Serum Prolactin Levels and Sexual Dysfunctions in Antipsychotic Medication, such as Risperidone

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Summary

Classical antipsychotic drugs increase the level of serum prolactin. The atypical antipsychotic clozapine barely increases prolactin levels. An open naturalistic study at the University Hospital of Groningen suggests that treatment with risperidone in comparison to classical antipsychotics seems to increase the risk of erectile and ejaculatory disorders in male patients and to menstrual disturbances in female patients. In the literature reviewed, risperidone is associated with higher prolactin levels in comparison to classical antipsychotics. It is still unclear which mechanism is responsible for the increase of serum prolactin levels and sexual dysfunctions in patients using risperidone. Dopaminergic and serotonergic receptor blockade seems to play an important role. Other possible mechanisms are discussed.
Chapter 2

Introduction

On the basis of a recent study in the Groningen University Hospital involving 95 patients who use antipsychotic drugs, it was found that 10% of the patients report spontaneous sexual dysfunctions. However, 55% of the patients are found to experience sexual function disorders, which they relate to the use of antipsychotic drugs, for a specifically directed anamnesis by means of a semi-structured interview or questionnaire (Knegtering et al. 1998). In many patients, prolactin levels are found to increase strongly via antipsychotic drug usage, and this is correlated with sexual function disorders, such as loss of libido and erection disorders. In our study, the antipsychotic drug risperidone, which is frequently indicated as being atypical, is found to cause sexual function disorders significantly more frequently (67%) than classical antipsychotic drugs (50%), and is found to cause higher prolactin levels as well (Knegtering et al. 2000). This was an unexpected finding, especially since the atypical antipsychotic drug clozapine allegedly causes fewer sexual function disorders, and hardly increases the prolactin levels at all.

We decided to carry out a survey of the literature regarding what is known about sexual function disorders and prolactin elevation when using classical antipsychotic drugs and risperidone. In addition, a literature survey was carried out regarding possible mechanisms for prolactin elevation and its relationship to sexual function disorders.

Method

For this literature study, a literature search was done starting from 1980, with the help of Medline and Index Medicus. The keywords were risperidone, schizophrenia, neuroleptics, adverse effects, side effects, prolactin, Hyperprolactinemia, endocrinological effects, neuroendocrine, serotonin, 5-HT₂, dopamine D₂, galactorrhea, sexual dysfunction, gender differences.

Within the context of this article, we understand sexual dysfunctions to mean loss of libido, erection disorders, orgasm disorders, ejaculatory disorders, galactorrhea and menstrual disorders.

Results

Risperidone, Classical Antipsychotic Drugs, Prolactin level, and Sexual Functioning

Table 2.1 reports all the (uncontrolled) studies that were found in which the relationship between the use of risperidone and prolactin concentrations and/or sexual dysfunctions is examined. In the studies by Gelders, Van den Bussche, Mesotten and Bersani, a distinct and enduring increase in prolactin levels is found to occur during the use if risperidone (Bersani et al. 1990; Bussche van den et al. 1988; Mesotten et al. 1989). From the studies by Huang et al., the increase in prolactin in people who use risperidone is found to be almost two times higher than when using haloperidol (Huang et al. 1993). Sexual dysfunctions were reported in only one of these publications. In a group of five women, Dickson found amenorrhea in all of these persons and, in addition, galactorrhea in three of them, whereby this is related to the use of risperidone (Dickson et al. 1995). In addition, this study found that prolactin levels returned to their original level after stopping risperidone.
Table 2.1. Non-comparative studies on risperidone, prolactin concentrations, and sexual dysfunctions

<table>
<thead>
<tr>
<th>Publication</th>
<th>Short description</th>
<th>Prolactin level</th>
<th>Sexual dysfunctions, galactorrhea, menstrual disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelders et al 1987</td>
<td>6 healthy men: 0.5 and 1 mg risperidone on a single occasion</td>
<td>Increased with a peak after 1 hour. Mean: 0.5 mg: 49.1 (±13.6) µg/L; 1.0 mg: 77 (±26.5) µg/L; significant correlation with risperidone level</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bussche van den et al. 1988</td>
<td>15 schizophrenic patients: risperidone in increasing dose levels up to 25 mg/day. Duration: 4 weeks</td>
<td>Increasing 7x after 1st administration. Increase remained until the end of the experiment (no numbers reported)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mesotten et al. 1989</td>
<td>17 psychotic patients: risperidone dose levels up to 25 mg/day. Duration: 4 weeks</td>
<td>Increased 7x after administration. Increase remained until the end of the experiment. Men: from 4.5 to 36.7 µg/L (day 29). Women: from 11.6 to 97.0 µg/L (day 29)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bersani et al. 1990</td>
<td>31 schizophrenic patients: risperidone in increasing dose levels up to 6 mg/day. Durations: 4 weeks</td>
<td>Determined in 12 patients: mean increase from 15.6 (±7.5) µg/L to 83.3 (±64.5) µg/L</td>
<td>Not reported</td>
</tr>
<tr>
<td>Huang et al. 1993</td>
<td>12 healthy men: 1 mg risperidone intravenously, intramuscularly, or orally, on a single occasion</td>
<td>Increased</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dickson et al. 1995</td>
<td>5 premenopausal women with schizophrenia. Treated with risperidone: dose and duration not reported; 1 patient used danazal (sic; possibly danazol)</td>
<td>Increased to a mean value of 124 µg/L. Decrease to a mean value of 13.5 µg/L after stopping risperidone</td>
<td>3 women galactorrhea; 5 women amenorrhea, galactorrhea disappeared and menstruation returned in 3/5 women after stopping risperidone</td>
</tr>
</tbody>
</table>

Peuskens found more erection disorders and ejaculatory disorders during treatment with 12 mg risperidone in comparison to 10 mg haloperidol. Marder and Meibach reported a higher frequency of dysmenorrhea and vaginitis (10 and 16 mg risperidone per day compared to 20 mg haloperidol). In an open study involving people who were using risperidone (median dose 3.2 mg/day; n = 28), Knegtering et al. found 78% sexual function disorders versus 46% among patients who were using classical antipsychotic drugs (median dose: 6.0 mg haloperidol equivalents/day; n = 27) (Knegtering et al. 1998). Prolactin concentrations were significantly higher in people who were using risperidone (median: 1235 mU/L) compared to patients who were using classical antipsychotic drugs (median: 638 mU/L); the highest prolactin levels were found in women. In a regression analysis
Table 2.2. Comparative studies on risperidone versus classical antipsychotics in relation to prolactin concentrations and sexual dysfunctions

<table>
<thead>
<tr>
<th>Publication</th>
<th>Short description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claus et al. 1992</td>
<td>Double-blind study: 12mg/day risperidone (18 schizophrenic patients) versus 10 mg/day of haloperidol (16 schizophrenic patients). Duration: 12 weeks</td>
</tr>
<tr>
<td>Marder and Meibach 1994</td>
<td>Double-blind study, schizophrenic patients: placebo (66 patients) versus 20 mg/day of haloperidol (66 patients), versus 2,6,10 and 16 mg/day risperidone (63,64,65 and 64 patients respectively)</td>
</tr>
<tr>
<td>Peuskens 1995</td>
<td>Double-blind study, schizophrenic patients: 1 mg/day risperidone (229 patients) vs 4 mg/day risperidone (227 patients) vs 8 mg/day risperidone (230 patients) vs 12mg/day risperidone (226 patients) vs 16mg/day risperidone (224 patients) vs 10mg/day haloperidol (226 patients) Duration: 8 weeks</td>
</tr>
<tr>
<td>Knegtering et al. 1998</td>
<td>Open study, 55 patients with functional psychosis after 6 weeks of antipsychotic drug usage. 28 patients, median dose 3.2 mg risperidone versus 27 patients, median dose 6.0 haloperidol-equivalent classical antipsychotic drugs. Study with semistructured questionnaire</td>
</tr>
</tbody>
</table>

* Risp. = risperidone, Halo = haloperidol
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### Table 2.1: Prolactin levels in µg/L and Sexual dysfunctions, galactorrhea, menstrual disorders

<table>
<thead>
<tr>
<th>Days medication</th>
<th>Prolactin levels µg/L</th>
<th>Number of patients</th>
<th>Risp.</th>
<th>Halo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>12.9</td>
<td>2/8</td>
<td>2/8</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>19.4</td>
<td>2/10</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>16.9</td>
<td>3/10</td>
<td>0/10</td>
</tr>
<tr>
<td>risperidone, 10 patients, men</td>
<td>4.6</td>
<td>10.1</td>
<td>3/8</td>
<td>4/8</td>
</tr>
<tr>
<td>haloperidol, 8 patients, men</td>
<td>18.6</td>
<td>38.2</td>
<td>1/8</td>
<td>4/8</td>
</tr>
<tr>
<td>risperidone, 8 patients, women</td>
<td>7.8</td>
<td>14.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>haloperidol, 8 patients, women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"No abnormal laboratory results that are clinically significant" ¼ dysmenorrhea if using 10 mg/day risperidone. 1/11 vaginitis if using 16 mg/day risperidone.

### Table 2.2: % of patients with sexual dysfunctions

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Risp* (men and women)</th>
<th>Halo* (men and women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amenorrhea</td>
<td>8.1</td>
<td>8.4</td>
</tr>
<tr>
<td>increased libido</td>
<td>5.7</td>
<td>8.0</td>
</tr>
<tr>
<td>decreased libido</td>
<td>10.1</td>
<td>14.2</td>
</tr>
<tr>
<td>erection test</td>
<td>8.5</td>
<td>17.7</td>
</tr>
<tr>
<td>ejaculation disturbance</td>
<td>9.2</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Percentages relate to the increase in symptoms relative to the baseline.

Median prolactin level in the risperidone group: 40.7 µg/L; significantly higher than the group using classical antipsychotic drugs with a median level of 22.4 µg/L.

### Table 2.3: Concluding statements regarding effects on prolactin concentrations

Marder and Meibach do not make any numerically substantiated concluding statements regarding effects on prolactin concentrations (Marder and Meibach 1994). Peuskens found a dose-related increase in prolactin that was related to risperidone and haloperidol, but he makes no comparative statements (Peuksen et al. 1998). Claus et al. found a significantly larger increase in prolactin concentrations after six weeks in men who were treated with risperidone, compared to a group that was treated with haloperidol (Claus et al. 1992).

Table 2.2 contains all the controlled studies which deal with increased prolactin concentrations and/or the occurrence of sexual function disorders.
of the data for the men from this study (n=37), the prolactin level explained one third of the sexual function disorders ($R^2 = 0.30$, $p=0.001$), especially erection disorders ($R^2=0.15$, $p=0.02$) (Knegtering et al. 1998). Summarizing: little research has been carried out regarding the frequency of sexual function disorders when using risperidone in comparison to classical antipsychotic drugs. The studies reported here exhibit methodological shortcomings that prevent unambiguous concluding statements being made. In clinically used dosages, risperidone probably causes higher prolactin levels than is the case with haloperidol or other classical antipsychotic drugs. In comparison to classical antipsychotic drugs, moreover, risperidone appears to cause more sexual function disorders, such as loss of libido, orgasm disorders, erection disorders and, possibly, menstrual disorders as well. In light of the fact that this profile of side effects deviates from that for the prototype of an atypical antipsychotic drug, clozapine, a discussion follows below regarding possible mechanisms for prolactin increase when using antipsychotic drugs, and the relationship between increased prolactin and sexual function disorders.

**Possible effects of increased prolactin on sexual function disorders**

Prolactin elevation above physiological values leads to loss of libido and orgasm disorders, whereby this is more so in men than in women. Schwarz et al. refer to studies from which it is found that up to 90% of male patients with Hyperprolactinemia – mostly within the context of a hypophysis adenoma – complain to some extent of sexual dysfunction, and especially of erection disorders (Schwartz et al. 1982). Gynecomastia is seen incidentally in men. Amenorrhea and galactorrhea occur particularly in the case of women with Hyperprolactinemia (Pollack et al. 1992). Improvement occurred in all cases after treating the Hyperprolactinemia. It is unclear why an increase in prolactin leads to sexual function disorders. An explanation could be that Hyperprolactinemia leads to hypogonadotrophy and a reduction in the plasma concentrations of testosterone and estrogens. However, sexual function disorders remained for men in whom the reduced testosterone concentrations had been corrected. Moreover, it is found that nocturnal erections are not influenced by Hyperprolactinemia, but sexual cognitions, such as the capacity to have sexual fantasies, are affected in this way in particular (Carani et al. 1996). Other mechanisms that are suggested are a reduction of luteinizing (hormone)-releasing hormone (LH-RH) levels and a direct effect on the hypothalamus (Hermanns and Hafez 1981). However, none of these theories is well-substantiated.

**Mechanisms for the regulation of prolactin secretion**

*Role of the dopaminergic system on prolactin secretion*

Prolactin is a polypeptide hormone that derives from the adenohypophysis. Prolactin plays an important role in the induction of lactation, in reproduction and in osmoregulation. Dopamine, synthesized by tubero-infundibular neurons, is released to the portal hypophysal circulation. Upon arrival in the adenohypophysis, dopamine is designed “Prolactin Inhibiting Factor” (PIF) (Tuomisto et al. 1985). Blockade of $D_2$ receptors in the tubero-infundibular system by classical antipsychotic drugs causes
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the disappearance of the inhibiting action of dopamine on prolactin secretion, and this leads to Hyperprolactinemia as a consequence (Gitlin 1994; Green and Brown 1988). The influences of dopamine, serotonin and hormones are summarized in figure 2.1.

Role of the serotonergic system on prolactin secretion
The role of the serotonergic system on prolactin secretion is complex. Serotonin (5-hydroxytryptamine, 5-HT) has a stimulating action on prolactin secretion, probably via an inhibiting effect on the secretion of dopamine in the portal system (Sailer et al. 1990). Blockade of 5-HT receptors causes a decrease in prolactin secretion. Thus, for example, ketanserin (a 5-HT2a antagonist) blocks the pregnancy-induced increase in prolactin in rats. In humans, serum prolactin can be increased with D-fenfluramine; this substance increases the release of serotonin and blocks its re-uptake. A serum prolactin increase that is caused by D-fenfluramine can be blocked by 5-HT2a/2c receptor blockade, e.g. with ritanserin or amisegride (Coccaro et al. 1996).

Microinfusions of serotonin in the mediobasal hypothalamus of rats increase prolactin levels, whereby this is an effect that can be blocked by metergoline, a 5-HT1a antagonist (Mulroney et al. 1994). Manipulation of the nipple leads to an increase in prolactin secretion via the so-called nipple reflex, whereby this is a process that is partially mediated by serotonergic mechanisms, and it can be blocked by 5-HT1a and, inter alia, other serotonin antagonist (Kar van de et al. 1996). Prolactin is then released in a “pulsating” manner in accordance with a circadian rhythm, i.e. with higher levels in the afternoon and during sleep. This frequency is regulated in part by 5-HT3 en 5-HT1 receptor–mediated mechanisms (Thorner et al. 1998; Ulrich et al. 1994).

Other systems for regulating prolactin secretion
Three “releasing factors” promote prolactin secretion: thyroid releasing hormones (TRH), vaso-intestinal peptide (VIP), and PHM-27, a peptide that is structurally similar to VIP. It is not known which factor had the greatest physiological effect (Reichlin 1992). Estrogens increase the number of prolactin-secreting cells in the hypothalamus. In addition, estrogens increase sensitivity to TRH which promotes prolactin secretion. Estrogens also decrease the number of hypophysial dopamine receptors. These three mechanisms all lead to an increase in prolactin secretion. The physiologically higher level of prolactin in women, in comparison to men, are possibly ascribable, in part, to effect by estrogens.
Serum prolactin levels may change through many mechanisms. The main mechanisms are summarized. Dopamine has inhibiting effects on lactotroph cells of the anterior pituitary through the tubero-infundibular pathway. This dopaminergic inhibition of prolactin secretion can be modulated through several different serotonergic pathways leading to prolactin elevation during nipple manipulation, pregnancy and early in the morning. Vasoactive intestinal peptide (VIP), thyrotrophin releasing hormone (TRH) and estrogen also influence prolactin secretion. Higher physiological prolactin levels in women in comparison to men are thought to be the result of higher estrogen levels in women. Diminished dopaminergic input may have direct effects impairing sexual performance and also through prolactin elevation. It is unclear if other hormones play an additional role in diminishing sexual performance.
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Figure 2.2. The influence of classical antipsychotics on serum prolactin levels and possible secondary effects of serum prolactin elevation.

All classical antipsychotics block, at least to some extend, post synaptic dopamine 2 receptors (big arrows). Disruption of the dopamine tuberoinfundibular neuronal pathway des-inhibits the dopamine mediated prolactin release in the anterior pituitary. This leads to prolactin elevation with possible effects on other hormones, sexual functioning, amenorrhea and galactorrhea.
Figure 2.3. The influence of new antipsychotics on dopaminergic and serotonergic pathways, the possible consequences for serum prolactin levels and other effects

The new antipsychotics like clozapine, olanzapine, quetiapine and risperidone block, at least to some extend, post synaptic dopamine 2 receptors like classical antipsychotics. Disruption of the dopamine tubero-infundibular neuronal pathway des-inhibits the dopamine mediated prolactin release in the anterior pituitary. This leads to prolactin elevation with possible effects on other hormones, sexual functioning, amenorrhea and galactorrhea. Serotonin inhibits through dopaminergic pathways the physiological inhibition of prolactin in the tubero-infundibular pathways. In theory 5HT2a blockade of new antipsychotics could result in modulation of prolactin elevation induced by the dopamine-blockade. This could in theory correct prolactin elevation, especially in cases when dopamine blockade is not to strong. This theory would predict that the final effect of an antipsychotic on serum prolactin levels and sexual functioning would depend on the balance between dopamine and serotonine blockade.
Other non-prolactin related mechanisms of sexual function disorders

In addition to prolactin-related sexual function disorders, antipsychotic drugs can also cause sexual function disorders via other mechanisms. Without going into all these mechanisms in detail, mention is made here of the most important ones to the extent that they are of importance in this article. Dopaminergic systems are involved in experiencing pleasure and sexuality. Blockade of dopamine causes the libido to decrease, while over-stimulation leads to increased libido and sexual activity in some cases (Gitlin 1994). An erection is produced via the interaction of the parasympathetic and sympathetic systems. Stimulation of the sacral parasympathetic nerves, or blockade of peripheral sympathetic innervation of the penis, leads to an erection via reduced venous drainage. The erection is terminated by peripheral sympathetic domination over the parasympathetic influence. Sympathetic influence takes place, inter-alia, via the α-adrenergic receptors of the cavernosa. Stimulation of the α(2)-receptors can cause impotence, and blockade can lead to priapism (Patel et al. 1996) (See also chapter 1).

Treatment with selective serotonin re-uptake inhibitors (Selective Serotonin Re-uptake Inhibitors: SSRI’s) is frequently associated with sexual dysfunctions, such as ejaculatory disorders and anorgasm (Lane 1997). Activation of 5-HT2 receptors should 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-HT2 receptor antagonist, is capable of eliminating SSRI-induced sexual dysfunction in men (Baldwin et al. 1997).

The receptor-binding profile of risperidone

In vitro, risperidone is found to be primarily an antagonist of the serotonergic 5-HT2a receptors, dopaminergic D2 receptors, adrenergic α1 and α2 receptors, and histaminergic H1 receptors. The binding affinity for these receptors is as follows: 5-HT2a > α1 > H1 > D2 (Grant and Fitton 1994; Leysen et al. 1992). The affinity for D2 receptors is 20x lower than for 5-HT2a receptors (Kar van de et al. 1996). Risperidone binds to serotonergic receptors, particularly to 5-HT2a receptors. The affinity for this subtype is 100x higher than for the other 5-HT receptors. Compared to haloperidol, in vitro binding of risperidone is 170x stronger to 5-HT2a receptors, and 2-3x weaker to D2 receptors. Compared to clozapine, risperidone in vitro binds 20x more strongly to 5-HT2a receptors and 50x more strongly to D2 receptors (Tuomisto et al. 1985). In vivo, risperidone occupies the 5-HT2, D2 and α1 receptors in particular (Bussche van den et al. 1988) 9-hydroxyrisperidone, the active metabolite that is formed by risperidone, has a pharmacological profile that corresponds, in an overall way, to that of risperidone, but it is 4-6x weaker (Leysen et al. 1994). In a positron emission tomography study (PET) involving three healthy male test persons, it was found that 60% of the 5-HT2 receptors in the frontal cortex are occupied, and that 50% of the D2 receptors in the striatum are occupied after four hours and also seven hours following the oral administration of 1 mg risperidone (Nyberg et al. 1993). It can be surmised in this connection that the degree of occupancy will be greater at therapeutic dosages (usually 4-6 mg/day). A high degree of D2 receptors occupancy was indeed found in a 123I-IBZM single photon emission computerized tomography study (SPECT) for one patient who was diagnosed as being schizophrenic and who was being treated with 12 mg per day
risperidone, and (the same result was also found) in $^{123}$I-IBZM single photon emission (computerized) tomography studies (SPECT) involving six patients who were diagnosed as being schizophrenic or schizo-affective and who were being treated with 4-12 mg per day risperidone (Bursatto et al. 1995; Bursatto and Pilowsky 1993). $D_2$ blockade of between 75 and 80% was found in a PET study involving patients who had been using approximately 6 mg risperidone per day for some time (Farde et al. 1995). The binding of risperidone to $D_2$ receptors in SPECT and PET studies can be compared to the binding which takes place in patients who are being treated with classical antipsychotic drugs (70-89%), and is higher than for treatment with clozapine (38-63%) (Boerden et al. 1996; Farde et al. 1992).

**Discussion**

Research into the occurrence of sexual function disorders is complicated by the fact that little is reported spontaneously in this regard. Direct questions by means of questionnaires show much higher frequencies of sexual function disorders than is the case with spontaneous reporting (Riley and Riley 1993). Women are found to be still less inclined to speak about sexual problems than men (Shen and Sata 1990). This explains why sexual function disorders are reported only to a small extent in standard (pre)clinical research, while it is found that sexual function disorders occur very frequently on the basis of research with (semi)structured interviews or questionnaires, both for classical antipsychotic drugs and still more with risperidone. It is found from our own research that, in comparison to the classical antipsychotic drugs, risperidone causes a more intense increase in prolactin, whereby this is associated with a significantly more frequent occurrence of erection disorders (50%) and orgasm disorders (56%) for men ($p < 0.05$).

Interpretation of the data needs to be considered within the perspective of the fact that, even without medication, people with schizophrenia possibly have reduced sexual desire, though without erection disorders and orgasm disorders (Aizenberg et al. 1995). An interaction between the effect of medication and the symptoms of schizophrenia possibly plays a role in loss of libido, in particular. It is likely from the literature, which is designated above, that risperidone causes higher prolactin levels than classical antipsychotic drugs and clozapine. It is in risperidone probably not a transient increase in prolactin at the beginning of the treatment, as is the case with clozapine. From our own observations it is suggestive that prolactin elevation is still present after many years of treatment. The reason why this is so remains unclear. In light of the 5-HT$_2$ blocking properties of risperidone, rather, a reduction in prolactin levels would be expected when using risperidone. PET and SPECT studies show high striatal $D_2$ receptor blockade for clinically effective dosages of 6 mg risperidone per day, though this is not higher than with classical antipsychotic drugs in clinically effective dosages. However, striatal $D_2$ receptor occupancy by both classical antipsychotic drugs and by risperidone in clinically effective dosages is significantly higher than with clozapine. Nevertheless, risperidone – in relatively low dosages (3.2 mg/day) – causes significantly higher prolactin levels in comparison to classical antipsychotic drugs. An explanation could be that risperidone exhibits a higher affinity for $D_2$ receptors in the tubero-infundibular system. However, no references to this are found in the literature. In our own PET-
study, this area was found to be inadequately imaged in standard recordings (Boerden et al. 1996).

The fact that prolactin levels are more elevated in women than in men, if using classical antipsychotic drugs and risperidone, can be explained by an interaction with estrogens. The disorders in sexual function that are found in men who use risperidone (erection disorders and orgasm disorders) may be linked, in part, to an increase in prolactin; however, a direct effect via D₂ blockade, can contribute to these effects. As was to be expected, risperidone causes menstrual disorders and galactorrhea in women, it has not been demonstrated that this occurs more frequently than with classical antipsychotic drugs. Evaluation of menstrual disorders is impeded by the fact that many women use oral contraceptives, which possibly can mask menstrual disorders.

More research is necessary attempting to find better explanations for the findings designated here. Thus it is important to have more information regarding the nature and frequency of sexual function disorders and prolactin elevations for other new antipsychotic drugs, such as olanzapine or quetiapine. It is important in this regard that the same method always be used with the help of standardized questionnaires and/or semi-structured interviews. Comparative studies are being conducted at the moment at the University Hospital of Groningen. Regarding clinical practice, it is important to know that sexual function disorders occur very frequently, that they are rarely reported spontaneously. Sexual dysfunctions can be a reason for the patient to stop taking his/her medication. Medication-induced sexual function disorders are almost always reversible, so that dose reduction, or possibly stopping the medication for several days, or changing over to another antipsychotic drug, can solve many problems.
Farde, L., Nyberg, S., Oxenstierna, G. et al. 1995. Positron emission tomography studies on D2 and 5HT-2 receptor binding in risperidone-treated schizophrenic patients. J Clin Psychopharmacol. 15 suppl1, 19S-23S.
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