Chapter 4

A Randomized Open-Label Comparison of the Impact of Olanzapine versus Risperidone on Sexual Functioning

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Summary

Objective:
To compare sexual functioning in patients treated with olanzapine or risperidone.

Method:
This open-label trial included 46 patients randomized to olanzapine (5-15 mg/day) or risperidone (1-6 mg/day) for 6 weeks. Sexual dysfunction was assessed by a semi-structured interview based upon the items of the UKU.

Results:
Three olanzapine-treated patients (12.0%) compared to 11 risperidone-treated patients (52.4%) reported sexual dysfunctions (p=.008) in the semi-structured interview. Only 4 patients (8.7%) spontaneously reported sexual dysfunction. The mean dose was 9.4 mg/day for olanzapine and 3.4 mg/day for risperidone. The mean (± SD) prolactin levels (ng/mL) in olanzapine- and risperidone-treated patients were 25.1 (± 23.5) and 43.5 (± 26.1), respectively.

Conclusion:
Less sexual dysfunction occurred in the group treated with olanzapine compared to risperidone. Direct questioning about sexual functioning is necessary to avoid underestimating the frequency of sexual side effects in patients with schizophrenia and related psychotic disorders.
Introduction

Sexual dysfunction in patients with schizophrenia seems to be related to the disease itself, psychosocial factors, medical health, as well as to the use of psychotropic medications (Aizenberg et al. 1995; Dickson and Glazer 1999). Many of the conventional or typical antipsychotics have been associated with sexual dysfunction, such as decreased libido, erectile dysfunction, anorgasmia, delayed or retrograde ejaculation, oligomenorrhea, and amenorrhea (Dickson et al. 2000; Ghadirian et al. 1982; Segraves 1988; Sullivan and Lukoff 1990).

The prevalence rate of sexual dysfunction in persons with schizophrenia is thought to be high. However, sexual dysfunction is rarely reported spontaneously by patients (Rubin 1987); therefore, clinical trials of antipsychotic medications that rely on spontaneous reporting by patients to assess side effects report low incidences of sexual dysfunction. In contrast, those studies using structured interviews or questionnaires result in 30 - 60% of the patients with schizophrenia reporting sexual dysfunctions (Sullivan and Lukoff 1990).

Although comparative studies are rare, the literature does suggest that antipsychotic medications differ in both the type and frequency of associated sexual dysfunction. For instance, a significantly greater percentage of patients on thioridazine report sexual dysfunctions versus patients treated with other typical antipsychotics (Kotin et al. 1976). The atypical antipsychotics (clozapine, olanzapine, quetiapine) are reported to cause less sexual dysfunction than the typical antipsychotics and risperidone (Aizenberg; et al. 1995; Aizenberg et al. 2001; Arvanitis and Miller 1997; Canuso et al. 1998; Currier and Simpson 1998; Dickson and Glazer 1999; Gazzola and Opler 1998; Madhusoodanan and Brenner 1996; Shiwach and Carmody 1998; Tran et al. 1997).

The pathomechanisms of antipsychotic-associated sexual dysfunction in patients with schizophrenia remain poorly understood (Tran et al. 1997). Most of the typical antipsychotics, as well as risperidone, can cause sustained elevation of the anterior pituitary hormone, prolactin (Ghadirian et al. 1982; Rubin 1987). Neuroleptic-induced hyperprolactinemia (NIHP) has been associated with a number of side effects including galactorrhea, menstrual disturbances, amenorrhea, and sexual dysfunction (Ghadirian et al. 1982; Dickson and Glazer 1999). Interestingly, antipsychotic medications have also been reported to cause priapism and ejaculation disturbances (Kuperman et al. 2001; Meston and Frohlich 2000; Nicolson and McCurley 1997; Patel et al. 1996; Sirota and Bogdanov 2000). However, the mechanism is probably associated with α-adrenergic blockade rather than increased levels of prolactin (Hansen et al. 1997; Patel et al. 1996).

The atypical antipsychotics, other than risperidone, do not appear to cause sustained elevated levels of prolactin, and the limited reports available, suggest that patients prescribed these antipsychotics have lower rates of sexual dysfunction. Clozapine, which does not induce significant prolactin elevation (Meltzer et al. 1979), in a recent study was reported to cause fewer sexual side effects than classical antipsychotics (Aizenberg et al. 1995), although Hummer and colleagues reported comparable frequencies of sexual dysfunctions in patients treated with clozapine or haloperidol (Hummer et al. 1999). Quetiapine-treated patients have been shown to experience prolactin levels similar to placebo and a
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low incidence of sexual dysfunctions (Borison et al. 1996; Dev and Raniwalla 2000; Small et al. 1997). Olanzapine has been shown to cause significantly less prolactin elevation than both haloperidol (Beasley et al. 1996; Crawford et al. 1997) and risperidone (Tran et al. 1997); the mild elevations of prolactin that may occur are usually transient (Crawford et al. 1997). At risperidone’s recommended dose range of 3-6 mg/day, significant and sustained prolactin elevation has been reported (Claus et al. 1992).

In a previous open-label naturalistic study, we found a higher incidence of sexual dysfunctions and significantly higher prolactin levels in patients treated with risperidone compared to patients treated with typical antipsychotics or olanzapine (Knegtering et al. 1998). However, in this study, selection-bias could have influenced the results, thus the need for the blinded randomized assignment to medication in the present study.

Material and methods

Study participants included inpatients and outpatients with schizophrenia who were to be switched to a new antipsychotic for clinical reasons as determined by the attending psychiatrists. Written and oral consent were then given by patients in accordance with the local ethical committee for research. Patients could be taking any antipsychotic before entering the study except depot neuroleptics, olanzapine or risperidone. Patients were randomized to either open-label olanzapine (starting dose 10 mg) or risperidone (starting dose 1 mg). For both groups, the dosage could be adjusted as deemed necessary on a weekly basis by the clinician (olanzapine, 5-15 mg/day; risperidone, 1-6 mg/day). The patients were informed that effects of the switch would be assessed but they were blinded in regard to the hypothesis to be tested.

Sexual dysfunction was assessed at 6 weeks post-randomization by a semi-structured interview based upon the items of the UKU (34) administered by 6 trained physicians. This interview was used in our previous studies and includes items assessing sexual side effects (libido, erection, ejaculation, orgasm), and galactorrhoea. Baseline sexual functioning was not recorded because most of the patients were psychotic and considered too ill at study entry to participate in assessment of sexual functioning. Prolactin levels were measured 6 weeks but not at baseline. The clinicians were also asked to assess efficacy of the treatment for psychotic symptoms using the Clinical Global Impressions- Global Improvement (CGI-I) scale.

The chi-square test was applied to categorical outcomes. The chi-square value was corrected for continuity because the sizes of the tables were all two by two. The Students t-test was used to analyze continuous outcomes including age and prolactin levels. Prolactin levels were normalized by converting to their natural logarithm. For all analyses, the effects were tested at the 2-sided $\alpha$ level of 0.05.
Results

Forty-six patients (olanzapine, N=25; risperidone, N=21), including 7 women and 39 men, agreed to participate in this trial (Table 1). The mean age (mean ± SD) of the olanzapine group (27.2 ± 7.2) was comparable to the risperidone group (26.0 ± 6.3). The patients’ age ranged from 19 to 40 years. Clinical diagnoses, according to DSM-IV were brief psychotic disorder (N=2), schizophreniform disorder (N=4), schizophrenia (N=31), schizoaffective disorder (N=1), delusional disorder (N=3), and psychosis NOS (N=5).

Prolactin levels could not be obtained in 13 patients because they refused blood sampling. At 6 weeks, the mean dosage of olanzapine and risperidone was 9.4 mg/day (range, 5-15 mg/day) and 3.4 mg/day (range, 2-6 mg/day), respectively.

Table 1. Demographic and illness characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine (N=25)</th>
<th>Risperidone (N=21)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>27.2 ± 7.2</td>
<td>26.0 ± 6.3</td>
<td>.52</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80.0</td>
<td>90.5</td>
<td>.43</td>
</tr>
<tr>
<td>Female</td>
<td>20.0</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief Psychotic Disorder</td>
<td>4.0</td>
<td>4.8</td>
<td>ns</td>
</tr>
<tr>
<td>Delusional Disorder</td>
<td>8.0</td>
<td>4.8</td>
<td>ns</td>
</tr>
<tr>
<td>Psychotic Disorder NOS</td>
<td>12.0</td>
<td>9.5</td>
<td>ns</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>4.0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>64.0</td>
<td>71.4</td>
<td>ns</td>
</tr>
<tr>
<td>Schizophreniform Disorder</td>
<td>8.0</td>
<td>9.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

*There were no statistically significant differences (ns) for any specific disorder between the treatment groups.

The CGI-I (rated as much worse, worse, unchanged, improved, or much improved) was used to assess treatment results by the attending physician. Both antipsychotics were considered effective: 75% of the patients were rated by their physician as being clinically significantly improved (improved and much improved) after 6 weeks. Although numerically more patients on risperidone were rated as improved in comparison to the olanzapine group, this difference was not significant (Mann-Whitney U 118.0; z=-645; p=.52).

Some patients could not reliably answer certain questions because they felt embarrassed or because it was difficult to be sure of the correct interpretation of the answer. Therefore, we report the number of patients with clearly specified sexual dysfunctions, which they attributed to the use of the antipsychotic medication. Unless indicated, the reported sexual dysfunctions exclude amenorrhoea.

A severity score was created for sexual dysfunctions. Each dysfunction could be rated as absent, giving some problems or giving many problems, and scored as 0, 1 or 2 points, respectively. Using this global rating, patients using risperidone experienced more serious problems in comparison to patients using olanzapine (Mann-Whitney U 121.0; z=-3.072; p=0.002). Of the 46 patients who completed the trial, only 4 (8.7%) reported sexual dysfunction spontaneously. In response to
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the semi-structured interview, 14/46 (30.4%) reported sexual dysfunctions (mild or severe). Only 3 of 25 olanzapine patients (12.0%) reported sexual dysfunction compared to 11 of 21 patients (52.4%) treated with risperidone (chi-square=7.13; df=1; p=0.008). The nature and frequency of the sexual dysfunctions are summarized in Table 2.

The mean (±SD) prolactin concentration was 25.1 ng/mL (± 23.5) in the olanzapine group and 43.5 ng/mL (± 26.1) in the risperidone group (t-test (natural log), t=2.49; df=26; p=.052).

Table 2. Prolactin levels and sexual dysfunction in patients taking olanzapine or risperidone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine (N=25)</th>
<th>Risperidone (N=21)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin (ng/mL, mean ± SD)</td>
<td>25.1 ± 23.5</td>
<td>43.5 ± 26.1</td>
<td>.02</td>
</tr>
<tr>
<td>Type of sexual dysfunction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased libido</td>
<td>12.0</td>
<td>33.3</td>
<td>.13</td>
</tr>
<tr>
<td>Decreased orgasm</td>
<td>0</td>
<td>19.0</td>
<td>.09</td>
</tr>
<tr>
<td>Any sexual dysfunction</td>
<td>12.0</td>
<td>52.4</td>
<td>.008</td>
</tr>
</tbody>
</table>

Sexual dysfunction and prolactin levels in men

As the majority of patients were men, their data were analyzed separately.

Ten male patients (25.6%) reported sexual dysfunction attributable to their antipsychotic medication (Table 3). Sexual dysfunction was more commonly reported in men treated with risperidone (9/19; 47.4%) compared to men treated with olanzapine (1/20; 5%) (Chi-square=6.65; df=1; p=0.01). Using the severity score described above, risperidone-treated patients experienced more serious problems in comparison to olanzapine-treated patients (Mann-Whitney U 79.0; z=-2.947; p=.003).

The mean (±SD) prolactin levels were significantly higher in male patients treated with risperidone (41.5 ± 19.5 ng/mL) compared to olanzapine-treated patients (15.9 ± 5.3 ng/mL) (t-test (natural log)=3.90; df=19; p=0.001).

Table 3. Prolactin levels and sexual dysfunction in male patients taking olanzapine or risperidone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine (N=20)</th>
<th>Risperidone (N=19)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin (ng/mL, mean ± SD)</td>
<td>15.9 ± 5.3</td>
<td>41.5 ± 19.5</td>
<td>.001</td>
</tr>
<tr>
<td>Type of sexual dysfunction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased erection</td>
<td>0</td>
<td>31.6</td>
<td>.04</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>5.0</td>
<td>31.6</td>
<td>.15</td>
</tr>
<tr>
<td>Decreased orgasm</td>
<td>0</td>
<td>21.1</td>
<td>.14</td>
</tr>
<tr>
<td>Ejaculation dysfunction</td>
<td>0</td>
<td>16.7</td>
<td>.27</td>
</tr>
<tr>
<td>Any sexual dysfunction</td>
<td>6.3</td>
<td>47.4</td>
<td>.01</td>
</tr>
</tbody>
</table>
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Sexual dysfunction and serum prolactin levels in women

Two of 7 women reported having a missed period and both had high prolactin levels (> 48.6 ng/mL). One patient was taking olanzapine (10 mg/day) and the other receiving risperidone (6 mg/day). However, there were not enough female patients to perform a separate analysis.

Discussion

As has been found in previous studies, (Lingjaerde et al. 1987) reliance on spontaneous reports underestimates the prevalence of sexual dysfunction in patients treated with psychotropic medications. The male risperidone-treated group reported significantly more sexual side effects compared to the olanzapine group. Prolactin levels were higher in patients using risperidone compared to patients using olanzapine. The findings of this prospective open-label randomized study of olanzapine and risperidone are consistent with prior studies and case reports of Hyperprolactinemia occurring in risperidone-treated patients (Chung and Eun 1998; Claus et al. 1992; Dickson et al. 1995; Tran et al. 1997) and associating risperidone treatment with sexual dysfunction (Gupta et al. 2001; Hardan et al. 1996; Kim et al. 1999; Madhusoodanan and Brenner 1996; Shiloh et al. 2001). These findings of increased risk and greater severity of sexual dysfunction in risperidone-treated patients are also consistent with those of our naturalistic study on typical antipsychotics, olanzapine and risperidone (Knegtering et al. 1999). Unfortunately, given the low number of female patients in each group, a separate analysis was not possible.

The few reports of sexual side effects in olanzapine treated patients include only cases of priapism, which is not etiologically attributable to Hyperprolactinemia (Gordon and de Groot 1999; Kuperman et al. 2001). Olanzapine generally reverses the effects of risperidone, and other antipsychotics, on prolactin levels and may in some case reverse sexual dysfunction (Canuso et al. 1998; Gazzola and Opler 1998).

Clearly, medication is not the only reason for patients to experience sexual dysfunction. Patients suffering from schizophrenia experience more sexual dysfunction, with or without medication (Aizenberg et al. 1995; Teusch; et al. 1995). The difference in the incidence of sexual side effects between patients treated with olanzapine and risperidone is likely related to the pharmacological properties of these drugs. However, given the lack of baseline ratings and the relatively small numbers, we cannot exclude differences in function that predate randomization. Nevertheless, significant differences in such a small sample size are considered important by many clinicians. Future studies should be randomized and double-blind.

Olanzapine doses used in this trial are probably associated with a relatively low $D_2$ occupancy of about 60% (Kapur et al. 1998; Nyberg et al. 1997), while risperidone, in doses of 2-6 mg/day, is associated with a higher $D_2$ occupancy (Busatto and Pilowsky 1993; Busatto et al. 1995). Since the dopamine system is involved in sexual arousal and the ability to experience pleasure, the blockade of this system might be one of the reasons for decreased libido (Segraves 1989).
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Prolactin elevation in patients with a prolactinoma is associated with amenorrhea, galactorrhea, erectile dysfunction, and possibly decreased libido (Pollack et al. 1992; Schwartz et al. 1982). However, the mechanism of sexual dysfunctions caused by prolactin elevation is not known. There is some evidence that prolactin elevation is related to a reduced capacity to create sexual fantasies, while nocturnal penile erections are not influenced (Carani et al. 1996). Another mechanism known to influence sexual dysfunction is α-adrenergic blockade (ejaculation disturbance), probably in balance with cholinergic functioning (Segraves 1989). Risperidone has α-adrenergic blocking properties that might contribute to sexual side effects. Olanzapine has a lower affinity for the α-adrenergic system compared to risperidone. Indeed, olanzapine appeared to have no effect on ejaculation or other sexual dysfunctions in this study.

A limitation of this study was that we could not show a relationship between prolactin levels and sexual side effects because of the small sample size and missing prolactin data (N=13). However, in a pooled analysis of several small studies, Knegtering and colleagues found a clear correlation between elevated prolactin levels and an increased incidence of sexual dysfunctions (Knegtering, Moolen, et al. 2003).

During this brief study, all patients initially randomized to receive either risperidone or olanzapine continued on their assigned medications for the 6 week study period, but medication compliance was not formally assessed. In our clinical experience, drug-induced sexual dysfunction is often cited by patients as the reason for medication discontinuation or request for treatment alternatives. We are not aware of any studies on the correlation between compliance and sexual side effects due to antipsychotic drugs, but studies suggest that clinicians do underestimate the frequency and importance of sexual side effects in patients with schizophrenia (Finn et al. 1990) and other psychiatric disorders (Singh and Beck 1997). Although further research is required on the relationship of specific side effects on compliance with prescribed psychotropic medications, physicians should be aware that sexual dysfunctions occur commonly in patients with psychotic disorders and that active questioning is required to elicit this sensitive information.
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