Chapter 10

General discussion

Summary

The aim of this thesis is to investigate the frequency and nature of sexual side effects and hormonal alterations related to treatment with antipsychotic drugs. Other goals are to increase insight into the pathophysiological mechanisms of antipsychotic-induced sexual side effects, and to generate information in order to improve clinical guidance of patients treated with antipsychotics. In this general discussion we will briefly summarize our findings. The focus will be on pathophysiological considerations, and on the role of dopamine and prolactin. Possible clinical consequences of prolonged elevation of serum prolactin levels are discussed for osteoporosis and cardiovascular disease, and for behavior in general. Clinical consequences and consequences for future studies will be considered.
The most important findings of this thesis

Sexual side effects are only infrequently (10%) spontaneously reported by patients. However, in response to structured questionnaires, 20-60% of the patients reported detrimental effects on libido, erection, lubrication, orgasm or ejaculation, which they attributed to the use of antipsychotics (Chapters 1,4,5,7,8,9). Only reduction in libido seems to be related to schizophrenia as well as to treatment with antipsychotics (Chapters 1,7). Other sexual dysfunctions seem mainly to be related to the antipsychotics prescribed (Chapters 1 and 7). Preliminary results from a cross-sectional study suggest that sexual side effects do not subside during prolonged (over many years) treatment with antipsychotics (Chapters 1 and 7). Although our studies, and studies done by others, show that sexual side effects are very important to patients, both patients and clinicians seem reluctant to discuss these side effects (Chapters 1 and 3). In our studies, interviewers were at first also reluctant to discuss sexual side effects with patients, but providing clinicians with a questionnaire (the Antipsychotics and Sexual Functioning Questionnaire (ASFQ)) has facilitated these discussions (Chapter 3). Although some patients experienced no sexual side effects and indicated that they felt little need for studying these effects, the vast majority of our patients felt that studying sexual side effects was important to them (Chapter 5).

Before starting our studies, little was known about the incidence of sexual side effects with different antipsychotics. Studies in this thesis show that not only sexual side effects do occur very often, but also that they occur more often with certain groups of antipsychotics. Antipsychotics which elevate serum prolactin levels the most induce the highest incidences of sexual side effects, as in the case of classical antipsychotics and even more with risperidone (Chapters 2,4,5,8 and 9). Patients treated with clozapine, olanzapine and quetiapine reported low frequencies of sexual side effects (Chapters 4,5,8 and 9). In chapter 2, studies are presented indicating that risperidone elevates serum prolactin levels more than most classical antipsychotics. These findings are confirmed in the comparison of risperidone with classical antipsychotics, clozapine, olanzapine and quetiapine (Chapters 4,5,8,9). The mechanism by which risperidone elevates serum prolactin levels so greatly is explored in chapter 6; the explanation may be the slow passage of the blood-brain barrier of the metabolite 9-OH-risperidone. Some investigators report that although serum prolactin levels may be elevated during treatment with some antipsychotics, there is little evidence of side effects induced by serum prolactin elevation during treatment with antipsychotics. By making multiple comparisons between treatment groups, chapter 9 tries to disentangle the role of serum prolactin in the occurrence of sexual dysfunction.

It was concluded that serum prolactin elevation is not just an epiphenomenon of cerebral postsynaptic dopamine blockage by antipsychotics. Serum prolactin probably plays a major role in the pathogenesis of sexual side effects during treatment with antipsychotics for libido, orgasm and ejaculation, explaining 8-24% of the statistical variance found in our studies (Chapter 9). Although women have higher baseline serum prolactin levels and higher serum levels during treatment with antipsychotics in comparison to men, men and women experience influences on libido and orgasm by antipsychotics in more or less the same frequencies (Chapters 5 and 9).
Can serum prolactin influence sexual behavior?

Serum prolactin elevation may inhibit several aspects of sexual behavior, perhaps best illustrated by sexual dysfunction related to prolactinoma. These sexual dysfunctions are sometimes the first symptom of this neuro-endocrine active tumor of the pituitary (Meston and Frohlich 2000; Meston and Frohlich 2001; Schwartz et al. 1982; Yen and Jaffe 1999). The symptoms in patients with prolactinoma suggest that prolactin elevation, not caused by postsynaptic dopamine 2 receptor blockage, can indeed inhibit sexual behavior. How serum prolactin levels influence sexual functioning remains unclear. Elevation of serum prolactin does not seem to influence nightly erections in men during REM sleep, but it may modulate libido and sexual behavior (Carani et al. 1996). This suggests that the mechanism enabling erection may not be influenced by serum prolactin level elevation. Interestingly, in line with the study by Carani, we found no clear correlation between erection and serum prolactin levels, but we did find a clear correlation with libido. A conclusion could be that the effects of serum prolactin may take place primarily through the central nervous system.

A secondary effect of serum prolactin elevation may be the lowering of serum testosterone (Siris et al. 1980). Recent studies suggest that lowering of testosterone, especially in women, may inhibit sexual behavior (Riley and Riley 2000). This lowering of serum testosterone seems to be associated with a lower frequency of sexual thoughts and a lower coital frequency. In men, low serum testosterone may decrease nightly erections. The role of serum testosterone in male sexual functioning is unclear (Carani et al. 1996).

Serum prolactin levels interfere with dopamine in the striatal and limbic areas of the brain and with neurogenesis in the olfactory system (Cruz-Casallas et al. 1999). From studies in animals and humans, the involvement of dopaminergic systems in all phases (appetitive, arousal, orgasm) of sexual behavior seems likely (Damsma et al. 1992; Meston and Frohlich 2000; Meston and Frohlich 2001; Pfaus et al. 1990; Pfaus et al. 1995; Pfaus and Phillips 1989).

Animal studies have shown that neurogenesis in the olfactory system may be involved in parenting behavior, especially in recognizing offspring by smell (Shingo et al. 2003). In humans, changes in olfactory function during pregnancy are also found. These changes are thought to protect the child by preventing the mother from eating potentially harmful foods, and by improving recognition of the child (DiPasquale et al. 2001; Kolble et al. 2001).

Recent studies in humans volunteers suggest that prolactin may also be involved in inhibition of sexual behavior after orgasm, suggesting it has a role in satiety (Haake et al. 2002). These studies have shown that serum prolactin levels rise during sexual activity, reaching a peak during orgasm. After orgasm, the elevation of serum prolactin lasted as long as people felt disinterested in sexual activity. Some volunteers did not show a rise in serum prolactin levels during sexual activities; this seemed to coincide with the absence of a post-coital period of inhibition towards sexual activity (Haake et al. 2002).

It may be speculated that prolactin is involved in inducing behavior switches, ending sexual and feeding activity and enhancing behavior involved in parenting. In line with this hypothesis, observations in several animal studies suggest that
prolonged prolactin elevation is associated with parenting behavior (Ziegler 2000). Artificially lowering serum prolactin levels, using gene knock-out techniques in mice, and by administering bromocriptine to marmosets (monkeys), all seemed to disrupt parental behavior (Lucas et al. 1998; Roberts et al. 2001). In humans, as in most mammals, serum prolactin levels are elevated during pregnancy and in the first months after childbirth during lactation. In prolonged lactation in humans, serum prolactin declines after three to six months, followed by resumption of the menstrual cycle. Based on these observations, it can be speculated that antipsychotics, by inducing prolonged prolactin elevation, accidentally induce a switch in behavior, physiologically and psychologically meant to prepare for parenting. The intertwining of serum prolactin and the dopamine system suggests that prolactin may be in a key position to change dopaminergic activities, possibly changing priority settings in such areas as attention, motivation, reward and sexual behavior.

Is prolonged artificial serum prolactin elevation a serious medical condition?

Possible secondary effects of long-term serum prolactin elevation include menstrual disorders, the development of breast cancer, decreased bone density and elevated risk for cardiovascular disorders (Dickson and Glazer 1999; Halbreich et al. 2003). Recent studies do seem to indicate an increased risk of developing breast cancer after treatment with prolactin-elevating medication (Wang et al. 2002). Other recent studies suggest that the duration of treatment with antipsychotics may be linked to a decrease in bone marrow density (Bilici et al. 2002).

Behaviorally, possible secondary effects of prolonged prolactin elevation, in combination with changes in the levels of other hormones, are not known. Still, we may wonder what these could be, especially in the maturing brains of young children. We know that the sensitivity of the brain to hormones influencing behavior varies throughout life, creating time windows for different influences. Also, the influence of hormones on the brain may change in the context of the concentrations of other hormones, or in the context of the order of hormone fluctuations (Pfaff 1999). For instance, in order for female rats to be in oestrus, increased levels first of estrogen, followed by an increase of progesterone are essential; giving these hormones together, or changing the order causes female rats not to be in oestrus, and not to exhibit sexual behavior. Several times in the past years we have been consulted about young boys who are showing breast development while being treated with prolactin-elevating antipsychotics. This made us worry about what effects prolonged serum prolactin elevation, which has possible secondary effects on testosterone, estrogens, progesterone and other hormones, may have on sexual behavior in later life. To our knowledge, this has not been studied, especially not in patients with schizophrenia being treated with antipsychotics. The only study addressing this concern we could find, by Siimes et al., was of children being treated for cancer. This study implies that these concerns may be more than a hypothetical problem (Siimes et al. 1993). The possible relationship between serum prolactin elevation and psychosexual development was studied, comparing pubertal stage, testicular size, serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, thyroxine, thyroid-
stimulating hormone (TSH), and prolactin concentrations in 94 adolescent males who had survived malignancies in childhood. Of the patients, 22% had elevated serum prolactin, > 300 mU/L. A significant inverse relation existed between serum prolactin concentration and dating with the opposite sex; none of the patients with elevated serum prolactin were dating. The investigators concluded that even a slight elevation of serum prolactin above normal is associated with or may be reflected in the psychosexual development of adolescent males who have survived malignancies in childhood.

We should be careful in interpreting these findings. Although prolactin-elevating antipsychotics have been available for more than 50 years and have been used extensively, only a few studies, all with clear methodological limitations, are suggesting that prolonged serum prolactin elevation may be hazardous. So it may be too early to state that antipsychotic-induced serum prolactin elevation is a serious medical condition. Clearly, more studies are needed, investigating possible influences of prolonged serum prolactin elevation on psychosocial behavior and possible health risks. For future drug development it is probably wise to develop antipsychotics that do not induce sustained serum prolactin elevation.

How should sexual side effects and serum prolactin elevation be weighed in the context of other side effects?

Antipsychotics are effective in the symptomatic improvement of psychotic symptoms, but cannot cure schizophrenia. So for many patients, prolonged treatment is necessary in order to prevent the recurrence of psychotic symptoms. As this prolonged treatment often continues for many years, or even lifelong, side effects inducing chronic discomfort or social and medical problem become very important. Side effect research is not popular with pharmaceutical industries, nor with clinicians; however, patients are extremely interested in and worried by side effects. None of the presently available antipsychotics, classical or atypical, are without important side effects. But the many different side effects are often difficult to compare in their clinical importance. Many classical antipsychotics cause all kinds of often very distressing movement disorders in about 60% of the patients. Most of these movement disorders are reversible, but some, like tardive dyskinesia, may be irreversible. Clozapine, being the first atypical antipsychotic without extrapyramidal side effects, is a very effective antipsychotic, but many patients experience serious sedation, dizziness, weight gain or even sporadic life-threatening cardiovascular or haematological side effects. Other newer antipsychotics may induce serious weight gain with long-term increased risks for developing diabetes and cardiovascular problems. None of these side effects occur in all patients. Some patients are clearly more sensitive to developing, for instance, movement disorders or weight gain than others. Most antipsychotics are more or less equally effective. But the side effects induced seem to vary a great deal between individuals. The available data do not permit preferring any single antipsychotic over the others in all cases.

Systematic side effect evaluation and systematic long-term follow-up studies evaluating medical and psychosocial (side) effects of antipsychotics following strict protocols are clearly needed. The systematic evaluation of side effects should be based on formal questionnaires like the UKU or Liverpool University Neuroleptic
Side Effect Rating Scale (LUNSERS), which includes sexual side effects (Day 1995). The objective medical condition and the subjective well-being of the patient should guide clinical practice (Ten Brink et al. 1998). A recently developed questionnaire, the Subjective Response to Antipsychotics (SRA), may help the patient and clinician to weigh the beneficial and detrimental effects of antipsychotic medication in the perspective of the patient’s subjective well-being (Wolters et al. 2002).

Laboratory investigation and physical examination on a regular basis should be included in good clinical practice for patients treated with antipsychotics over a long period. Evaluation of sexual and hormonal aspects should be incorporated into the daily routine of clinical practice, neither overemphasizing nor neglecting this important aspect of human life.

**What are the clinical consequences of this thesis?**

Sexual side effects frequently occur in patients treated with classical antipsychotics and even more so in patients treated with risperidone. Men and women seem to be equally likely to experience sexual side effects. As patients often do not report these effects spontaneously, clinicians should actively inquire about these side effects, and should discuss the individual impact with patients. The use of questionnaires like the ASFQ may help clinicians to discuss these problems with patients.

Some patients feel relieved by a diminished sexual drive, some patients even seem to feel rather indifferent about sexual side effects, but for the majority of the patients sexual side effects are a burden. Sexual side effects of antipsychotics can be managed well. In patients treated with prolactin-elevating antipsychotics and experiencing sexual side effects, switching to an antipsychotic that does not raise prolactin levels is probably the best option. Alternatively, lowering the dosage could be considered. If switching to another antipsychotic or lowering dosages are not possible, adding a dopamine agonist may be considered (Matsuoka et al. 1986, Smith, S. 1992).

Some clinicians tend to alter the antipsychotic treatment in response to raised levels of serum prolactin, often accidentally found. Up to now, there is no evidence to support changing treatment only because of serum prolactin elevation. Also, there is no reason to advise clinicians to evaluate serum prolactin levels routinely. In our opinion, the symptoms of the patient rather than alterations in laboratory findings should direct clinical guidance.

In the rehabilitation of patients, including socio-sexual rehabilitation, clinicians should consider the possible changes in sexual behavior and fertility when switching to antipsychotics with less detrimental effects on sexual performance. Clinicians should provide adequate sex education and contraception and clinical guidance within a comprehensive treatment plan (Lukoff et al. 1986; Cournos et al. 1994; Hilger et al. 1983; Jacobs and Bobek 1991; Dickson and Edwards 1997; Dickson and Dawson 1998; Currier and Simpson 1998; Dickson and Glazer 1999).
General discussion

What new research on sexual dysfunctions and serum prolactin elevation is needed?

More studies allowing for the evaluation of sexual functioning in more detail and for comparison of treatment with different antipsychotics are needed. Larger sample sizes of women and also of each antipsychotic will increase the reliability of the studies. The influence of prolactin-elevating antipsychotics on other hormones like estrogen, progesterone and testosterone, which possibly contribute to the side effects profile, is understudied.

Possible secondary effects of long-term serum prolactin elevation on menstruation, the development of breast cancer, decreased bone density or elevated risk for cardiovascular disorders have been suggested but only infrequently studied (Bilici et al. 2002; Halbreich and Palter 1996; Wang et al. 2002; Halbreich et al. 1995; Halbreich et al. 2003). Future studies are needed to address these possible serious medical consequences.

Recently, some clinicians reported successful treatment of sexual side effects induced by antipsychotics with sildenafil (oral communication). These clinical observations should be studied in a controlled trial as they may offer a treatment alternative, and may enlarge our understanding of the pathophysiology of sexual functioning.

In our studies a significant proportion of the variance of the reported sexual dysfunctions remain unexplained. This suggests that other possible factors influence the findings on sexual functioning, including methodological, pharmacological, social and disease-related factors. These factors need to be addressed in future studies. It is also important to investigate the influence of prolonged treatment with prolactin-elevating antipsychotics on psychosocial and sexual development, especially in children and adolescents (Siimes et al. 1993; Dickson and Glazer 1999).
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