Antipsychotic Treatment and Sexual Functioning
Role of Prolactin

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Chapter 1

Schizophrenia, Sexual Functioning and Antipsychotic Treatment: a Review

Introduction

Over the past several years several patients on our research ward for people with schizophrenia and related psychotic illnesses at the University Hospital in Groningen began reporting sexual problems and amenorrhoea while undergoing treatment and asked for consultation. Turning to the literature, however, we discovered there was surprisingly little to support clinical guidance. Briefly put, it was this glaring lacuna and, of course, the growing awareness that sexual problems psychiatric patients are suffering may well be related to the treatment they are receiving, that prompted us to undertake a number of research activities. Among the questions raised are the following:

1. How is sexual functioning in patients with schizophrenia viewed from a historical and social perspective?
2. How important is sex for people with schizophrenia and to what extent are their doctors aware of this?
3. What weight do the sexual complaints of people with schizophrenia have for the doctors that treat them?
4. How often do patients with schizophrenia experience sexual dysfunctions?
5. What mechanism are involved in antipsychotic induced sexual dysfunctions?
6. In what way do antipsychotics influence individual aspects of a patient’s sexual performance?

In this chapter these and other questions will be addressed in the following way. First, the importance will be traced of social-related, disease-related and treatment-related factors with regards to sexual dysfunctions in patients with schizophrenia. Next, psychopharmacological mechanisms involved in antipsychotic-related sexual side effects will be discussed. Then, the focus will be on sexual dysfunctions themselves and their relevance in clinical studies in schizophrenia. Finally, conclusions and clinical implications will be discussed.

How do sexual symptoms relate to schizophrenia?

In the early 20th century schizophrenia was thought to develop because of deficiencies in sex hormones (Jacobs and Bobek 1991). Later psychoanalytic theories suggested that psychosis might derive from unconscious homosexual tendencies (Norman 1948). Erotic sexual behaviors were also seen as possible causal factors in schizophrenia in pre-schizophrenic patients (Ariety 1967). Mainly theory-driven and not based on any empirical research, these ideas have been abandoned in modern research.

According to case reports, patients sometimes do experience censedastic hallucinations of sexual nature, erotomanic delusions, delusions related to sexual identity and hypersexuality during an acute psychotic episode (Akhtar and Thomson 1980; Connolly and Gittleson 1971). But such psychotic manifestations
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are uncommon and usually disappear after the start of antipsychotic medication (Fortier et al. 2000).

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

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

According to Skopec et al. most patients with schizophrenia do not differ from controls in terms of actual sexual behavior (Skopec et al. 1981). Though relatively rare, some patients show a lack of inhibition in their sexual behavior as a direct result of psychotic symptomatology, i.e. schizophrenia can be associated with altered sexual behavior. Moreover, patients with schizophrenia can become preoccupied with sex in seemingly distorted and bizarre ways. Preoccupations and delusions may center on the sexual act and pregnancy, but they are seldom acted upon (Jacobs and Bobek 1991). In fact, most sexual activity is expressed in either fantasy or masturbation. According to earlier studies, male patients practice masturbation two to three times more frequently, albeit less pleasurable than men in the general population (Skopec et al. 1981). 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 was 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. Moreover, a study by McEvoy of chronically institutionalized women found that most of them had continuing interest in sex and were indeed sexually active (McEvoy et al. 1983). 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 (Rabo 1984). At the same time, the sex-life of patients who did live harmoniously with a partner seemed to be no different from controls who were not mentally ill (Rabo 1984).

It has been suggested that schizophrenia influences the sexual behavior in men and women in different ways (Verhulst and Schneidman 1981). For example, women with schizophrenia have better social outcome, as they date, have sex, marry and raise children more often than men do (McGlashan and Bardenstein
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1990). McEvoy and colleagues studied the sexual activity and attitude in chronic in-
patients with schizophrenia (McEvoy et al. 1983). Some female subjects reported
to have increased sexual activity, while others reported alternating periods of
hyper-sexuality and hypo-sexuality. Female patients often considered their sexual
partners to be undesirable, while both male and female patients tended to feel
guilty about their sexual preoccupations. A majority of female patients with chronic
schizophrenia continued to be interested in sex, and about one half of them wanted
to become pregnant, many of them unaware of the limitations in their parenting
abilities.

In another study of sexual problems in 20 male and 20 female outpatients suffering
from schizophrenia, 80% indicated that sexuality was important to them and 68%
indicated to long for sexual contact (Buddeberg et al. 1988). More than one third
did have regular sexual contacts. On the other hand, inhibition of sexual desire was
also reported, with many men having erectile dysfunctions and women reporting
more general sexual dysfunctions. The authors concluded that sexual dysfunctions
seemed to be related to antipsychotic treatment and an impaired capacity for
maintaining interpersonal relationships.

Summary: only a limited number of studies have evaluated sexual functioning in
schizophrenic patients. Whether or not schizophrenia is linked to problematic
sexual behavior has yet to be settled. Clear is that institutionalization impairs
sexual functioning. Psychotropic medication may be affiliated with the induction of
sexual dysfunction. Still, most patients with schizophrenia show an interest in sex
that differs little from the general population. Compared with 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.

How do patients and doctors weigh the burden of sexual complaints?

In a study of 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) up to 5 (most serious). Patients rated prosecutory hallucinations
as heavy burden (frequency in patients reporting the symptom 66%, and the
corresponding burden 4.34). Significantly, the burden of impotence (frequency
34%, burden 4.5) and absence or painful ejaculation (frequency 12%, burden 4.0)
were rated in the same range.

More recently, a survey of over 2000 mental health service users published by the
English National Schizophrenia Fellowship showed that a large proportion of
people experienced side effects from their antipsychotic medication and that sexual
side effects were deemed to be the most troublesome (Smith et al. 2002).

It has also been shown that sexual side effects are of high importance to patients
and that they have a great influence on compliance (Finn et al. 1990). Still, patients
and clinicians are equally reluctant to discuss these matters (Strauss and Gross
1984).
Strauss and Gross interviewed 86 psychiatrists on the importance of sexual side effects of psychopharmacological treatment (Strauss and Gross 1984). Most psychiatrists considered sexual side effects to be clinically relevant in two out of three patients. Also many of the psychiatrists felt that these side effects were likely to influence treatment compliance in a negative way. Moreover, a majority was convinced that most patients would not discuss sexual items spontaneously. Yet, only 10% of the psychiatrists had actually asked their patients about sexual side effects. Why the other 90% refrained from doing so remained unexplained in this study. Importantly, in their opinion antipsychotic drugs in general influenced sexual functioning and about half of these psychiatrists asked actually used these side effects for the clinical management of abnormal sexual behavior.

In a large study of Lingjaerde et al. on antipsychotics medication, patients indicated that neurological, psychic, autonomous and sexual side effects contributed to the global side effects rating, all more or less to the same extent (Lingjaerde et al. 1987). On the other hand, doctors judged the neurological and psychological side effects to correlate most with the overall global side effects rating. This suggests that doctors tend to underestimate the impact of sexual side effects for the patients.

**Summary:** Patients with schizophrenia consider sexual problems to be relevant to them. However, both clinicians and patients seem to be reluctant to discuss these side effects. Therefore, in clinical practice frequency and impact of sexual problems may be widely underestimated.

**How often do people with schizophrenia experience sexual dysfunctions?**

Adequate evaluation of sexual dysfunctions in patients with schizophrenia is hampered by the fact that alterations in sexual performance patients experience may result from their primary illness, the way it is being treated as well as the social consequences that adhere in being schizophrenic (Nestoros et al. 1981). Clinical trials assessing sexual side effects of antipsychotics are rare; comparative studies are virtually absent (Nestoros et al. 1981; Peuskens et al. 1998; Knegtering et al. 2000). The studies we were able to identify as relevant in the literature are listed in tables 2-4. Studies using spontaneous accounts of patients report low incidences of sexual dysfunctions related to treatment with antipsychotics, actually less than 10% of the patients report sexual dysfunctions spontaneously when asked for side effects (Knegtering et al. 1999). On the other hand, studies using structured interviews or questionnaires tend to report high incidences of sexual side effects related to treatment with antipsychotics. In such studies, 30% to 60% of the patients with schizophrenia report sexual dysfunctions (Lingjaerde et al. 1987; Sullivan and Lukoff 1990). Lingjaerde and colleagues interviewed 2,391 patients treated with antipsychotics, using the Udvalg for Klinische Undersøgelser (UKU). This scale evaluates a wide range of side effects including sexual side effects. The study was a cross-sectional study including patients of all ages and varying duration of treatment, 58% of them suffering from schizophrenia. The most reported side effect was libido reduction in 37% of male and female patients. Orgasmic dysfunction was found in 19% of female and 16% of male patients. Sexual side effects seemed to be less
pronounced for high-potency antipsychotics. Even years after treatment initiation, the sexual side effects did not seem to subside.

In a study by Pfeiffer et al. sexual dysfunction was evaluated in 103 outpatients during long-term treatment with psychotropic medication (Pfeiffer et al. 1991). Fifty-three percent of the patients using antipsychotics reported sexual dysfunctions versus 10% of the patients using antidepressants and 31% of the patients using lithium.

Aizenberg et al. compared sexual functioning in 122 male subjects: 20 drug-free patients with schizophrenia, 51 neuroleptic-treated (depot form) patients with schizophrenia and 51 normal controls (Aizenberg et al. 1995). A high frequency of sexual dysfunction was reported by both schizophrenic groups of patients. The treated patients in particular reported impairments in arousal items (erection) and orgasm during sex. Desire parameters (libido) were reduced in both groups of patients, but reduction in the frequency of sexual thoughts was confined to the untreated one. Treated patients reported dissatisfaction with their sexual function. Aizenberg concluded that treatment with antipsychotics might be associated with restoration of sexual desire while impairing erectile, orgasmic, and sexual satisfaction problems.

Ghadirian et al. examined a random sample of 55 schizophrenic outpatients. Selected from a long-term follow-up clinic (26 men and 29 women) were treated with classical neuroleptics. The patients rated their current sexual functioning on specially designed scales. Fifty-four percent of male and 30% of female patients reported impaired sexual functioning during neuroleptic treatment. Men reported mainly erection disturbance (Ghadirian et al. 1982a).

Teusch and coworkers compared sexual dysfunctions in male and female patients with schizophrenia, opiate addiction, neurosis and normal controls (Teusch et al. 1995). We restrict our discussion to patients with schizophrenia (N=45, 30 male, 15 female) and normal controls (N=41, 22 male, 19 female). Eleven patients used a phenothiazide derivates, 11 clozapine, 19 other antipsychotics, 4 no medication (2 male, 2 female patients). Male patients with schizophrenia reported in 88% of the cases sexual dysfunctions versus 27% of the controls (p=0.00). Female patients with schizophrenia reported in 93% of the cases sexual dysfunctions (including menstrual disorders) versus 63% of the controls (p=0.01).

Although comparative studies are rare, the majority of the literature suggests that antipsychotics might differ in the type and frequency of sexual dysfunctions they cause (Ghadirian et al. 1982b; Knegethering et al. 1999). For instance, thioridazine seems to cause more sexual dysfunctions (erection and ejaculation) compared with other classical antipsychotics (Kotin et al. 1976).

In a study by Smith et al. 101 patients using conventional antipsychotics were compared with 57 normal controls and 55 patients attending a sexual dysfunction clinic. Sexual dysfunctions were found in 45% of the patients using conventional (classical) antipsychotics, 17% of normal controls and 61% of controls attending a sexual dysfunction clinic. Male patients reported normal libido, but were highly likely to report erectile and ejaculation dysfunction. In women, thioxanthenes substitutes, benzamides, and aliphatic phenothiazines were more likely to be associated with sexual dysfunction than with other neuroleptics (Smith et al. 2000).
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Clozapine is an “atypical” antipsychotic that causes no extrapyramidal side effects and virtually no prolactin elevation. In addition, Crenshaw stated that clozapine also had a lower liability for sexual dysfunctions (Crenshaw and Goldberg 1996). However, Hummer et al. did a comparison study between clozapine and haloperidol in which patients were treated for six weeks with either clozapine or haloperidol and sexual dysfunctions were evaluated weekly using the UKU (Hummer et al. 1999). At week 6 more than 50% of the patients had reported sexual side effects, but no differences were found between patients using haloperidol versus clozapine (Hummer et al. 1999). Hummer then continued the assessments on a monthly basis. Both treatment groups improved on sexual dysfunctions from week 6 till week 18 (male patients from 53% sexual dysfunctions and in female patients from 23% to 0%). At the same time it should be noted, that over-time no subsiding sexual dysfunctions were found in several other studies reporting continuation of sexual side effects even after years of treatment (Lingjaerde et al. 1987; Pfeiffer et al. 1991).

In a recent study on sexual side effects 60 outpatient men using long-term classical antipsychotics were randomly assigned to either continue classical antipsychotics treatment or switch to clozapine (Aizenberg et al. 2001). They concluded that maintenance therapy with the atypical neuroleptic clozapine was associated with a lower degree of sexual dysfunction than classical antipsychotics. Moreover, sexual side effects did continue over longer treatment periods, albeit with possibly fewer sexual side effects in patients treated with clozapine (Aizenberg et al. 2001).

Summary: studies using questionnaires suggest that 40 to 60% of the patients report sexual dysfunctions, possibly related to the use of antipsychotics. Some problems in sexual functioning of people with schizophrenia mainly occur as a direct result of their primary psychotic symptoms and impaired social skills that complicate contacting potential partners. Libido reduction often seems, at least partly, to be associated with schizophrenia itself. It is suggested that this decreased libido in patients with schizophrenia might be linked to the general reduction of initiative patients experience, often referred to as negative symptoms. Still, most sexual problems seem to be related to the treatment with antipsychotics. Although not all studies agree, there may be no tolerance for sexual side effects when patients use these antipsychotics for a long time. There is some evidence that antipsychotics might differ in the frequency and kind of sexual dysfunctions being induced but there is a lack of well-controlled comparative studies.

Which mechanisms are involved in antipsychotic induced sexual dysfunctions?

Introduction
All available antipsychotic drugs exert their antipsychotic effect through dopamine antagonism. However, these drugs vary strongly with respect to, among others, biochemical structure, receptor binding profile and pharmaco-kinetics. In addition, impairment of sexual performance can be due to a variety of factors. The clinically most important mechanisms through which antipsychotics may induce sexual side
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effects will be summarized here (Segraves 1989; Meston and Gorzalka 1992; Meston and Frohlich 2000). Antipsychotics interact with many different neurotransmitter systems in the brain and other parts of the body. Affinity for the dopamine system is a property shared by all of these drugs, but the affinity for the serotonergic, noradrenergic, histaminic and cholinergic neurotransmitter systems may differ among the various groups of antipsychotics (table 1) (Leysen 1981; Leysen et al. 2000).

Table 1. Receptor binding affinity profiles of most antipsychotics discussed in this thesis

<table>
<thead>
<tr>
<th></th>
<th>D&lt;sub&gt;1&lt;/sub&gt;</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>5HT&lt;sub&gt;2a&lt;/sub&gt;</th>
<th>Alfa&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Alfa&lt;sub&gt;2&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M&lt;sub&gt;1&lt;/sub&gt;</th>
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<td>Chlorpromazine</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Clozapine</td>
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<td>Haloperidol</td>
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<tr>
<td>Olanzapine</td>
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<td>+++</td>
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<td>Pimozide</td>
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<td>+</td>
<td>0</td>
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<td>Quetiapine</td>
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<tr>
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<td>Sertindole</td>
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<td>+++</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Thioridazine</td>
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<tr>
<td>Ziprasidone</td>
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</tbody>
</table>

Affinity for receptor: + low, ++ moderate, +++high, ++++ very high; 0 absent.

This table represents global ratings based on data of Leysen (Leysen, J. E. 1981; Leysen, J. E. et al. 2000)

Since all antipsychotics are dopamine antagonists, the question raises as to how and to which extent dopamine blockade may contribute to libido loss, erectile disorders and orgasm disturbance (Giuliano and Allard 2001). Dopamine is an important neurotransmitter in experiencing motivation and rewards, probably including sexual motivation (libido) and sexual reward (orgasm) (Feldman et al. 1997). Studies in animals and reports in humans suggest that dopamine can increase sexual desire and behavior (Deelen van et al. 2002; Fibiger et al. 1992; Giuliano and Allard 2001; Pfaus et al. 1995). The role of dopamine in female sexual functioning is less well understood. Low dosages of dopamine agonists increase receptivity in female rats with low receptivity, while high doses have the opposite effect in rats exhibiting high receptivity (Giuliano and Allard 2001). In healthy men with normal erectile capacity apomorphine, a dopamine-D<sub>1</sub>/D<sub>2</sub> agonist, facilitates erections. In patients with Parkinson’s disease levo-dopa treatment can provoke sexual hyperactivity (Deelen van et al. 2002; Uitti et al. 1989). Of importance, the effects of dopamine-induced erection in male rats can be blocked by dopamine antagonists like haloperidol. Taken together, there is a growing body of evidence that dopamine is involved sexual arousal and orgasm (Giuliano and Allard 2001).

In addition to its central role in reward and motivation, dopamine inhibits the release of prolactin from the pituitary gland. On the other hand, prolactin modulates dopaminergic transmission in the brain. Binding sites of prolactin have been identified in the hypothalamus and substantia nigra (Sobrinho 1993). Hyperprolactinemia stimulates dopamine turnover in several areas of the brain,
including the nucleus accumbens, and reduces turnover in other regions, e.g. the substantia nigra. Thus, complex interactions between prolactin and dopamine take place.

On the level of actual behavior, prolactin is involved in a sexual behavior feedback system. Serum prolactin levels raise during orgasm, while conversely sexual behavior is reduced after orgasm for as long as plasma prolactin levels stay elevated (Exton et al. 2000; Haake et al. 2002).

As stated above, the release of prolactin takes place under tonic inhibitory control by dopamine in the tuberoinfundibular system. Therefore, an ensuing effect of dopamine blockade by antipsychotics is a diminished inhibition of the prolactin output. As a result, serum prolactin levels raise, at least temporarily, when antipsychotic treatment is initiated. Indeed, prolactin elevation is an indirect indicator of dopamine blockade (Kapur et al. 2001). However, the regulation of prolactin release is clearly subject to a variety of factors. For example, interference with serotonin receptor subtypes, i.e. the 5HT_{1A} or 5HT_{2C} receptors, can modulate the inhibitory effect of dopamine on prolactin release (for more details, see chapter 2). As to antipsychotic-induced Hyperprolactinemia, at least in men, worsening of sexual dysfunctions correlates with serum prolactin elevation (Ghadrian et al. 1982a; Burke et al. 1994; Segraves 1989). Although some authors suggest here a causal relationship between prolactin elevation and sexual side effects, this is still under debate (Arato et al. 1979; Kleinberg et al. 1999; Petty 1999a). Other mechanisms associated with prolactin elevation contain a wide range of changes in the levels of other hormones, including a decrease in serum testosterone level, that might diminish sexual performance in men as well as in women (Rinieris et al. 1989).

Although prolactin is the most widely studied hormone in sexual dysfunctions, other hormone systems might also be involved. Some authors found a reduction of LH levels, during treatment with antipsychotics like chlorpromazine, in both men and women. Mechanisms suggested are dopamine blockade or noradrenaline blockade by chlorpromazine (Rinieris et al. 1988; Praag van and Korf 1975). Some studies found high LH levels correlating with normal sexual activity without detecting a clear correlation between sexual dysfunction and prolactin levels (Arato et al. 1979).

Sedating properties of antipsychotics also have an influence on sexual performance. Histamine-H_{1} receptor blockade is related to the sedating properties of antipsychotics (Leysen et al. 2000). And, of course, sedation itself might be responsible for diminishing sexual performance.

Many antipsychotics have α-blocking properties. The α_{1}-blocking properties possibly contribute to a diminishing ability for erection, vaginal lubrication and ejaculation. These noradrenergic (α_{1}) effects seem (partly) to be in balance with (anti-)cholinergic effects leading to final effects on erection that might turn into erection disturbance (often) or priapism (rare) and/or ejaculation disturbance. For instance, antipsychotics like thioridazine or sertindole with α_{1}-antagonistic properties are associated with priapism (central α_{1}-antagonism?) or ejaculation disturbance (diminished semen volume) (Thompson Jr et al. 1990). Some antipsychotics have α_{2}-blocking properties. Linked to sexual dysfunctions in treatment with antipsychotics this has hardly been described. In theory, as in the α_{2}-blocking yohimbine, it may stimulate erection (Linnankoski et al. 1992; Smith et
The role of serotonin in sexual behavior is highly complex and shows sex differences (Rosen et al. 1999). The clinical importance of the serotonergic system becomes evident in patients treated with Selective Serotonin Re-uptake Inhibitors (SSRIs) (Waldinger 1999). Treatment with SSRIs is frequently associated with sexual dysfunctions, such as ejaculatory disorders and anorgasmy (Lane 1997). Activation of 5-HT$_2$ receptors seems to act in an inhibiting manner on sexual stimulation and activity in men, while precisely the opposite occurs in the case of women (Wilson 1993). Cyproheptadine, a 5-HT$_2$ receptor antagonist, is capable of eliminating SSRI-induced sexual dysfunction in men (Baldwin et al. 1997). Since many antipsychotics are 5HT$_{2a}$ and some 5HT$_{2c}$ antagonists, no important influence on sexual functioning might be expected from these receptor systems. Antidepressants, like mirtazepine, with 5HT$_{2c}$ antagonistic aspects are thought to compensate for serotomimetic aspects, reducing the inhibitory effects on sexual behavior (Gelenberg et al. 2000). For antipsychotics one might expect these complex interactions in compounds like ziprasidone, that combines 5HT$_{2a}$, 5HT$_{2c}$ antagonistic properties with 5HT$_{1a}$ agonistic aspects. Today no studies are known to us on the influence of ziprasidone on sexual behavior.

**Summary:** Many different mechanisms may contribute to the effects of antipsychotics on sexual functioning. Dopamine is involved in almost all aspects of sexual behavior and dopamine blockade induced by antipsychotics seems to play a role in the inhibition of all stages of sexual performance. Associated with dopamine blockade is prolactin elevation, which may interfere with erection as well as with possibly other aspects of sexual performance in a dose dependent way. Some antipsychotics induce noradrenergic blockade, which appears to be associated with disturbances in ejaculation and possibly lubrication. In addition serotonergic, histaminergic and hormonal effects may contribute to the actual sexual performance.
### Table 2. Main mechanisms and effects of antipsychotics on sexual performance

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Libido</th>
<th>Erection or Vaginal lubrication</th>
<th>Orgasm</th>
<th>Ejaculation</th>
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<tr>
<td>Cholinergic (M) receptor blockade</td>
<td>Inhibition?</td>
<td>When not in balance with noradrenergic functions: Priapism?</td>
<td></td>
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<tr>
<td>Dopamine (D) receptor blockade</td>
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<td>?</td>
<td>Inhibition</td>
<td>?</td>
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<tr>
<td>Noradrenergic ($\alpha_1$) receptor blockade</td>
<td>When not in balance cholinergic functions: Priapism?</td>
<td>Inhibition of ejaculation</td>
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<td>Facilitation?</td>
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<tr>
<td>Prolactin elevation</td>
<td>Inhibition</td>
<td>Inhibition</td>
<td>?</td>
<td>Inhibition of ejaculation?</td>
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<tr>
<td>LH decrease</td>
<td>Inhibition</td>
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<tr>
<td>Testosterone decrease</td>
<td>Inhibition?</td>
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In what way do antipsychotics influence individual aspects of sexual performance?

In the first part of this review was focused on sexual dysfunctions in general. This part of the review concentrates on the frequency of specific sexual dysfunctions in schizophrenic patients with antipsychotic treatment. In the following subsections first dysfunctions involving libido will be discussed, then those related to erection, and finally ones reported for lubrication. For each definitions, physiology, underlying pathophysiological mechanisms and relevant findings in clinical studies will be presented.

**Libido**

**Physiology**

Libido is a term often used as the equivalent for sexual desire, the latter 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 and Frohlich 2000). Libido is closely connected with sexual arousal. Sexual arousal is defined both in subjective (feeling sexually excited) and objective physiological terms (e.g. genital vasocongestion, erection).

There is a good deal of evidence showing that mechanisms in the brain involved in motivation and initiating of behavior in general are, at least partly, the same as...
those involved in sexual motivation, in the context of this chapter called libido (Pfaff 1999). Cerebral mechanism involved may be analyzed in terms of e.g. endocrine influences, brain centers or brain-circuitries involved. Although uncontented, it is generally assumed that the preoptic region and possibly other regions of the hypothalamus are involved in thermoregulation, aggression and sexual motivation (Robbins and Everitt 1999). Hypothalamic nuclei contain high concentrations of steroid receptors (e.g. for prolactin, estradiol, progesterone and testosterone), especially in the medial preoptic region and the ventromedial hypothalamus. Individual hormones (progesterone, estrogen, progesterone and testosterone) and the interaction of these hormones with each other can at least in theory have influence on libido (Yen and Jaffe 1999). This nicely illustrated by the way progesterone administration, after estrogen priming, provokes a release of prolactin and Luteinizing Hormone (LH) in animal models and women (Robbins and Everitt 1999). In rodents this is expressed in behavior seen as an equivalent of libido in humans (Pfaff 1999). In line with these rodent studies, in human sexual behavior there seems to be a peak in arousability (libido) and sexual behavior in women in the late follicular phase of the menstrual cycle, observations (Yen 1999).

When focusing on brain circuitry, it is important to realize that neurological and endocrine systems are closely intertwined, with for instance the dopaminergic system having inhibiting influences on prolactin elevation and prolactin elevation influencing dopaminergic transmission. The dopamine system, especially the mesolimbic and mesocortical dopaminergic projections, plays an important role in the appetitive aspects of motivational behavior probably including libido (Feldman et al. 1997).

**Pathophysiology**

The mechanisms of libido-reduction during treatment with antipsychotics are as yet not well understood. As dopaminergic systems are involved in experiencing motivation, a blockade of the dopaminergic transmissions, especially in the mesolimbic pathways may be related to a diminished initiation of behavior possibly, including sexual behavior. The subjective experience linked to the inhibition of sexual initiative is libido reduction. Indeed, drugs like antipsychotics that diminish dopamine transmission are generally correlated to libido-reduction. On the other hand dopaminergic drugs, like L-dopa or apomorphine, may initiate an increase in libido (Martin-Du Pan 1978; Bowers et al. 1971; Hyyppa et al. 1975; Uitti et al. 2002).

It is unclear to what extent libido reduction may also be affected by secondary effects of dopamine blockade by antipsychotics, like prolactin elevation, reduction of serum-testosterone, FSH or LH, or a diminished subjective well-being (Siris et al. 1980; Kruger et al. 2002). There is some suggestion in the literature that, as a consequence of dopamine blockade induced prolactin-elevation, the capability to have sexual fantasies is diminished (Carani et al. 1996). Loss of libido is also seen in patients with prolactinomas. This suggests that loss of libido in patients treated with antipsychotics at least partly can be induced by serum prolactin elevation (Thorner et al. 1998).
Findings in clinical studies

Un-medicated patients with schizophrenia often report libido reduction. This disease-related libido 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 (often called negative symptoms). Libido reduction then occurs as a consequence of these negative symptoms. In addition the social consequences concomitant with schizophrenia can be contributory to a decrease in libido.

In early studies on sexual dysfunctions related to schizophrenia or antipsychotic medication, libido was touched upon. In a review on drug therapy and sexual dysfunction in men, Mitchell and Popkin (1982) quoted nine case reports indicating libido reduction related to the use of antipsychotics, but cases with normal libido were also reported. In a study by Aizenberg (1995) libido was found to be more reduced in both groups of male patients with schizophrenia being treated with antipsychotics compared with patients not using antipsychotics. Patients with schizophrenia reported significantly more frequent libido reduction versus unaffected controls. Reduction in the frequency of sexual thoughts was confined to the untreated patients. Patients being treated with antipsychotics were less easily sexually aroused.

As we saw, in the study of Lingjaerde et al. using the UKU of 2391 patients treated with antipsychotics 37% of male and female patients reported libido reduction. Interestingly, 20% reported an increase of libido (Lingjaerde et al. 1987). Although some patients studied were being treated with antipsychotics for up to 10 years, about the same frequencies of libido reduction were reported irrespective of the duration or the dosage of treatment. Libido reduction was rated in half of the cases as probably drug related while libido increase was considered to be drug related in one out of four.

Teusch et al. showed that 60% of male patients with schizophrenia report a libido reduction versus 14% of the controls (Teusch et al. 1995). Of the female patients in this study 60% reported libido reduction versus 26% of the controls.

In the study by Hummer, quoted above, libido reduction was reported in more than 50% of the male patients treated with either haloperidol or clozapine and in about 30% of the female patients (Hummer et al. 1999). Patients treated with haloperidol versus clozapine did show comparable frequencies of libido reduction.

Summary: libido reduction in patients with schizophrenia seems to be related to their psychotic illness as well as to antipsychotic medication. During treatment with antipsychotics, some patients experience a restoration of libido, but the majority experience libido reduction. Inhibition of dopaminergic pathways as well as interference with endocrine functioning are probably the main reasons why antipsychotics induce a general inhibition of initiative, including sexual initiative. Literature suggests, but remains inconclusive about, the possible involvement of other mechanisms like Hyperprolactinemia in antipsychotic induced loss of libido.
Erection disturbance: impotence

Physiology
Erection describes the non-flaccid state of the penis and is in most cases the physiological expression of sexual arousal. Impotence refers to the inability of men to achieve and/or maintain erection. In clinical practice patients often report problems in case of a delayed, shortened or diminished ability to reach full erection. It is these aspects of erectile dysfunction that we will discuss in the following, grouping them all together under the heading of impotence. Although erections often co-occur with the subjective feelings of sexual excitement, it can also occur without arousal, for instance during Rapid Eye Movement (REM) sleep. Erection begins with smooth muscle relaxation in the sinusoidal spaces of the penis, mediated by noradrenergic-noncholinergic autonomic nerves, together with the vascular endothelium release nitric oxide (NO) into the corpus cavernosum (Creed et al. 1991; Meston and Frohlich 2000). The smooth muscle relaxation reduces vascular resistance so that erectile bodies can fill with blood. Detumescence occurs with the release of catecholamines during orgasm and ejaculation.

Pathophysiology
The possible mechanisms for antipsychotic induced erection disturbances are unclear. From patients with Hyperprolactinemia induced by prolactinomas we learn that prolactin elevation can be correlated with erectile dysfunction (Thorner et al. 1998). Schwarz et al. refer to studies in which up to 90% of male patients with Hyperprolactinemia, mostly within the context of a hypophysis adenoma, complain to some extent of sexual dysfunction, especially of erection disorders (Schwartz et al. 1982). In fact, impotence is sometimes the first symptom of a prolactinoma. Still, it is unclear whether prolactin has a direct effect on erectile functioning. Prolactin elevation may also have secondary effects through inducing the lowering of plasma testosterone, TSH and LH levels and/or changes in mental attitudes (Tuomisto and Mannisto 1985). It has been suggested that, as a consequence of prolactin-elevation, there is no change in nocturnal (REM sleep linked) erections but the capacity to have sexual fantasies are diminishes (Carani et al. 1996). So erection disturbance in patients using antipsychotics may well be secondary to the libido reduction, next to having a primary affect primary effect on erectile mechanisms.

Findings in clinical studies
In many studies assessing arousal, questionnaires are used evaluating quantitative (duration, frequency) and qualitative (rigidity) aspects of erection and in women sometimes lubrication. 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 excepted in routine clinical practice or clinical trials evaluating side effects of these drugs. This explains why studies evaluating sexual side effects in patients using antipsychotics on the whole relied on questionnaires. Aizenberg et al. found that erection in patients with schizophrenia, who had a sexual partner, was slighter during coitus (Aizenberg et al. 1995). Patients using antipsychotics experienced significantly more erection disturbance, during sexual
intercourse as well as during masturbation compared with patients without antipsychotics. At the same time, no change occurred in waking erections (an expression of REM sleep correlated erections) in these patients. Weizman evaluated sexual performance in 13 men treated with sulpiride (6 patients schizophrenia, 7 anxiety disorder). Sulpiride (dose range 100-600 mg/day) was associated with a dose dependent significant prolactin increase (35-190 ng/ml) and induced in 5 patients erectile dysfunctions that correlated with dose and prolactin levels (Weizman et al. 1985). Lingjaerde et al. evaluated erection disturbance in 1259 men being treated with antipsychotics using the UKU (Lingjaerde et al. 1987). They found in 22% of the patients erectile dysfunctions. As in libido, the percentage of patients with erectile dysfunction hardly changed during prolonged treatment with antipsychotics, i.e. for up to 10 years and more. Half of the cases of erectile and ejaculatory dysfunctions were rated as probably drug induced. In the study of Teusch et al. 33% of 30 inpatients with schizophrenia being treated with antipsychotics reported erection disturbance versus 9% in healthy controls (Teusch et al. 1995). Hummer et al. did not find significant differences in patients being treated with haloperidol versus clozapine, both groups reporting around 25% erectile dysfunctions (Humper et al. 1999). Smith et al. found that men using antipsychotics were 3.73 times more likely to complain about erectile dysfunction than controls. Anticholinergic side effects and medication correlated with erectile dysfunction (Smith et al. 2002).

The scant literature available suggests that erectile dysfunctions might be related to schizophrenia as well as to antipsychotic medication. Dopamine and prolactin are closely intertwined through feedback mechanisms. Apart from prolactin, dopaminergic mechanisms are probably involved in all stages of sexual performance, so dopamine may well be involved directly and indirectly in influencing erection. Which, in turn, might explain why apomorphine (a dopamine agonist) is effective in treatment of erectile dysfunction (Uitti et al. 1989).

Summary: Erectile dysfunction or impotence has been reported to be related to the use of antipsychotics. The incidence may be 20 to 30% of the patients. Dopamine blockade and prolactin elevation are thought to be causal in these erectile dysfunctions.

Erection disturbance: priapism

Pathophysiology
Priapism is a protracted and often painful erection of the penis (Compton and Miller 2001). On the whole, priapism induced by antipsychotics seems to be a rare but serious complication, especially as many different antipsychotics may be at play here, those with strong α2-antagonistic properties apparently heading the list (Compton and Miller 2001). How priapism results from the treatment of antipsychotics remains unclear. One suggestion is through a lack of balance between noradrenergic and cholinergic effects, whose final effects on erection may then turn into priapism (Patel et al. 1996; Compton and Miller 2001; Thompson et al. 1990). Priapism, of course, also has numerous alternative etiologies. Obviously, the onset can be sexual stimulation, but the condition itself persists long after sexual excitement has
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subsided. If untreated, impotence is a common sequela. In other words, it ought to be viewed as a medical emergency requiring immediate attention. Urological consultation and, sometimes, surgical intervention may prove necessary.

Findings in clinical studies
Priapism is a rarely occurring effect of antipsychotics initially observed with thioridazine and chlorpromazine (Goff and Shader 1995; Mitchell and Popkin 1982). Priapism related to the treatment with antipsychotics has shown up only in case reports, which relate priapism to many different antipsychotics, such as risperidone (Emes and Millson 1994; Raja 1999), haloperidol (Morera et al. 1988), clozapine (Bongale et al. 2001; Thompson Jr et al. 1990; Seftel et al. 1992; Moinfar et al. 1994), quetiapine (Pais and Ayvazian 2001) and olanzapine (Kuperman et al. 2001; Deirmenjian et al. 1998; Gordon and de Groot 1999). However, in most case reports in the literature it is chlorpromazine and thioridazine that come to the fore (Compton and Miller 2001). I should add that besides the references mentioned, no other detailed or comparative studies appear to be available on priapism related to the treatment with antipsychotics.

Summary: Priapism is a medical emergency, occasionally reported in case studies as being induced by antipsychotics. The incidence of antipsychotic-induced priapism is unknown. Priapism is a potentially destructive side effect and should be treated as soon as possible.

Vaginal lubrication

Physiology
Vaginal lubrication is the excretion of a lubricifying fluid by the vaginal wall that facilitates penetration of the penis during sexual intercourse, and is one of the physiological responses in women associated with sexual arousal. It is unclear which neurotransmitters are involved in arterial smooth muscle dilatation and lubrication. Animal studies suggest that adrenergic nerves induce contraction and α-adrenergic receptors mediate contraction in both clitoral cavernosal and vaginal tissue (Meston and Frohlich 2000). Vasoactive Intestinal Peptide (VIP) may play an important role in the relaxation of vaginal tissue (Levin 1992).

Pathophysiology
Lubrication has hardly been studied in patients treated with antipsychotics. No pathophysiological considerations were found in the literature, scanned for this research, other than the suggestions that lubrication disturbance (dry vagina) may well be an equivalent of impotence in men, having the same causes including dopamine blockade and prolactin elevation.
Clinical studies
Although vaginal lubrication in women may be viewed as a physiological equivalent of erection, it has hardly been studied in relation to schizophrenia or antipsychotic medication. Lubrication can be evaluated indirectly by measuring vaginal bloodflow using for instance photoplethysmography, or by indirect measures of heat dissipation and Doppler techniques. As they require insertion by a tampon shaped device into the vagina, these instruments are to intrusive to be used in routine clinical practice or clinical research (Meston and Frohlich 2000). Only in some surveys patients indicated that psychotropic medication had an impairing impact on lubrication (Miller 1997). Traditional questionnaires evaluating side effects of medications developed before 1999 almost never contain items evaluating lubrication during sexual arousal or other possible side effects that might be especially relevant for women, such as painful sexual intercourse. An exception is the UKU that has one item for vaginal lubrication (vaginal dryness) (Lingjaerde et al. 1987). Only recently have questionnaires become available that include specific items for women like the Dickson Glazer Scale of Sexual Function (DGSF) (Dickson et al. 2001) or the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) (Knegtering and Castelein 2001).

To our knowledge, besides the validation-studies of the UKU, only one other study included lubrication as an item. This study, by Teusch et al., compared sexual dysfunctions in patients with schizophrenia (n=45), opiate addiction (n=37), neurotic patients (n=50) and normal controls (n=41). Although only 15 women with schizophrenia were included, a group too small to reach statistical significant results, 33.3 % of them reported reduced lubrication versus 10% of the control group (Teusch et al. 1995). In the UKU studies, 9% of the patients using antipsychotics reported dryness of the vagina, with the highest frequency after 6 to 12 months of treatment. Nevertheless, lubrication did not show a clear relation to duration of treatment (Lingjaerde et al. 1987).

Summary: although physiologically comparable to erection in men, vaginal lubrication has hardly been studied in relation to the use of antipsychotics. What we have, primarily, are some hints in the literature that antipsychotics may diminish lubrication in about 8-10% of the patients.

Orgasm

Physiology
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 and Frohlich 2000). As discussed earlier, dopaminergic systems are involved in attention, motivation, as well as initiation of behavior and reward (Feldman et al. 1997). As a consequence, dopamine is thought to be involved in all stages of sexual functioning including experiencing orgasm (Giuliano and Allard 2001).

To what extent central neurophysiological events are related to the intensity or experience of orgasm is unknown (Meston and Frohlich 2000). While orgasm is generally the result of both genital and psychological stimulation, evidence
suggests that central stimulation alone may trigger orgasm (Levin 1992; Schiavi and Segraves 1995).

Pathophysiology
As dopaminergic systems are heavily involved in experiencing rewards, including orgasm, the dopaminergic blockade of antipsychotics is most probably the reason for inhibiting orgasm or decreasing the quality of a person's orgasmic experience. But not all antipsychotics show the anti-dopaminergic activity in the same intensity. For instance, quetiapine and clozapine only temporarily block the dopamine system, unlike many classical antipsychotics which bind more firmly to the dopamine receptors (Kapur and Seeman 2001; Kapur et al. 2001). This suggests that antipsychotics may differ in inducing sexual side effects, including orgasm. Unfortunately, not only are comparative studies rare, they are also often contradictory and thus inconclusive.

Clinical studies
In studies evaluating sexual dysfunctions, orgasm is evaluated as an individual item in questionnaires. Most studies assess the agree to which the patient indicates he or she is capable of experiencing an orgasm (Teusch et al. 1995). In the study of Teusch et al. 53,5% of the men and 26,7% of the women treated with antipsychotics reported difficulties in achieving an orgasm, versus 9,1% of the male controls and 10,5% of the female controls.

In the study of Lingjaerde et al. 19% of women and 16% of men reported orgasmic dysfunction, it was recorded as probably drug induced in one third of those affected. Some studies also noted a disturbance in the quality of the orgasm. In some case-reports, patients using thioridazine mentioned a change in the quality of their orgasm (Haider 1966; Kotin et al. 1976; Ying 2002). In the study of Ghadarian 58% of the male patients reported a decrease in ability and change in quality of orgasms related to the antipsychotic medication they used. In female patients 22% reported a decrease in the ability to experience an orgasm while 33% reported a change in quality (Ghadirian et al. 1982a). In the study of Aizenberg patients using clozapine reported the quality of their orgasm had improved, unlike patients using classical antipsychotics (Aizenberg et al. 2001).

Summary: treatment with classical antipsychotics, and possibly to a lesser degree clozapine, have been associated with anorgasmia or an alteration in the quality of orgasm in 16 to about 50% of the patients. Central dopaminergic blockade is thought to be responsible for these side effects.

Ejaculation
Physiology
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 or retrograde ejaculation. Shader states that retrograde ejaculation and aspermia or
often used wrongly as synonyms (Shader and Elkins 1980). Aspermia can be defined as the absence of ejaculate in the presence of erection, muscular ejaculation and orgasm (Girgis 1968). Retrograde ejaculation refers to ejaculate being released into the bladder during orgasm as can be shown by analyzing the urine for the presence of semen after orgasm. Aspermia does not always imply retrograde ejaculation.

The emission state of orgasm is thought to be under thoracolumbar control. Seminal fluid is propelled into the bulb urethra via the release of norepinephrine that acts on $\alpha$-adrenergic receptor and controls smooth muscles of the vas efferens, prostate and seminal vessels. During the ejaculatory phase, which is mediated by a sacral spinal reflex, semen is released through the urethra via constrictions of the striated muscles that surround the bulb urethra (Schiavi and Segraves 1995).

**Pathophysiology**

The mechanism of a reduction in ejaculation volume during treatment with antipsychotics is as yet not precisely known. Various antipsychotics with $\alpha_1$-antagonistic properties are presumed to alter the sympatic tonus of the bladder or urethral sphincter, allowing semen to pass retrogradely into the bladder during ejaculation (Shiloh et al. 1999). The diminished semen volume during orgasm in patients using thioridazine might be caused by retrograde ejaculation (Pollack et al. 1992). Still, such explanations do not cover all observations. For instance, dry ejaculation in patients using sertindole, an antipsychotic having $\alpha_1$-adrenergic antagonistic properties, has been observed frequently, but this probably does not involve retrograde ejaculation as no semen could be detected in the urine after orgasm (Kammen van et al. 1996). Shader expresses doubts as to the mechanisms involved in DEV, showing that indeed many antipsychotics with $\alpha$-antagonistic are associated with DEV, but that this side effect often does not seem to correlate with other signs of $\alpha$-antagonistic side effects (Girgis 1968; Shader and Elkins 1980).

An alternative mechanism has been suggested involving calcium channels on the vas deferens. Contractions of the vas deferens are known to be affected in vitro by calcium channel antagonists. Some antipsychotics show dose dependent calcium-blocking features. Chlorpromazine and thioridazine are calcium blockers, so this may contribute to DEV (Gould et al. 1984).

**Clinical studies**

Some patients treated with antipsychotics report the complete absence of ejaculate (dry ejaculation) during an orgasm. DEV and dry ejaculation are reportedly related to the use of several antipsychotics like thioridazine, chlorpromazine or sertindole (Girgis 1968; Shader and Elkins 1980; Patel et al. 1996).

Kotin reported retrograde ejaculation in 49% of the patients (n=57) using thioridazine, but in none of the patients treated with other antipsychotics (n=64) (Kotin et al. 1976; Schiavi and Segraves 1995).

Ghadirian reported a decreased quantity of ejaculate in 46% of the patients, the vast majority using fluphenazine (n=55) (Ghadirian et al. 1982a; Schiavi and Segraves 1995). Lingjaerde et al. using the UKU found that 19% of patients
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treated with antipsychotics indicated ejaculation dysfunction (Lingjaerde et al. 1987; Schiavi and Segraves 1995). This finding seems to be in line with the study of Hummer also using the UKU. Where Hummer et al. 20% of the patients treated with haloperidol and 23 % of the patients treated with clozapine indicated ejaculatory dysfunction (Hummer et al. 1999). According to the study of Lingjaerde et al. ejaculatory dysfunction occurred more frequently in patients using high dosages of antipsychotics (26%) versus patients using low dosages (11%) (Lingjaerde et al. 1987). In this study the duration of treatment with antipsychotics up to 10 years did not influence the frequency of ejaculatory dysfunction.

In the registration studies of the antipsychotic sertindole, about 20% of the patients treated with sertindole reported DEV versus 8% of patients treated with haloperidol. DEV in patients using sertindole was not associated with an increase in other sexual dysfunctions nor with prolactin elevation (Kammen van et al. 1996). In the study of Smith and coworkers patients using antipsychotics were 16.4 time more likely to complain of DEV than controls. Anti-adrenergic (noradrenergic) side effects were associated with abnormal ejaculation (Smith et al. 2002).

Summary: decreased ejaculatory volume (DEV) is frequently (8-40%) reported in patients treated with antipsychotics. Although the mechanisms are not completely known, antipsychotics with α-blocking properties and possibly also calcium channel blockers are thought to be most likely to induce DEV.

Other aspects of sexual functioning

Apart from the more or less detailed aspects of sexual functioning discussed above, some studies have tried to evaluate the subjective judgment of the patients about the overall quality of their sexual experience. Aizenberg included such items in his questionnaire as ‘enjoyment of sex’ and ‘sexual satisfaction’ (Aizenberg et al. 2001). As mentioned in the section on orgasm the study of Ghadarian et al. include one item about change in the quality of orgasm (Ghadirian et al. 1982a). Aizenberg found that ‘enjoyment with sex’ and ‘sexual satisfaction’ was significantly higher in patients treated with clozapine than in those treated with classical antipsychotics (Aizenberg et al. 2001)

Some studies mention pain during orgasms. For instance, in the study of Ghadarian 2 out of 27 female patients experienced mild pain during orgasm (Ghadirian et al. 1982a). Berger reported painful ejaculation, also called ordynogasmia, being a possible consequence of treatment with haloperidol or trifluoperazine (Berger 1979; Donnellan et al. 2001). But on the whole pain during orgasm as item is absent in most studies and the patho-physiological mechanisms in relation to treatment with antipsychotics remains unclear.
Chapter 1

Menstruation disturbance, galactorrhoea and gynecomastia

Although menstruation disturbances, gynecomastia and galactorrhoea are not by themselves sexual dysfunctions, they do tend to coincide with some of the sexual dysfunctions since, at least partly, they originate from the same source: high serum prolactin levels. The focus of this study is, of course, on sexual side effects, but as in following chapters these subjects are discussed here briefly so as to have covered all possible aspects.

Definitions
Menstruation disturbance can be divided into menorrhagia and amenorrhea. Menorrhagia (hypermenorrhoea) is defined as a excessively prolonged or profuse menstruation. Amenorrhea is the absence or abnormal cessation of the menses. Amenorrhea is mostly defined as a cessation of the menses for at least half a year. In case of cessation of the menses for shorter periods one speaks mostly of a “missed period”. Galactorrhoea is a flow of milk from the breasts other than from normal lactation. Sometimes this flow is spontaneous, sometimes it only shows when squeezing the nipples. Gynecomastia is the excessive development of the mammary glands.

In discussing the physiology of menstruation and lactation we will restrict our scope to information that is directly relevant in the context of treatment with antipsychotics. Before pregnancy prolactin levels are more or less stable, showing some daily and seasonal variation (see next chapter). Prolactin levels rise during pregnancy, peaking till shortly after labor (Barbieri 1999). As estrogen and prolactin prepare them for lactation, the breasts enlarge mainly due to ductal proliferation with periductal oedema. Having risen further immediately after childbirth, prolactin levels stay high during the first few months. During this period prolactin levels peak further shortly after the initiating of each breastfeeding, returning to prior levels about two hours later. After several months, even with continued breastfeeding, prolactin levels will come down to the values they had before pregnancy. Breastfeeding in this period can continue without elevated prolactin levels. During the rise of prolactin after childbirth, amenorrhea continues and is thought to be related to the elevated prolactin levels. Suckling itself can inhibit the release of gonadotrophin releasing hormone (GnRH) through many different systems, reinforcing to amenorrhoea. Generally, several months after childbirth and after prolactin levels have normalized, the monthly GnRH, LH and FSH cycle, estrogen and progesterone cycle will return resulting in the resumption of the menstruation cycle. For the majority of cases the menstruation cycle will have resumed within 6 months after delivery.

Pathophysiology
Serum prolactin elevation is probably an important factor not only in causing sexual side effects but also in inducing galactorrhoea and gynecomastia (Halbreich et al. 1995; Maguire 2002). Prolactin elevation may also influence the menstrual cycle in patients with schizophrenia, though this may not be the only cause (Canuso et al. 2002).
In response to elevation of prolactin above a certain threshold, LH, estrogen and progesteron will lower and stop showing a cycling plasma level pattern through the month, corresponding with amenorrhea (Oseko et al. 1988). Elevation of prolactin levels by itself, but even more so in collaboration with estrogen, provokes ductal growth in the breasts: gynecomastia (Barbieri 1999). This is often followed by the production of milk. As prolactin levels during treatment with antipsychotics are not as high as shortly after childbirth, there is often only minimal milk production. The latter often shows only after squeezing the breasts or nipples but sometimes also appears spontaneously. Although only a few studies are known, switching from a prolactin elevating antipsychotic to a prolactin sparing antipsychotic or lowering serum prolactin levels by co-administering a dopamine agonist, will in most cases correct these side effects (Matsuoka et al. 1986; Gazzola and Opler 1998; Kim et al. 2002).

**Clinical studies**

Classical antipsychotics frequently increase serum prolactin levels (Dickson and Glazer 1999). Increased prolactin levels are associated with amenorrhea, galactorrhea and sexual dysfunctions (Windgassen et al. 1996). Some new (atypical) antipsychotics like clozapine, olanzapine orquetiapine, hardly influence prolactin levels at all (Crawford et al. 1997; Hamner et al. 1996). For that reason, these antipsychotics are sometimes called prolactin sparing antipsychotics. Other new antipsychotics like risperidone and amisulpride increase prolactin levels significantly and are denominated prolactin elevating antipsychotics (Grunder et al. 1999; Petty 1999b).

Systematic studies on amenorrhea, gynecomastia, and galactorrhea induced by antipsychotics are scarce. Most information that is available consists of case reports suggesting that antipsychotics which induce prolactin elevation indeed may lead to amenorrhea, gynecomastia and galactorrhea (Gingell et al. 1993; Kim et al. 1999). From these studies it is unclear how these possibly antipsychotic induced side effects behave over time. The only systematic, and also most informative, study is that of Lingjaerde (1987). In this study in patients treated with (prolactin elevating) classical antipsychotics, menorrhagia, amenorrhea, galactorrhea and gynecomastia were rated. Menorrhagia was reported in 13% and amenorrhea in 22% of the women. Galactorrhea was reported in 5% of the women and in 3% of men. Gynecomastia was reported in 3% of the women and in 6% of the men. These symptoms were seldom considered by the patients themselves to be drug related. Menstruation disorders and gynecomastia showed in the age category below 60 little relation to age. At the same time, menstruation disorders, galactorrhea and gynecomastia showed an uncertain relation to treatment duration, although galactorrhea had a vague peak between 3 and 6 months of treatment.

Not all data point in the same direction. Canuso et al. compared the menstruation in 8 patients treated with prolactin elevating classical antipsychotics or risperidone and 8 patients treated with prolactin sparing olanzapine or clozapine. After weekly blood sampling, 6 patients turned out to have Hyperprolactinemia. No difference was found in rates of menstrual dysfunction or ovarian hormones (estradiol, progesterone) between patients with or without prolactin elevation. Irrespective of medication type or prolactin status, most subjects had peak estradiol levels below
normal reference values for the preovulatory phase of the menstrual cycle. The authors conclude that antipsychotic induced Hyperprolactinemia alone may not adequately explain the observed ovarian dysfunction in women with schizophrenia.

Summary: treatment with antipsychotics inducing significant prolactin elevation may be associated with amenorrhea, gynecomastia and galactorrhea. There is not enough information to estimate the incidence during short and long-term treatment with antipsychotics. The limited literature that is available suggests that lowering of prolactin levels with a dopamine agonist or by switching to a prolactin sparing antipsychotic will often be successful in treating these side effects.

Conclusions and clinical implications

There are only few studies, each with its own methodological limitations that deal with sexual dysfunctions related to psychotic illnesses and treatment with antipsychotics. As randomized comparative trials with validated evaluating instruments are absent so to date only tentative conclusions are justified. Studies using semi-structured questionnaires evaluating sexual dysfunctions suggest that libido reduction is often reported in patients with schizophrenia, but even more so in patients being treated with antipsychotics. Treatment with antipsychotics might induce several sexual dysfunctions, amenorrhea and galactorrhea. Most of these side effects are unlikely to subside during prolonged treatment. Although comparative controlled studies are lacking, it can be hypothesized that antipsychotics differ in their propensity to induce these effects. Factors probably involved in inducing sexual side effects are dopamine blockade and, linked to this, prolactin elevation. Serotonin, histamine or noradrenalin blockade might also be of importance as well as sedative properties of antipsychotics. Prolactin elevation might also induce other side effects like galactorrhea and amenorrhea.

Notwithstanding the absence of good clinical evidence, some clinical conclusions are justified. Doctors and patients seem to be reluctant to discuss these issues despite their high relevance in the motivation of patients to continue the medication. In this respect, educating physicians, providing tools (questionnaires) and encouraging them to discuss sexual side effects appears highly important. Dose reduction should be tried as a first step to reduce these side effects. An alternative strategy may be switching to another antipsychotic. Although hardly investigated, a prolactin sparing antipsychotic, in theory, may induce less sexual side effects and less amenorrhea and galactorrhea. In other words, switching from a prolactin elevating antipsychotic to a prolactin sparing antipsychotic may be advisable as a treatment option (Bunker et al. 1997; Gazzola and Opler 1998; Kim et al. 2002). An alternative can be adding a prolactin agonist like amantadine or bromocriptine to antipsychotic treatment with a prolactin elevating antipsychotic (Matsuoka et al. 1986; Correa et al. 1987; Smith, S. 1992). Although some authors feel that treatment with amantadine or bromocriptine may be a safe treatment alternative, others warn for a possible increase of psychotic symptoms (Rego and Giller Jr. 1989).

Given the virtual absence of comparative studies about sexual dysfunctions in patients being treated with antipsychotics, there is a clear and urgent need for
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Table 3. Main studies on antipsychotics and sexual side effects

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<th>Design</th>
<th>N</th>
<th>Age, SD (and range)</th>
<th>Questionnaire</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aizenberg et al. 1995</td>
<td>Open study, male, 21-45 years, stable relationship with female partner for at least 6 months.</td>
<td>N=20 schizophrenia, drug free for more than 6 months N=151 schizophrenia, using neuroleptics (29 fluphenazine decanoate, 22 haloperidol decanoate) N=151 healthy volunteers</td>
<td>Drug free 35 (SD 6.6); Treated 36 (SD 5.7); Controls 33 (SD 6.5);</td>
<td>Structured interview of Schiavi et al including items on desire, arousal, sexual activity, orgasm, erection, ejaculation and satisfaction</td>
<td>DSM III diagnosis schizophrenia</td>
</tr>
<tr>
<td>Ghadarian et al 1982</td>
<td>Random sample, outpatients, using classical antipsychotics more than a year</td>
<td>N=55 (men/women = 26/29)</td>
<td>Men: 5 with partner; Women: 13 with partner</td>
<td></td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Hummer et al. 1999</td>
<td>Open prospective study, inpatients, using haloperidol or clozapine, data from a drug monitoring program</td>
<td>N=153 (men/women = 116/37)</td>
<td></td>
<td></td>
<td>DSM III R schizophrenia or schizophriform disorder</td>
</tr>
<tr>
<td>Kotin et al. 1976</td>
<td>Open study, male in and out-patients using thioridazine or other antipsychotics, at least two weeks. Retrospective information included</td>
<td>N=87 patients, 121 periods of drug prescription.</td>
<td></td>
<td></td>
<td>75% schizophrenia</td>
</tr>
<tr>
<td>Smith et al. 2000-2002</td>
<td>Comparing out-patients on antipsychotics with patients attending an clinic for sexual dysfunction and controls</td>
<td>N=101 attendees of sex clinic N=57 controls N=55</td>
<td></td>
<td></td>
<td>No information about diagnosis</td>
</tr>
<tr>
<td>Teusch* et al. 1995</td>
<td>Unselected sample of inpatients with schizophrenia or controls</td>
<td>N=45 (men/women 30/15) all but 4 treated with antipsychotics &gt; 6 months Controls N=41 (men/women 22/19) Other diagnosis N=87</td>
<td></td>
<td></td>
<td>ICD-9 N=45</td>
</tr>
<tr>
<td>Weizman et al. 1985</td>
<td>Married male patients being treated with sulpiride</td>
<td>N=6</td>
<td>N=7</td>
<td></td>
<td>Self report, rating scale, evaluating libido, erection, ejaculation and satisfaction</td>
</tr>
</tbody>
</table>

** UKU = Udvalg for Kliniske Undersøgelser (Lingjaerde, O. et al. 1987)
### Table 4. Main studies on antipsychotics and sexual side effects, results in men

<table>
<thead>
<tr>
<th>Author</th>
<th>Decreased Libido</th>
<th>Inhibition Achieving Erection</th>
<th>Inhibition Maintaining Erection</th>
<th>Decreased Erection (not specified)</th>
<th>Decreased Orgasm</th>
<th>Decrease in Ejaculate Volume</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aizenberg et al 1995</td>
<td>Frequency of sexual thought reduced in untreated patients. Treated patients were less aroused. Lack of desire in both patient groups.</td>
<td>Patients more erectile problems during sexual intercourse.</td>
<td>Degree of erections was less in patient groups, but most in the treated group. Waking erections unchanged in both patient groups.</td>
<td>Number of orgasms/month did not differ between the three groups. Patient treated with antipsychotics had less frequent orgasms.</td>
<td>More masturbation in patients with schizophrenia. Patients using antipsychotics were less satisfied with the pleasure in sex.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghaderan et al 1982</td>
<td>Not asked</td>
<td>38%</td>
<td>42%</td>
<td>56% decreased orgasm</td>
<td>46% changed quantity of ejaculation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hummer et al 1999</td>
<td>Haloperidol: 63%</td>
<td>Clozapine: 57%</td>
<td>Haloperidol 27%</td>
<td>Haloperidol 20%</td>
<td>Clozapine: 21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolin et al 1976</td>
<td>Thioridazine: 44%</td>
<td>Other antipsychotics: 9% (P&lt;0.01)</td>
<td>Thioridazine: 4 patients</td>
<td>Other antipsychotics 2 reduced quality</td>
<td>Thioridazine: 49%</td>
<td>Haloperidol: serum levels correlated with sexual dysfunctions.</td>
<td></td>
</tr>
<tr>
<td>Lingjaerde et al 1987</td>
<td>Decreased sexual desire 37%</td>
<td>22%</td>
<td>15%</td>
<td>19%</td>
<td>Increased sexual desire 20%.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al 2000/2002</td>
<td>Libido not different from controls</td>
<td>Antipsychotic users 3.7 times more likely than controls erectile dysfunctioning</td>
<td>Antipsychotic users 16.4 times more likely than controls ejaculation disorders.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teusch et al 1995</td>
<td>Patients: 60%</td>
<td>Controls: 14% (p&gt;0.00)</td>
<td>Patients: 53%</td>
<td>Patients: 43%</td>
<td>Patients: 23% reported completely missed ejaculation during orgasm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weizman et al 1984</td>
<td>?</td>
<td>?</td>
<td>Patients 38%</td>
<td>?</td>
<td>5 patients impotent, three restoration of potency after lowering the dosage, two after switch to haloperidol.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 5. Main studies on antipsychotics and sexual side effects, results in women

<table>
<thead>
<tr>
<th>Author</th>
<th>Decreased Libido</th>
<th>Decreased Lubrication</th>
<th>Dyspareunia</th>
<th>Decreased Orgasm</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghadarian et al 1982</td>
<td>Not asked</td>
<td>Not asked</td>
<td>Not asked</td>
<td>33% changes in quality of orgasm</td>
<td>22% decreased ability to achieve orgasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7% pain during orgasm</td>
</tr>
<tr>
<td>Hummer et al 1999</td>
<td>Haloperidol: 33%</td>
<td>Haloperidol: 0%</td>
<td>Clozapine: 4%</td>
<td>Haloperidol: 0%</td>
<td>Clozapine: 4%</td>
</tr>
<tr>
<td></td>
<td>Clozapine: 28%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lingjaerde et al 1987</td>
<td>37%</td>
<td>8%</td>
<td></td>
<td>19%</td>
<td>Increased sexual desire 20%</td>
</tr>
<tr>
<td>Smith et al 2000/ 2002</td>
<td>No differences between controls and patients using antipsychotics</td>
<td></td>
<td></td>
<td>Female antipsychotic users were 9.6 times more likely to complain about orgasm versus controls</td>
<td></td>
</tr>
<tr>
<td>Teusch et al 1995</td>
<td>Patients: 60%</td>
<td>Patients: 33%</td>
<td>Patients: 13%</td>
<td>Patients: 27%</td>
<td>Controls: 11%</td>
</tr>
<tr>
<td></td>
<td>Controls: 26%</td>
<td>Controls: 21%</td>
<td>Controls: 16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reference List


Schizophrenia, sexual functioning and antipsychotic treatment, a review


Schizophrenia, sexual functioning and antipsychotic treatment, a review


Chapter 1


