Antipsychotic treatment and sexual functioning
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2003

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Chapter 8

What are the Effects of Antipsychotics on Sexual Dysfunctions and Endocrine Functioning?

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Summary

The literature is reviewed and preliminary results of new studies are presented showing that treatment with classical antipsychotics, as well as risperidone, induces sexual dysfunctions in 30% to 60% of the patients. These antipsychotics also frequently induce amenorrhoea and galactorrhoea. Although comparative studies are rare, it is likely that prolactin-sparing antipsychotics, as recently shown in a randomized trial of olanzapine versus risperidone, induce less sexual side effects. From these studies, it becomes apparent that prolactin elevation induced by classical antipsychotics and risperidone is probably a factor in inducing sexual dysfunctions, amenorrhoea and galactorrhoea. The role of other factors inducing sexual dysfunctions like sedation, α-blockade, testosterone, dopamine, and serotonin is discussed. Finally, it is concluded that sexual and hormonal effects of antipsychotics, although clearly important, are often neglected, in research as in clinical practice. Lowering the dosage or switching to a prolactin-sparing antipsychotic often reduces sexual side effects, amenorrhoea, and galactorrhoea.
Chapter 8

Preview

Chapter 8 has been published in psychoneuroendocrinology in 2002. The content includes a review of the literature and recent findings of our studies, presented in chapter 1, 2, 4. The data of the patients presented in chapter 2, 4 and from ongoing open studies of patients treated for 6 weeks with antipsychotics are analysed in a summative dataset allowing analyses in a broader context. In this book chapter 8 overlaps in some aspects with chapter 9. The advantage of this overlap is that each chapter can be read independently.

Introduction

There is a growing awareness of sexual side effects and changes in endocrine functioning induced by antipsychotics, a field of research that has been neglected for a long time. We will combine a review of the literature with results of recent studies from our research group. In conclusion, we discuss the findings and reflect on possible pathogenetic mechanisms, clinical implications, and future directions of studies.

What are the effects of antipsychotics on sexual dysfunctions?

A problem in evaluating sexual dysfunctions in patients with schizophrenia is that some patients with schizophrenia may experience alterations in sexual performance as a result of their primary illness and the social consequences of this illness (Nestoros et al., 1981). Others might experience problems in sexual functioning primarily related to treatment with antipsychotic medication. Studies show that most patients with schizophrenia are sexually active, often by masturbation although many patients also have sexual contacts with a partner. Studies evaluating sexual performance in unmedicated patients with schizophrenia show that these patients tend to experience a reduced libido, but no other sexual dysfunctions (Aizenberg et al., 1995). This decreased libido might be linked to the general reduction of initiative, often referred to as negative symptoms. Another problem is that patients, as a consequence of their symptoms, experience many social problems complicating contacting potential partners.

Many pharmacological properties of antipsychotics may influence sexual performance. Segraves and Meston et al. reviewed these mechanisms. The most important ones will be mentioned here (Segraves 1989; Meston et al. 1992; Meston and Fröhlich 2000).

All antipsychotics are dopamine antagonists. Dopamine is involved in sexual arousal and orgasm. Dopamine blockade might contribute to libido loss and orgasm disturbance. A secondary effect of dopamine blockade, above a certain threshold, in the tuberoinfundibular system of the brain is prolactin elevation. The mechanisms are being discussed elsewhere in this journal supplement. As a consequence of prolactin elevation, many changes in other hormone levels might occur, including a decrease in serum testosterone levels that might influence sexual performance in men as well as in women. The prolactin elevation itself as
What are the effects of antipsychotics on sexual dysfunctioning and endocrine functioning?

well as decreased levels of testosterone and possibly other hormones may decrease some aspects of sexual behavior. Antipsychotics, partly from being histamin antagonists, have sedating properties diminishing sexual performance. Some antipsychotics have alpha blocking properties that might diminish erection, vaginal lubrication and ejaculation. These noradrenergic effects seemed to be partly balanced with (anti-) cholinergic effects leading to final effects on erection that might turn into erection disturbance (often) or priapism (rare). The main mechanisms and effects of antipsychotics on sexual performance are summarized in table 1.

Table 1. Possible mechanisms of antipsychotics influencing sexual functioning

<table>
<thead>
<tr>
<th></th>
<th>Libido</th>
<th>Erection or Vaginal lubrication</th>
<th>Orgasm</th>
<th>Ejaculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic blockade</td>
<td>Inhibition?</td>
<td>If in unbalance with noradrenergic functions: Priapism?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine blockade</td>
<td>Inhibition</td>
<td>?</td>
<td>Inhibition</td>
<td>?</td>
</tr>
<tr>
<td>Histamine blockade, sedation</td>
<td>Inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenergic (α) blockade</td>
<td>If in unbalance with cholinergic functions: Priapism?</td>
<td>Inhibition of ejaculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin (5HT2a) Blockade</td>
<td>?</td>
<td></td>
<td>Inhibition</td>
<td>?</td>
</tr>
<tr>
<td>Prolactin elevation</td>
<td>Inhibition</td>
<td>Inhibition</td>
<td>?</td>
<td>Inhibition of ejaculation?</td>
</tr>
<tr>
<td>Testosterone decrease</td>
<td>Inhibition?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*= possible influence, but no consensus in the literature.

Studies that assess sexual side effects of antipsychotics are rare; comparative studies almost absent (Nestoros et al., 1981; Knegtering et al., 2000; Peuskens et al., 1998). Studies using spontaneous reports of patients report low incidences (10% or less) of sexual dysfunctions (Knegtering et al., 1999). In contrast, studies using structed 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 (Lingjearde et al., 1987; Sullivan and Lukoff 1990). Classical antipsychotics frequently show a higher incidence of amenorrhoea, galactorrhoea, and impotence in comparison to placebo (Ghadirian et al., 1982). These effects are associated with prolactin elevation. According to Alazenberg et al, untreated male schizophrenic patients exhibit decreased sexual desire. Their study suggests that antipsychotics might lead to a
restoration of sexual desire while impairing erectile, orgasmic, and sexual satisfaction problems (Aizenberg et al., 1995).

Ghadirian et al. examined a random sample of 55 schizophrenic outpatients (26 men and 29 women) treated with classical antipsychotics selected from a long-term follow-up clinic. The patients rated their current sexual functioning on specially designed scales. More than 58% of the male (reduced erection and orgasm) and 33% of the female patients (orgasm) reported impaired sexual functioning during treatment with antipsychotics. Ninety-one per cent of the female patients reported changes in menstruation (Ghadirian et al. 1982).

Although comparative studies are rare, the majority of the literature suggests that antipsychotics might differ in the type and frequency of sexual dysfunctions (Knegtering et al., 1999). For instance, thioridazine seems to cause more sexual dysfunctions (erection and ejaculation) in comparison to other classical antipsychotics (Kotin et al., 2001).

In a study by Smith et al. (2000), 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 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, thioxanthene substitutes, benzamides, and aliphatic phenothiazines were more likely to be associated with sexual dysfunction than with other antipsychotics.

Clozapine, which induces no significant and sustained prolactin elevation, causes few sexual dysfunctions according to some authors (Crenshaw and Goldberg 1996). But according to a study by Hummer et al. (1999), the prolactin-elevating classical antipsychotic haloperidol and (non prolactin-elevating) clozapine showed comparable frequencies of sexual dysfunctions. In this study, 153 patients were treated for six weeks with either clozapine (N=100) or haloperidol (N=53). Sexual dysfunctions were evaluated in weekly assessments. In the last week of their study, there was a difference in sexual dysfunctions; haloperidol causing more sexual dysfunctions in comparison to clozapine. In their final analysis carried out on a last-observation-carried-forward basis, more than 60% of men and 30% of women in both treatment groups, reported sexual dysfunctions, no statistical significant differences were found between the treatment groups (Hummer et al., 1999). In contrast Aizenberg et al. (2001) in a study with 60 outpatient men using long-term classical antipsychotics, 30 being switched to clozapine, found that maintenance therapy with the atypical antipsychotic clozapine may be associated with a lesser degree of sexual dysfunction than the classical antipsychotics.

In 1997 we initiated a research-program aiming at the evaluation of the effects of antipsychotics on sexual functioning and the (mediating) influence of endocrine functions in bringing about eventual effects.

In an open randomized clinical trial (RCT) we compared sexual dysfunctions in patients treated with olanzapine versus patients treated with risperidone. Twenty-five patients received olanzapine, mean dosage 9.4 (range 5-15) mg/day; 21 patients received risperidone, mean dosage 3.4 (range 2-6) mg/day. Sexual functioning was assessed by means of a semi-structured questionnaire based upon the UKU (Lingjaerde 1987): the Antipsychotics and Sexual Functioning Questionnaire (ASFQ)
What are the effects of antipsychotics on sexual dysfunctioning and endocrine functioning? (Knegtering and Castelein 2000). The ASFQ guides the interviewer in introducing the subjects of the interview and provides more detailed scoring instructions than the UKU. Patients were asked if they experienced a change in sexual functioning which they relate to the medication used last month. Sexual dysfunctions most probably related to the use of antipsychotics could be rated as much improved, improved, unchanged, worse, much worse or in case the answer was not clear, unknown. As almost no patient reported improvement in sexual performance during treatment with antipsychotics, we converted the ratings into the dichotomized ratings unchanged or worsened before some of the statistical analyses. Sexual dysfunctions were rated and blood sampling was done after six consecutive weeks of treatment with antipsychotics. Patients received general information about side effects but were blind for any specific hypothesis. No statistical significant differences were found between the treatment groups in demographical data and diagnosis. Sexual dysfunctions (libido reduction, problems achieving an orgasm, erectile dysfunction or ejaculatory dysfunction) were reported by 3 out of 25 patients (12%) in the olanzapine-group, and by 11 out of 21 patients (52%) in the risperidone-group. Statistical test-results: chi-square value= 6.99; df= 1; p= .004; 95% confidence-interval for the difference: 16% - 65% (Knegtering et al. 2001).

We combined the dataset of this RCT with the dataset of an open study that started in 1997 and is still going on. The patients of the open study and of the RCT were from the same population of patients with a first psychotic episode. All patients were recruited from the inpatient or outpatient departments of our university hospital. The main criteria for inclusion in the open study were: treatment of the patients for a functional psychosis with anti-psychotic medication for four to six weeks. No co-medication with known influence on sexual performance was allowed. Sexual functioning was assessed by the same method as was used in the RCT. Preliminary results on the first 95 patients were reported in 1999 (Knegtering et al., 1999). Tentative conclusions were then: a) olanzapine had less detrimental effects on sexual functioning than classical antipsychotics or risperidone, b) olanzapine did better in this respect than classical antipsychotics, but not markedly so, and c) patients reporting sexual dysfunctions had on average higher serum prolactin levels than those without such dysfunctions.

The combined dataset now contains data of 199 patients (134 men, 65 women). The current analysis is targeted at the pairwise comparison of a group of patients using classical antipsychotic medications versus olanzapine versus risperidone. Table 2a shows, for each medication (-group): the mean dosages of the antipsychotics, the percentages of patients (men and women combined) who reported sexual dysfunctions and the observed mean prolactin levels. We did pairwise comparisons. The statistical methods applied were: chi-square tests for pairwise differences in percentages patients with sexual dysfunction; two sided t-tests for pairwise differences in mean prolactin levels (natural log transformed) in addition 95% confidence intervals were calculated for all differences. The corresponding results of the statistical evaluation are shown in table 2b.
Table 2a. Sexual dysfunctions in men and women

<table>
<thead>
<tr>
<th></th>
<th>Libido reduction</th>
<th>Orgasm Disturbance</th>
<th>Any sexual dysfunction</th>
<th>Mean prolactin levels (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=40</td>
<td>40%</td>
<td>18%</td>
<td>43%</td>
<td>41.6 (SD 40.6)</td>
</tr>
<tr>
<td>Olanzapine N=40</td>
<td>18%</td>
<td>3%</td>
<td>18%</td>
<td>18.2 (SD 17.4)</td>
</tr>
<tr>
<td>Risperidone N=82</td>
<td>50%</td>
<td>50%</td>
<td>64%</td>
<td>58.4 (SD 44.7)</td>
</tr>
</tbody>
</table>

**Legend table 1**

Classical antipsychotics: broomperidol N=1 (dosage 9 mg/day), haloperidol N=5 (Mean dosage 4 mg/day SD 2.5), perphenazine N=3 (mean dosage 77 mg/day SD 148), pimozide N=19 (Mean dosage 7 mg/day SD 5.2), sulpiride N=2 (Mean dosage 250 mg/day SD 71). Olanzapine N=10 (Mean dosage 45 mg/day SD 90).

Olanzapine Mean dosage 10.2 mg/day SD 3.6
Risperidone Mean dosage 4 mg/day SD 2.0

Table 2b. Statistical results of pairwise comparisons between antipsychotics: differences in percentages patients experiencing sexual dysfunction and mean prolactin levels

<table>
<thead>
<tr>
<th></th>
<th>Classical antipsychotics vs. Olanzapine</th>
<th>classical antipsychotics vs. risperidone</th>
<th>olanzapine vs. risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>libido reduction</td>
<td>4.14; p=.04</td>
<td>1.14; p=.29</td>
<td>10.32; p=.001</td>
</tr>
<tr>
<td>* chi-square value (df= 1)</td>
<td>2% - 42%</td>
<td>-9% - 30%</td>
<td>15% - 49%</td>
</tr>
<tr>
<td>* 95% confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orgasm disturbance</td>
<td>3.51; p=.06</td>
<td>9.88; p=.001</td>
<td>20.27; p=.000</td>
</tr>
<tr>
<td>* chi-square value (df= 1)</td>
<td>0% - 29%</td>
<td>15% - 50%</td>
<td>33% - 60%</td>
</tr>
<tr>
<td>* 95% confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any sexual dysfunction</td>
<td>4.85; p=.03</td>
<td>4.36; p=.04</td>
<td>19.24; p=.000</td>
</tr>
<tr>
<td>* chi-square (df= 1)</td>
<td>4% - 46%</td>
<td>2% - 41%</td>
<td>29% - 63%</td>
</tr>
<tr>
<td>* 95% confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolactin levels</td>
<td>3.31; p=.002</td>
<td>2.25; p=.03</td>
<td>5.96; p=.000</td>
</tr>
<tr>
<td>(In-transformed)</td>
<td>.28 - 1.13</td>
<td>.05 - .77</td>
<td>.74 - 1.47</td>
</tr>
<tr>
<td>* t-value (varying df's)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* 95% confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

df= degrees of freedom

Summarizing the data in tables 2a and 2b: sexual dysfunctions in men and women (reduced libido and/or orgasm) were reported in 18% of the patients treated with olanzapine, 43% classical antipsychotics and 64% risperidone. The results suggest that olanzapine is significantly less detrimental to experienced sexual functioning than risperidone. The classical antipsychotics used in this study induced significantly more sexual dysfunctions than olanzapine but significantly less than risperidone. The three treatment groups differed significantly in prolactin elevation, olanzapine induced only little prolactin elevation. Classical antipsychotics and even more (so) risperidone induced significant prolactin elevation.

As the majority of the patients participating in our studies are men we analyzed their data separately (tables 3a and 3b). The same variables as before are used supplemented with variables describing specific male sexual problems. The statistical tests and techniques are the same.
What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning?

Table 3a. Sexual dysfunctions in men

<table>
<thead>
<tr>
<th></th>
<th>Libido reduction</th>
<th>Erection disturbance</th>
<th>Orgasm Disturbance</th>
<th>Reduction Of ejaculation volume</th>
<th>Any sexual dysfunction</th>
<th>Mean prolactin levels (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=27</td>
<td>39%</td>
<td>19%</td>
<td>20%</td>
<td>20%</td>
<td>44%</td>
<td>26.2 SD 19.6</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=30</td>
<td>20%</td>
<td>20%</td>
<td>4%</td>
<td>4%</td>
<td>28%</td>
<td>14.1 SD .2</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=55</td>
<td>46%</td>
<td>42%</td>
<td>43%</td>
<td>36%</td>
<td>60%</td>
<td>38.1 SD 20.5</td>
</tr>
</tbody>
</table>

Classical antipsychotics: bromperidol N=1 (dosage 9mg/day), haloperidol N=4 (Mean dosage 4.25 mg/day SD 2.87), pimozide N=14 (Mean dosage 8.31 mg/day SD 5.78), sulpiride N=2 (dosage 300 mg/day), zuclopentixol N=6 (Mean dosage 65 mg/day SD 115.7).

Olanzapine Mean dosage 9.92 mg/day SD 3.97
Risperidone Mean dosage 4 mg/day SD 1.92

Table 3b. Statistical test-results of pairwise comparison of anti-psychotics in men

<table>
<thead>
<tr>
<th></th>
<th>Classical antipsychotics vs. Olanzapine</th>
<th>Classical antipsychotics vs. Risperidone</th>
<th>Olanzapine vs. Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>libido reduction</td>
<td>* chi-square value (df= 1) * 95% confidence interval</td>
<td>.20; p= .15 -6% - 43%</td>
<td>.35; p= .55 -15% - 30%</td>
</tr>
<tr>
<td>erection disturbance</td>
<td>* chi-square (df= 1) * 95% confidence interval</td>
<td>.01; p= .95 -23% - 21%</td>
<td>3.98; p= .05 3% - 43%</td>
</tr>
<tr>
<td>orgasm disturbance</td>
<td>* chi-square value (df= 1) * 95% confidence interval</td>
<td>2.68; p= .10 -2% - 33%</td>
<td>3.92; p= .05 2% - 44%</td>
</tr>
<tr>
<td>reduction ejaculation volume</td>
<td>* chi-square value (df= 1) * 95% confidence interval</td>
<td>2.68; p= .10 -2% - 33%</td>
<td>2.00; p= .16 -5% - 36%</td>
</tr>
<tr>
<td>any sexual dysfunction</td>
<td>* chi-square (df= 1) * 95% confidence interval</td>
<td>1.51; p= .22 -9% - 42%</td>
<td>1.77; p= .18 -7% - 38%</td>
</tr>
<tr>
<td>prolactin levels (ln-transformed)</td>
<td>* t-value (varying df's) * 95% confidence interval</td>
<td>2.35; p= .02 .07 - .95</td>
<td>2.21; p= .03 .04 - .80</td>
</tr>
</tbody>
</table>

df= degrees of freedom
Summarizing the data in tables 3a and 3b: sexual dysfunctions (libido, erection, orgasm, ejaculation) in men were reported in 28% of the patients treated with olanzapine, 44% classical antipsychotics and 60% risperidone. Patients treated with olanzapine reported significant less frequently libido reduction, orgasm disturbance and reduction of ejaculation volume in comparison to patients with risperidone. The classical antipsychotics used in this study induced significant less frequently erection disturbance and orgasm disturbance in comparison to risperidone.

**What are the effects of antipsychotics on the endocrine system?**

*The influence of prolactin elevation*

Prolactin controls the lactation process, but it has also a gonadotrophic function and regulates the libido and possibly some aspects of sexual behavior (Carani et al., 1996). Prolactin levels show daily and seasonal variation and might be influenced by many factors like pregnancy, lactation, stress, sexual activity, and nipple manipulation.

Although many neurotransmitters might play a role in prolactin regulation, modulation by dopaminergic mechanisms is probably the most important neurotransmitter system involved. All antipsychotics are dopamine blockers, while some antipsychotics are also serotonin blockers. Blockade of dopamine receptors by antipsychotics in the tubero-infundibular tract releases the inhibition of prolactin storage cells, resulting in elevation of prolactin levels. In contrast to dopamine, serotonin acts to stimulate prolactin release by an inhibiting effect on the dopaminergic influence on the tubero-infundibular tract. A consequence of this mechanism is that serotonergic influences can modulate (dopamine-mediated) prolactin release, but serotonin can only show this effect as long as the dopaminergic influence is present.

Some atypical antipsychotics are antagonists of both, serotonin and dopamine, so exerting opposing effects on prolactin release. The net effect would depend on the relative strength of the two actions.

Elevation of the prolactin level can have different consequences for male and female antipsychotic users. Luteinising hormone (LH) stimulates testosterone production in men. If prolactin levels are raising, gonadotropin-releasing hormone (GnRH) levels and consequently LH-levels will fall. This might result in a decrease of testosterone levels, which might contribute to sexual function disorders. In women, elevated prolactin levels can result in changes of pulse released GnRH, which can induce inhibition of the menstrual cycle. If GnRH levels rise even more, estrogen lack may occur and the ovarian function can stop. In short term, this can lead to amenorrhoea, but long-term complications of lack of estrogen may result in osteoporosis and cardiovascular diseases (Dickson and Glazer 1999). Chronic Hyperprolactinemia decreases bone density in both men and women probably caused by decreased gonadal functioning, but possibly also by a direct effect of prolactin on bone (Thörner et al., 1998).

Much of the influences of prolactin elevation on other hormone systems are learned from patients with prolactinomas. However prolactinomas are in general associated with higher prolactin levels than patients using antipsychotics.
What are the effects of antipsychotics on sexual dys functioning and endocrine functioning?

Only few studies are known to evaluate these hormonal effects in patients using antipsychotics. Smith examined the influence of antipsychotics on several hormones (Smith et al., 2000). They evaluated sex hormone profiles in 67 patients using classical antipsychotics. In men, prolactin, SHBG, FSH, TSH, LH, and testosterone were evaluated. In women, prolactin, FSH, TSH, LH, oestradiol, and progesterone were evaluated. In men, there was a significant positive relation between antipsychotic dose and serum prolactin levels. In women, there was a significant positive correlation between antipsychotic medication dose and prolactin levels while there was a negative correlation between antipsychotic dose and progesterone levels. In men, the mean prolactin levels were in the normal range, although they correlated with the dosage. In women, there was Hyperprolactinemia, mean estrogen and progesterone levels were below the normal range. The authors concluded the classical antipsychotics induced in women a hypogonadal state, possibly reducing fertility.

We examined the correlation between prolactin and testosterone levels in 38 men who had been treated with risperidone for six weeks (mean dosage 4.1, range 3-5 mg/day). Mean prolactin levels were modestly elevated in most patients and in 11 patients prolactin levels were markedly elevated (mean 23.6 ng/ml, range 2.3-93.5 ng/ml). Testosterone levels stayed in the normal range in all patients (mean 18.6 nmol/l, range 2.1-37 nmol/l) and no significant correlation was found between prolactin levels and testosterone levels (Pearson correlation 0.181, p=0.277).

This lack of predicted testosterone changes is in line with the study of Rinieris et al. who examined prolactin levels and testosterone levels in 15 patients being treated with a dose range of 7.5 to 60 mg haloperidol/day (Rinieris et al., 1989). A significant decrease in serum testosterone levels was found in patients treated with 30 to 60 mg/day but not in lower dose ranges. The studies on the relation between prolactin, testosterone and antipsychotics are comparisons between individuals using different antipsychotics. It cannot be ruled out that within individuals antipsychotic induced prolactin elevation might diminish testosterone levels.

Prolactin levels in unmedicated patients suffering from schizophrenia are normal, with the possible exception that the circadian rhythm of prolactin, especially in women, might be advanced by 1.0-1.5 hours compared to healthy controls, a finding with unknown significance (Rao et al, 1994; Melzer et al., 1974). All classical antipsychotics, being powerful dopamine 2 antagonists, cause a significant elevation of plasma prolactin levels (Green and Brown 1988).

If antipsychotics induce major elevation of prolactin, the levels can rise up to 150 ng/ml and remain at a high level when continuing medication. Although elevation is dose-dependent, dose reduction does not always give a decrease of prolactin levels. Stopping medication tends to normalize prolactin levels (Santoni and Saubuda 1995). Amenorrhoea and galactorrhoea, as well as infertility in women (caused by hypo-estrogenemia) usually completely recovers after normalisation of serum prolactin levels.

Most atypical antipsychotics like clozapine, olanzapine, sertindol, or quetiapine give less blockade of dopamine receptors in the tubero-infundibular pathway (anterior pituitary) than most classical antipsychotics and risperidone. The amount of dopamine blockade is partly related to a fast dissociation from the dopamine
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receptor (Kinon and Lieberman 1996; Kapur and Seeman 2001; Kapur et al. 2000; Kapur et al. 1999). Due to this mechanism, these antipsychotics generally only give a short-lived and low elevation of prolactin level, which is completely normalized after a few hours and will often be undetected in standard laboratory control.

Risperidone is an exception. It gives a significant elevation of prolactin, possibly even more than some classical antipsychotics (Knegtering et al. 2000; Shiwach and Carmody 1998). In the previously described randomized trial comparing sexual dysfunctions in patients with olanzapine versus risperidone, prolactin levels were significantly higher in patients using risperidone (Knegtering et al. 2001). The antipsychotic amisulpride, often described as atypical, seems to elevate serum prolactin levels as well (Stanniland and Taylor 2000).

What is the role of prolactin and other hormones in inducing sexual side effects?

The association between the dosage of classical antipsychotics, degree of prolactin elevation and sexual dysfunction suggests a possible causal relationship.

Prolactin elevation in patients with a prolactinoma is associated with amenorrhoea and galactorrhoea in women. Prolactinoma is also associated with erectile dysfunction in men and possibly with decrease of libido and orgasm in men as well as women (Schwartz et al. 1982; Pollack et al. 1992).

In antipsychotic-induced Hyperprolactinemia worsening of sexual dysfunctions correlates with serum prolactin elevation (Ghadirian et al. 1982; Burke et al., 1994).

Our dataset of 199 patients (men and women), combining open and controlled studies, enabled us to compare patients using prolactin-elevating with patients using non-prolactin-elevating antipsychotics (see data in tables 2a, 2b, 3a and 3b).

Antipsychotics elevating prolactin (classical antipsychotics and risperidone) (n=123) were associated with high frequencies of sexual dysfunctions (libido loss (43.9%), orgasm disturbance (31.7%)). Antipsychotics that hardly elevated prolactin (clozapine, olanzapine, quetiapine, sertindole) (n=76) were associated with much lower frequencies of sexual dysfunctions (libido loss (11.8%), orgasm disturbance (5.2%)). We compared summative scores of sexual dysfunctions in both treatment-groups including libido and orgasm. The summative scores ranged from 0 (libido and orgasm not changed) to 4 (libido and orgasm both much worse). Prolactin elevating antipsychotics induced sexual side effects more frequently and seriously in comparison to prolactin sparing antipsychotics (Mann Whitney U, Z= –5.129, p=0.000).

Analyzing the data in a subgroup of 66 patients using risperidone, a clear correlation is found between risperidone dosage and prolactin levels (Pearson correlation 0.44, p=0.000). In men (n=50), the dosage of risperidone and the prolactin levels correlated significantly with sexual dysfunction (Pearson correlation 0.34, p=0.005).

However, not all studies find a relation between prolactin elevation and sexual side effects. A review of Kleinberg et al. (1999) summarizes all data from

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randomized, double-blind studies of risperidone in patients with chronic schizophrenia. The two largest studies (the North American and multinational trials) included 841 patients (259 women, 582 men) with paired prolactin level data and 1,884 patients (554 women, 1,330 men) with data on six adverse events possibly associated with increased prolactin levels (amenorrhoea, galactorrhoea, and decreased libido in women; erectile dysfunction, ejaculatory dysfunction, gynaecomastia, and decreased libido in men). They concluded that among women, the risperidone dose was not correlated with adverse events, nor were the adverse events correlated with endpoint prolactin levels. Among men, the incidence of adverse events was positively correlated with risperidone dose; however, at risperidone doses of 4 to 10 mg/day the incidence of adverse events was not significantly higher than that observed in patients receiving placebo. Furthermore, adverse events in men were unrelated to plasma prolactin levels. Risperidone-associated increase in serum prolactin levels was not significantly correlated with the emergence of possible prolactin-related side effects. The study of Hummer et al. (1999) also suggests a more limited role for prolactin in inducing sexual dysfunctions.

However, both the Kleinberg and Hummer studies have severe limitations. The study of Kleinberg et al. is not based on structured interviews or questionnaire data. As mentioned earlier in this article spontaneous reporting of sexual dysfunctions is rare and therefore the frequency of sexual dysfunctions is probably heavily underreported. This makes it unlikely that correlations between prolactin and sexual dysfunctions could be detected. A limitation of the study of Hummer is the fact that any sexual dysfunction reported in any week during six observations in six subsequent weeks was taken into account. But in the first week, carryover effects of former antipsychotics, sedating, and \( \alpha \)-blocking effects of clozapine must have influenced the observations. So the final analysis should have been made in the last week. In that week, clozapine indeed induced less sexual dysfunctions than haloperidol.

The final conclusion from the majority of these studies seems to be that prolactin might play an important role in inducing sexual dysfunctions, amenorrhoea, and galactorrhoea.

By what mechanism prolactin elevation is correlated to sexual dysfunction is not known. A reduced capacity to create sexual fantasies might be a contributing factor (Carani et al. 1996). As mentioned earlier, reduction of testosterone levels secondary to elevated prolactin levels is also a factor suggested to play a role in Hyperprolactinemia-related sexual dysfunctions, but this effect might be occurring only in high dose ranges.

Correcting prolactin levels with the help of dopamine agonists like bromocriptine 10 mg/day or amantadine 100 mg/day improves many of the symptoms induced by antipsychotic-induced hyperprolactinaemia, like sexual dysfunctions, amenorrhoea, and galactorrhoea (Netto and Claro 1993; Valevski et al. 1998). This restoration of sexual dysfunctions seems to set off before correcting decreased plasma testosterone levels, suggesting that prolactin might have an immediate effect on sexual activity (Barnes and Harvey 1993) while the role of testosterone is not very convincing.

Prolactin elevation is also an indirect indicator of dopamine blockade (Kapur et al. 1998). Dopamine is an important neurotransmitter in experiencing motivation and
rewards, probably including sexual motivation (libido) and reward (orgasm) (Feldman et al. 1997). So it is likely that not only prolactin elevation but also the dopamine blockade itself might contribute to inducing sexual dysfunctions.

In fact there is no conclusive evidence from the available studies that antipsychotic-induced prolactin elevation is directly responsible for sexual dysfunctions (like in prolactinoma). Prolactin elevation may also (partly) be an epiphenomenon, a marker, of dopamine blockade.

Other factors may play a role too. For instance, antipsychotics like thioridazine or sertindole with \( \alpha \)-antagonistic properties are associated with priapism or ejaculation disturbance (diminished semen volume) (Patel et al. 1996). The serotonergic system is also involved in sexual behavior. However there is no indication that the serotonin-blocking properties of atypical antipsychotics contribute to sexual dysfunctions; it might even help to improve, for instance SSRI induced, sexual dysfunctions (Baldwin et al. 1997).

**Conclusions and clinical consequences**

Classical antipsychotics, risperidone, and amisulpride used in standard dosages elevate prolactin significantly; this even more so in women, compared with men. There are few studies of sexual dysfunctions related to treatment with antipsychotics. All known studies are open studies and one should be cautious in drawing firm conclusions.

Less than 10% of the patients mention sexual dysfunctions spontaneously, in response to structured questionnaires, 40-60% of the patients report experiencing sexual dysfunctions which they attribute to the use of classical antipsychotics or risperidone. Although not all studies agree, libido and orgasm disturbances are found in men and women in more or less the same frequencies.

Comparative studies are rare, still it seems likely that prolactin-sparing antipsychotics induce sexual dysfunctions only infrequently in comparison to prolactin elevating antipsychotics. In our randomized study of olanzapine versus risperidone we indeed found that the prolactin-sparing effects of olanzapine are associated with significantly less sexual dysfunctions.

Serum prolactin elevation and dopamine blockade are probably important factors, not only in inducing sexual dysfunctions but also in causing amenorrhoea and galactorrhoea.

Sedation, noradrenergic, serotonergic and cholinergic mechanisms might play an additional role in inducing some sexual side effects.

More studies are clearly needed comparing antipsychotics and their tendency to induce sexual side effects, but also amenorrhoea and galactorrhoea. Furthermore, studies on the pathogenetic mechanisms of sexual dysfunctions are lacking. Studies comparing classical antipsychotics, risperidone, quetiapine and clozapine, for short term and long term effects on sexual performance, amenorrhoea and galactorrhoea are underway in our center. Especially the effects of (long-term) prolactin elevation on sexual behavior, social behavior and health risks like bone demineralization are needed (Halbreich and Palter 1996; Halbreich et al., 1995).

Although sexual side effects are often very important to patients and might influence compliance, patients as well as clinicians are reluctant to discuss it
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(Finn et al. 1990; Strauss and Gross 1984). Clinicians should always actively query patients for side effects of antipsychotics, especially for sexual dysfunctions, amenorrhoea, or galactorrhoea. These side effects occur often, but seem to be difficult to talk about. It is our clinical experience that almost all patients appreciate when clinicians systematically ask for side effects, including sexual side effects. Dose reduction or switching to a prolactin-sparing antipsychotic is usually effective in reducing sexual side effects. In some cases, adding bromocriptine or amantadine to antipsychotic treatment might be an alternative.

In cases of prolonged amenorrhoea during treatment with antipsychotics, with or without Hyperprolactinemia, especially when continuing after switching to a prolactin-sparing antipsychotic, a closer analysis of alternative causes is necessary.


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