

# A 6-Month Prospective Observational Study on the Effects of Quetiapine on Sexual Functioning

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**Objective:** The aim of this study was to assess the long-term impact of quetiapine on sexual functioning of patients with schizophrenia treated in a real practice setting.

**Methods:** This was a multicenter, noncomparative, open-label, and naturalistic study conducted in outpatients with a diagnosis of schizophrenia or schizophreniform disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients were evaluated at baseline, day 15, and at the end of months 1, 3, and 6 using the Brief Psychiatry Rating Scale, the Clinical Global Impression Severity and Improvement Scales, and the Psychotropic-Related Sexual Dysfunction Questionnaire. All primary effectiveness analyses were based on the intent-to-treat sample and consisted primarily of last-observation-carried-forward analysis of Psychotropic-Related Sexual Dysfunction Questionnaire, Brief Psychiatry Rating Scale, and Clinical Global Impression Improvement of Illness Scale.

**Results:** Eighty-six patients were recruited by 19 investigators, and 82 patients were included in the intent-to-treat sample. Psychotropic-Related Sexual Dysfunction Questionnaire total scores for the patients decreased progressively and significantly from baseline to the study end point. When only patients who initiated quetiapine treatment without being switched from another antipsychotic ( $n = 28$ ) were included in the intent-to-treat analysis, Psychotropic-Related Sexual Dysfunction Questionnaire scores remained almost unchanged throughout the study. Sexual dysfunction rates, defined as a change in the score of any item greater than 0, were 3.7%, 2.4%, 2.4%, and 4.9% for decreased libido, delayed ejaculation/

orgasm, lack of ejaculation/orgasm, and difficulties with erection/lubrication, respectively. Overall, quetiapine was efficacious and well tolerated.

**Conclusion:** Despite the limitations of the design, our results suggest that quetiapine shows a low frequency of sexual dysfunction during long-term treatment of patients with schizophrenia or schizophreniform disorder in the clinical practice setting.

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**S**exual dysfunction (SD) is a common side effect of psychotropics including antipsychotics.<sup>1</sup> Moreover, it seems that, in addition to anticholinergics and diuretics, men treated with antipsychotics are at a greater risk of a certain types of SD, namely, erectile dysfunction.<sup>2</sup> SD adversely affects patients' satisfaction with their medication,<sup>3</sup> and it is associated with reduced adherence to antipsychotic therapy.<sup>4</sup>

Although new atypical antipsychotics were expected to be associated with a lower incidence of sexual adverse events as compared with conventionals,<sup>5</sup> high rates of SD have been consistently reported with risperidone, ranging from 43% to 67%.<sup>6–8</sup> Olanzapine exhibits a significantly lower incidence of SD as compared with risperidone,<sup>6,7,9</sup> but it does not seem to be negligible with rates varying from 19%<sup>9</sup> to 35%.<sup>8</sup> Moreover, olanzapine-induced SD has been reported to be dose-related.<sup>7,8</sup> Despite that, it has been found that clozapine produced little or no change on serum prolactin concentrations,<sup>10</sup> comparable and relatively high rates of sexual side effects were found for clozapine and haloperidol in a prospective drug monitoring program.<sup>11</sup> This finding also supports that, in addition to hyperprolactinemia, there are several possible mechanisms of antipsychotic-induced SD including sedation due to histaminic blockade, cholinergic blockade, and adrenergic blockade.<sup>12,13</sup>

Quetiapine is a novel dibenzothiazepine atypical antipsychotic which shows affinity for various neurotransmitter receptors including serotonin, dopamine, histamine, and adrenergic receptors and has binding characteristics at the dopamine 2 receptors similar to those of clozapine.<sup>14</sup> It is at least as effective as standard antipsychotics and appears to have similar efficacy to risperidone and olanzapine; its tolerability profile distinguishes it from other commonly used atypical agents.<sup>15</sup> An analysis of plasma prolactin concentrations performed on data obtained during 3 clinical trials showed that, across the dose range studied, quetiapine did not differ from placebo in its effect on plasma prolactin levels after up to 6 weeks of treatment.<sup>16</sup> Moreover, an analysis of a pool of 2387 patients treated with quetiapine showed a very low

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incidence of reproductive and hormonal side effects.<sup>17</sup> In a cross-sectional naturalistic study, quetiapine, but not olanzapine or risperidone, showed a significant lower risk of SD than haloperidol during short-term treatment.<sup>8</sup> In an interim analysis of a large prospective and naturalistic trial,<sup>9</sup> the frequency of adverse events related to sexual functioning was found to be similar in olanzapine-treated and quetiapine-treated patients and significantly less prominent in these treatment groups than in the haloperidol and risperidone treatment groups. SD was also significantly less common in patients treated with quetiapine (16%) than with risperidone (50%) in a recently reported 6-week, randomized, open-label study.<sup>18</sup>

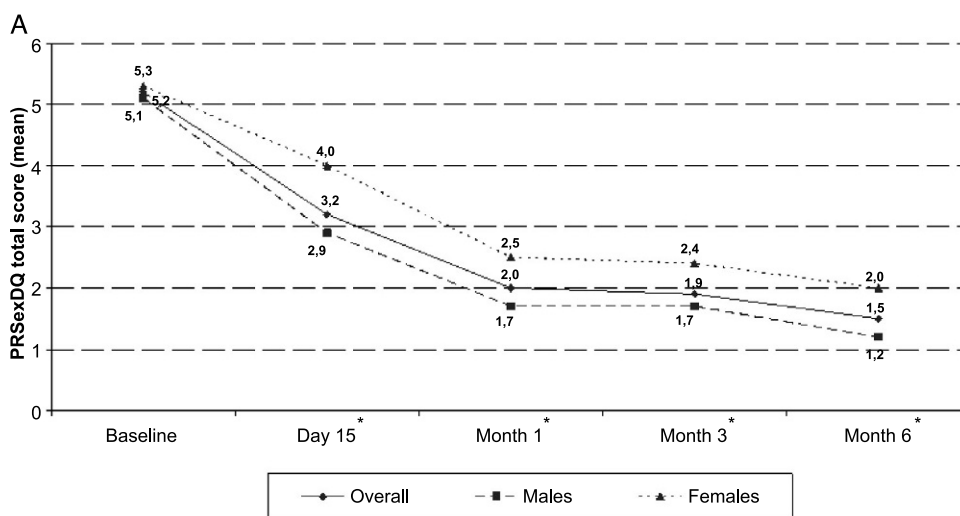
The objective of this study was to assess the long-term impact of quetiapine on sexual functioning of patients with schizophrenia treated in a real-practice setting.

## METHODS

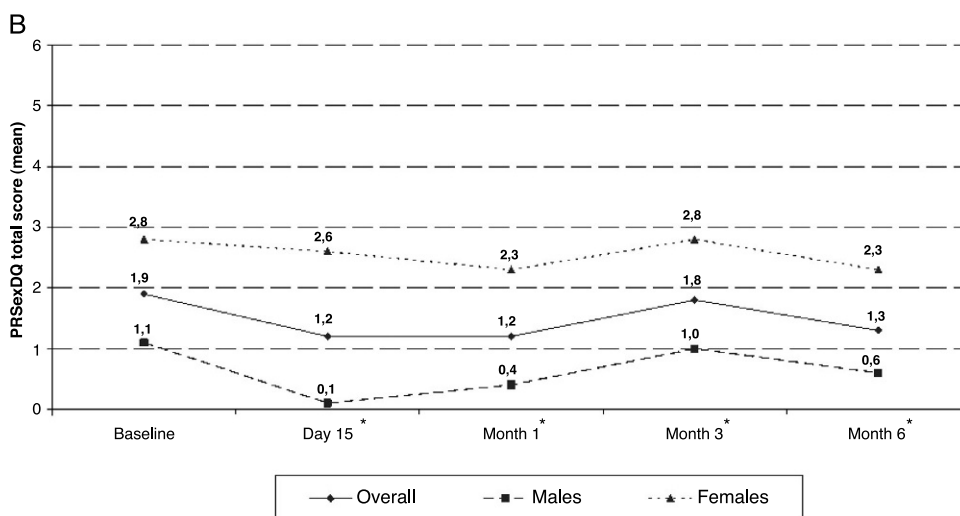
### Subjects

Male or female patients, aged 18 years or older, with a diagnosis of schizophrenia or schizophreniform disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, for whom the investigators have decided to prescribe quetiapine as part of their normal clinical practice and who gave their written consent were included in the study.

Patients were excluded if they had any contraindication listed in the quetiapine package insert (ie, known hypersensitivity to this medication or any of its ingredients), were receiving or requiring concomitant treatment with another antipsychotic, and were treated with other medications



\* $P < 0.001$  vs baseline score for all visits and samples except for females on Day 15 ( $P < 0.05$ ) and Month 3 ( $P < 0.01$ )



\* $P = NS$  vs baseline for all follow-up visits and samples.

**FIGURE 1.** (A) Sexual functioning throughout the study for the whole sample (ITT-LOCF analysis,  $n = 82$ ). (B) Sexual functioning throughout the study for subset of patients who initiate quetiapine treatment (ITT-LOCF analysis,  $n = 28$ ).

with well-recognized effects on sexual functioning, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, venlafaxine, a mood stabilizer, antihypertensives or H2 blockers. Patients were also excluded if they were current users of recreational drugs or have medical illnesses which could affect sexual functioning including diabetes, hypertension, primary hyperprolactinemia, prostatic cancer, asthma, chronic obstructive pulmonary disease, and myocardial infarction.

### Study Design and Evaluations

This was a multicenter, noncomparative, open-label, and naturalistic study conducted in 19 centers in Spain. After fulfillment of eligibility criteria was ensured, patients received open treatment with quetiapine and were followed up for 6 months. Dose requirements and titration, treatment withdrawal criteria, and use of concomitant medications after study entry were established by the investigators in an individual basis according to their clinical judgement.

The study was reviewed and approved by the ethics committee of the Hospital Universitario de Salamanca (Spain) and was carried out in accordance with the Declaration of Helsinki. Following the Spanish regulations on postmarketing studies, the study was reported to the Ministry of Health.

**TABLE 1.** Demographics, Clinical Characteristics, and Sexual Activity

Item	n	%	Mean	SD
Sex				
Male	56	66.7		
Female	28	33.3		
Age (y)			36.5	12.4
Age at onset (y)			24.6	6.7
Length of illness (y)			10.8	8.9
DSM-IV diagnosis				
Schizophrenia	78	92.9		
Schizophreniform disorder	6	7.1		
Sexual activity				
Currently not in a sexual relationship	44	52.4		
Importance of sex — none or little importance	8	9.5		
Not having any intercourse*	36	42.9		
Not having any sexual activity with a partner*	33	39.3		
Not having masturbatory activity*	18	21.7		
Sexual activity satisfaction				
Very satisfied	8	9.5		
Somewhat satisfied	20	23.8		
Nor satisfied, neither dissatisfied	24	28.6		
Somewhat dissatisfied	21	25.0		
Very dissatisfied	11	13.1		

DSM-IV indicates *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition*.

\*In the past six months.

**TABLE 2.** Sexual Dysfunction Rates at Month 6 (PRSexDQ)

Sexual Dysfunction	Male (n = 55)		Female (n = 27)		All (n = 82)	
	n	%	n	%	n	%
Decreased libido	2	3.6	1	3.7	3	3.7
Delayed ejaculation/orgasm	0	0	2	7.4	2	2.4
Lack of ejaculation/orgasm	2	3.6	0	0	2	2.4
Difficulties with erection/lubrication	2	3.6	2	7.4	4	4.9
Any sexual dysfunction	4	7.3	4	14.8	8	9.8

Baseline efficacy evaluations included the Brief Psychiatry Rating Scale (BPRS),<sup>19</sup> the Clinical Global Impression (CGI) Severity of Illness Scale,<sup>20</sup> and a set of questions on sexual activity. Medical evaluations included an assessment of medical and psychiatric history, physical examination, and recording of vital signs (heart rate and blood pressure) and weight. Due to the naturalistic design, no routine laboratory tests were scheduled.

Patient visits were scheduled at day 15 and the end of months 1, 3, and 6. Antipsychotic effectiveness was assessed by completion of BPRS and CGI Improvement Scale at each visit. Sexual functioning was evaluated at baseline and at each study follow-up visit using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ), which has been validated in a Spanish psychiatric population showing to have adequate feasibility and psychometric properties.<sup>21</sup> The PRSexDQ consists of 7 items pertaining to SD. The first item is a screening item to assess whether the patient has any sort of SD. The second item assesses whether the patient has reported spontaneously any SD to his or her physician. The next items (items 3–7) assess 5 dimensions of SD according to severity or frequency: loss of libido (0 = nil, 1 = mild, 2 = moderate, and 3 = severe), delayed orgasm or ejaculation (0 = nil, 1 = mild, 2 = moderate, and 3 = severe), lack of orgasm or ejaculation (0 = never, 1 = occasionally, 2 = often, and 3 = always), erectile dysfunction in men/vaginal lubrication dysfunction in women (0 = never, 1 = occasionally, 2 = often, and 3 = always), and patient's tolerance of the SD (1 = good, 2 = fair, and 3 = poor). A full description of the PRSexDQ can be found elsewhere.<sup>22</sup> In addition, a CGI of severity and improvement of sexual functioning was used.

Vital signs and weight were measured at baseline and at each follow-up visit. Treatment emergent adverse reactions were elicited by an open question and a modified version of the Udvalg for Kliniske Undersogelser [UKU] Side Effect Rating Scale<sup>23</sup> thereafter. The modified UKU included only those items corresponding to the most commonly ( $\geq 3\%$ ) observed adverse events associated with the use of quetiapine in clinical trials (ie, asthenia/lassitude, sleepiness/sedation, reduced salivation, constipation, dyspepsia, abdominal pain, orthostatic dizziness, and palpitations/tachycardia) and these 4 side effects: amenorrhea, menorrhagia, galactorrhea, and gynecomastia. The modified UKU was applied at baseline and at every follow-up visit.

**TABLE 3.** Course of Sexual Dysfunction by SD Dimension of the PRSexDQ

Item/Dimension	Baseline Mean (SD)	Month 6 Mean (SD)	P
Decreased libido	1.0 (1.0)	0.3 (0.6)	<0.001
Delayed orgasm/ejaculation	1.1 (1.2)	0.3 (0.7)	<0.001
Anorgasmia/no ejaculation	0.9 (1.0)	0.3 (0.6)	<0.001
Erectile dysfunction/decreased vaginal lubrication	0.9 (1.0)	0.2 (0.5)	<0.001
Tolerance of the SD	1.3 (1.2)	0.4 (0.8)	<0.001

### Statistical Analysis

Demographic and baseline clinical characteristics were described using the mean, standard deviation, and range for continuous measures (eg, age and BPRS score), and the frequency and percentage for categorical variables (eg, sex and comorbidity).

The intention-to-treat (ITT) sample included those patients who were prescribed quetiapine and had at least one postbaseline sexual functioning evaluation. Analysis of the ITT sample was performed with the last-observation-carried-forward approach (LOCF). All primary effectiveness analyses were based on the ITT sample. The analysis consists primarily of LOCF analysis of PRSexDQ, BPRS, and CGI improvement of illness.

The occurrence of SD according to the PRSexDQ was defined as a change in the score of any item greater than 0 (ie, score at the corresponding visit minus the score at baseline >0). The efficacy variables were BPRS total score and response rate, with response defined as a reduction of at least 30% from baseline in BPRS score at any time during the study. A CGI global improvement rating of at least "much improvement" also constituted therapeutic response. The significance of within-group changes from baseline to end point in the PRSexDQ and BPRS total scores was calculated with the Student *t* test or a nonparametric test. Formal statistical analyses were performed for each study visit and were 2-tailed; they were considered significant if the *P* value was less than or equal to 0.05.

All patients who entered in the study and had at least one follow-up visit or had a reported adverse reaction were included in the analysis of tolerability. Descriptive statistics were used to summarize treatment-emergent adverse reactions communicated by the patient or elicited through the modified UKU. An increase from baseline severity score in the items of the UKU which was rated possibly or probably related with quetiapine administration was considered an adverse reaction; missing evaluations of causal relationship were also considered possibly related with quetiapine.

## RESULTS

### Subjects

In total, 86 patients were recruited by 19 investigators. Tolerability sample comprised 84 patients (2 patients lacked

of any postbaseline data) and was used for baseline descriptions. Eighty-two patients were included in the ITT sample (3 patients lacked PRSexDQ postbaseline data, and 1 patient lacked PRSexDQ baseline data) and were used for sexual functioning and antipsychotic effectiveness analyses.

Overall, 26 (30.2%) patients of the 86 recruited withdrew from the study. Twelve (13.9%) were lost to follow-up; 8 (9.3%) did so because of lack of efficacy; 2 (2.3%) withdrew consent, 1 (1.2%) because of adverse reactions, and 3 (3.5%) for other reasons.

Demographic and clinical characteristics are presented in Table 1. Most patients (*n* = 56, 66.7%) were under antipsychotic treatment and were switched to quetiapine because of inadequate response to previous treatment (*n* = 16, 19.1%), intolerable adverse reactions to previous treatment (*n* = 26, 30.9%), or both (*n* = 14, 16.7%). A summary of sexual activity data is also presented in Table 1.

### Quetiapine Dosage

The mean daily dose of quetiapine at the study end point was 525.4 mg (standard deviation, ±158.6). At month 6, 11.1% of the patients were receiving a dose less than 400 mg/d ("low dose"); 34.9% were receiving a dose greater than 400 mg/d but less than 600 mg/d ("intermediate dose"), and 54% received a dose more than 600 mg/d ("high dose").

### Sexual Functioning

SD rates as defined above for the ITT sample are presented in Table 2. PRSexDQ total scores for the patients decreased progressively and significantly from baseline to the study end point (Fig. 1A). An analysis item by item showed the same pattern regardless of the dimension studied (Table 3). When only patients who initiated quetiapine treatment without being switched from another antipsychotic (*n* = 28) were included in the ITT analysis, PRSexDQ scores remained almost unchanged throughout the study (Fig. 1B). This latter group also showed a slightly higher rate of SD: 5 (17.8%) of the 28 patients exhibited some type of SD.

### Antipsychotic Effectiveness

BPRS scores for the patients decreased progressively and significantly from a baseline score of 45.7 to 34.2 at the study end point (*P* < 0.001, LOCF analysis). The number of patients responding to quetiapine according to the BPRS was 47 (57.3%) of 82 at month 6.

### Tolerability

The most frequent adverse reactions as elicited by the modified UKU (ie, those reported by at least 5% of the patients) were somnolence/sedation (*n* = 37, 44%), asthenia/lassitude (*n* = 22, 26.2%), concentration difficulties (*n* = 16, 19%), constipation (*n* = 10, 11.9%), palpitations/tachycardia (*n* = 9, 10.7%), orthostatic dizziness (*n* = 8, 9.5%), reduced salivation (*n* = 7, 8.3%), and failing memory (*n* = 7, 8.3%). There were no cases of menorrhagia, amenorrhea, galactorrhea, or gynecomastia according to the analysis of the modified UKU.

Weight analysis was performed using a conservative approach of observed cases within the specified time intervals. Overall, the mean weight (in kilograms) significantly increased from  $75.7 \pm 12.9$  at baseline to  $78.2 \pm 13.2$  at month 6. Ten patients (11.9%) were found to have a clinically relevant weight increase (ie,  $>7\%$ ) during the study. Using the same approach, a slight decrease was observed in systolic blood pressure (from  $126 \pm 11.7$  mm Hg at baseline to  $122.6 \pm 10.6$  mm Hg at the study end point,  $P = 0.03$  by Wilcoxon test) and diastolic blood pressure (from  $75.7 \pm 9.5$  to  $73.6 \pm 8.8$  mm Hg, not significant by Wilcoxon test). A slight but not statistically significant increase in heart rate at month 6 was also observed.

## DISCUSSION

Overall, our results suggest that quetiapine shows a low frequency of SD during long-term treatment of patients with schizophrenia or schizophreniform disorder in the clinical practice setting. This study has several limitations, with the major limitation being the lack of a control group. However, our results are consistent with those of a similar naturalistic study with the same study duration. In a 6-month naturalistic study of quetiapine in 421 men and 265 women in Spain, Bobes et al<sup>24</sup> reported similar figures using the UKU: decreased libido, 4.6% and 3.7% for men and women, respectively; erectile dysfunction, 3.3%; ejaculatory dysfunction, 3.3%; dry vagina, 1.7%; and female orgasmic dysfunction, 1.1%. Slightly higher figures of 18% and 16% of patients exhibiting some kind of SD have been reported in a 6-month interim analysis of a large multinational naturalistic study using an unspecified adverse reaction questionnaire<sup>9</sup> and in an open-label, 6-week, randomized trial using a semistructured interview based on the UKU,<sup>18</sup> respectively.

Another important limitation of this study is that most patients included were switched from another antipsychotic which, in one third ( $n = 29$ , 34.5%) of the cases, was risperidone. This could bias the results in favor of quetiapine because risperidone accounts with the higher reported rates of SD.<sup>6–8,18</sup> This also probably explains why, in fact, we observed an overall improvement of the sexual functioning. However, when only patients who initiated quetiapine treatment without being switched from another antipsychotic ( $n = 28$ ) were included in the analysis, thus limiting this bias, the rate of SD increased up to 17.8%, a rate similar to that of previous prospective studies (16%–18%).<sup>9,18</sup> In addition, and although it is beyond the scope of this study, the improvement of sexual functioning observed in our study also suggests that switching to quetiapine could be a suitable alternative for treating antipsychotic-induced SD. Very preliminary data support this hypothesis. Switching to quetiapine in 8 patients with antipsychotic-induced SD resulted in consistent and marked improvements in the sexual functioning as evaluated with the Arizona Sexual Experience Scale.<sup>25</sup>

The use of quetiapine or other antipsychotics with low rates of SD could improve the quality of life of patients with schizophrenia and other psychotic disorders and may in-

crease the likelihood of being compliant with the antipsychotic treatment, thus leading to a better treatment outcome. This should be further investigated in controlled studies.

## ACKNOWLEDGMENTS

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## Erratum

This erratum is in regard to the article "Rapid antidepressant response after nocturnal TRH administration in patients with bipolar type I and bipolar type II major depression" by Martin P. Szuba, MD, and Jay D. Amsterdam, MD, which was published in the August 2005 issue of the *Journal of Clinical Psychopharmacology* (2005;25:325-330).

The editors were informed on August 9, 2005 by Dr Jay Amsterdam, coauthor of this article, that the names of 4 additional coauthors were inadvertently omitted from this paper. Dr Amsterdam was unaware that other investigators were involved in the research effort and were revising a draft of the manuscript until he was contacted by Dr Andrew Winokur.

The first author of this article, Dr Martin Szuba, died in September 2002 and, before his untimely death, had not communicated to Dr Amsterdam the research contributions of the other 4 investigators.

Dr Amsterdam expresses his sincere apologies for the oversight, and he would like to acknowledge and recognize all the authors who made a substantive contribution to this work.

It should also have been noted that the work was presented in part at the 1996 American College of Neuropsychopharmacology Annual Meeting and at the 1997 Society of Biological Psychiatry Annual Meeting.

Dr Winokur and his colleagues appreciate Dr Amsterdam's swift action to rectify this situation once he became aware of this unintended oversight.

The order of the authors on this paper should be updated as follows:

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The Editors-in-Chief