat tevens leidt tot een stijging van het prolactine), terwijl aripiprazol een partiële dopamine agonist is, wat betekent dat het zowel blokkerende als stimulerende effecten op het dopamine systeem heeft (Hoofdstuk 6).

Sommige antipsychotica veroorzaken meer seksuele bijwerkingen dan verwacht zou worden op basis van alleen hun blokkerende effect op het dopamine system. Waarschijnlijk is de mate waarin een middel de bloed-hersenbarrière passeert een aanvullende factor. Antipsychotica die de bloed-hersenbarrière moeizaam passeren (bijvoorbeeld risperidon en zijn afbraak product (metaboliet) 9-OH-risperidon, ook bekend als paliperidon) moeten relatief hoog gedoseerd worden om in de hersenen een effect te bewerkstelligen, waarbij er in de rest van het lichaam een relatief hoge concentratie van het middel aanwezig is. De hypofyse produceert prolactine dat wordt gereguleerd door dopamine. Aangezien de hypofyse buiten de bloed-hersenbarrière ligt, wordt het blootgesteld aan een relatief hoge concentratie van het dopamine blokkerende antipsychoticum, waardoor het prolactine sterk stijgt. Prolactine speelt waarschijnlijk een rol bij (seksuele) verzadiging (Hoofdstuk 2, 3).

Concluderend is de mate van dopamine blokkade door een geneesmiddel waarschijnlijk de belangrijkste factor bij antipsychotica gerelateerde seksuele disfunctie. Prolactine verhoging is een andere factor, die afhankelijk is van de mate van dopamine blokkade en de mate waarin een antipsychoticum de bloed-hersenbarrière passeert. Dit verklaart waarom middelen die het dopamine sterk blokkeren, zoals risperidon en haloperidol, frequent seksuele disfunctie veroorzaken, terwijl olanzapine, quetiapine en clozapine minder vaak leiden tot seksuele problemen en prolactine verhoging. Aripiprazol hecht wel sterk aan de dopamine receptor, maar is een partiële dopamine agonist, wat verklaart dat seksuele disfunctie nauwelijks voorkomt en dit middel eveneens niet leidt tot prolactine verhoging.

Wat is het effect van de fosfodiësteraseremmer tadalafil op erectiestoornissen gerelateerd aan het gebruik van antipsychotica?

In hoofdstuk 8 wordt een dubbelblinde placebogecontroleerde gerandomiseerde cross-over pilot studie beschreven, waarbij 15 mannen met antipsychotica gerelateerde erectiestoornissen werden behandeld met tadalafil of placebo. De primaire uitkomstmaat was de verandering in het vermogen een erectie te krijgen en te houden zoals gemeten met een speciale vragenlijst, de International Index of Erectile Function Questionnaire (IIEF). Secundaire uitkomstmaten waren het effect van tadalafil op de erectiestoornis gemeten met de Improvement Global Usefulness Question (IGUQ), en de effecten op seksueel functioneren gemeten met de Antipsychotics and Sexual Functioning Questionnaire (ASFQ). Mogelijk verbetert tadalafil erectiestoornissen bij gebruik van antipsychotica, maar de power van deze studie was onvoldoende om dit met zekerheid te kunnen vaststellen. Wel komt het resultaat overeen met andere recent gepubliceerde studies die suggereren dat fosfodiësteraseremmers zoals tadalafil of sildenafil erectiestoornissen bij gebruik van antipsychotica kunnen verbeteren.

Welke behandelingsstrategieën zijn beschikbaar voor seksuele disfunctie gerelateerd aan het gebruik van antipsychotica?

Het is belangrijk is om gericht naar seksuele bijwerkingen te vragen tijdens gebruik van antipsychotica (en overigens ook bij gebruik van andere geneesmiddelen, zoals antidepressiva), en deze samen met de patiënt te evalueren. Bij het evalueren van seksuele functiestoornissen wordt bij voorkeur een gevalideerd meetinstrument gebruikt. Kennis over de onderliggende farmacologische mechanismen van geneesmiddelen helpt artsen en patiënten om te kiezen voor passende behandelingsstrategieën om ongewenste effecten van medicatie te verminderen, in het bijzonder ongewenste effecten op seksueel functioneren. Ten eerste kunnen dosisverlaging of het switchen naar een middel met minder kans op seksuele bijwerkingen worden overwogen. Als dit niet effectief is, kan ook het toevoegen van een dopamine agonist, aripiprazol of een fosfodiësteraseremmer een gunstig effect hebben. Meer onderzoek is nodig naar wat de beste strategie is om door antipsychotica veroorzaakte seksuele problemen beter te helpen behandelen (Hoofdstuk 2, 8).

Take-home messages

- Schizofrenie is een ernstige psychiatrische aandoening die gekenmerkt wordt door een combinatie van positieve symptomen (wanen, hallucinaties), negatieve symptomen (bijvoorbeeld verminderd initiatief) en cognitieve symptomen, waardoor patiënten vaak veel belemmeringen ervaren in hun dagelijks functioneren.
- In de behandeling van schizofrenie spelen antipsychotica een belangrijke rol. Daarmee nemen psychotische verschijnselen meestal af, maar deze middelen hebben ook ongewenste effecten, waaronder seksuele bijwerkingen.
- Patiënten rapporteren in 16% tot 60% van de gevallen problemen in het seksueel functioneren die gerelateerd zijn aan het gebruik van antipsychotica. De kans op seksuele bijwerkingen verschilt per antipsychoticum.

- Patiënten met schizofrenie vinden seksueel functioneren een belangrijk onderwerp, maar zowel patiënten als artsen zijn vaak terughoudend in het bespreken hiervan, wat leidt tot een onderschatting van het probleem. Seksuele bijwerkingen zijn geassocieerd met een verminderde kwaliteit van leven en therapietrouw.
- Het is belangrijk dat artsen actief vragen naar seksuele bijwerkingen en samen met de patiënt de last overwegen, waarbij het gebruik van een gevalideerde vragenlijst behulpzaam kan zijn.
- In 2013 waren er zes gevalideerde meetinstrumenten beschikbaar om seksueel functioneren in kaart te brengen bij patiënten die antipsychotica gebruiken, waaronder de Antipsychotics and Sexual Functioning Questionnaire (ASFQ), waarvan de psychometrische eigenschappen in dit proefschrift onderzocht zijn.
- Bij het ontstaan van seksuele bijwerkingen spelen onder andere de mate van dopamine blokkade en verhoging van het prolactine een rol. Seksuele disfunctie komt frequent voor bij patiënten die risperidon en klassieke antipsychotica gebruiken, terwijl het minder vaak voorkomt bij gebruik van clozapine, olanzapine, quetiapine en aripiprazol. Deze verschillen zijn te herleiden tot de farmacologische kenmerken van de verschillende antipsychotica.
- Qua behandelingsstrategieën bij seksuele bijwerkingen kan in de eerste plaats dosisverlaging of het switchen naar een antipsychoticum met minder kans op seksuele bijwerkingen worden overwogen. Als dit niet effectief is, kan ook het toevoegen van een dopamine agonist, aripiprazol of een fosfodiësteraseremmer een gunstig effect hebben.

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Curriculum Vitae

Marrit Kristine de Boer was born on March 23rd, 1984. After finishing grammar school (gymnasium), she started studying Medicine at the University of Groningen in 2002 and graduated cum laude for her Medical Qualifying Examination (artsenbul) in 2008. From 2008 to 2013, she worked as a resident in psychiatry in the Department of Psychiatry of the University Medical Center Groningen (UMCG). Since 2010, she has been combining her clinical work with the scientific research described in this PhD thesis. Since 2013, she has been working as a psychiatrist at the specialized outpatient department of depression of the Department of Psychiatry of the UMCG. She is planning to continue her research in the field of mood disorders, partly with sexual functioning in patients with a psychiatric disorder as an area of special interest.

Marrit is living together with Ronald. Together they enjoy travelling, salsa dancing and gastronomic experiences.