A Pilot Study to Determine a Prolactin Threshold that Identifies Improved Sexual Functioning when Switching from a Prolactin-Elevating to a Prolactin-Neutral Antipsychotic

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Abstract

This pilot study, among men with schizophrenia or schizoaffective disorder who had antipsychotic-associated sexual dysfunction (while taking an antipsychotic with prolactin-elevating effects), examined if there is an antipsychotic-associated prolactin threshold that identified patients who experienced improvement in sexual functioning when switched to an antipsychotic with neutral effects on prolactin levels (quetiapine). Twenty male patients, who were experiencing risperidone-associated sexual dysfunction, were switched to six weeks of either double-blind (n=10) or open-label (n=10) quetiapine (mean dose=295.0 mg/day) treatment. Baseline prolactin levels were obtained. The Arizona Sexual Experience Scale (ASEX) was used to assess sexual functioning. The optimal antipsychotic-associated prolactin threshold that best identified improvement in sexual functioning (defined as ≥20% reduction in ASEX total scores) was determined with a Receiver Operating Characteristic (ROC) analysis and Odds Ratios. A prolactin threshold of ≥17 ng/mL, with 75% sensitivity and 75% specificity, best identified male patients who experienced improvement in sexual functioning when switched to an antipsychotic with neutral prolactin effects (quetiapine). The odds of responding to quetiapine switch were nine times higher in patients with a prolactin level of ≥17 ng/mL versus <17 ng/mL (p<.03). Among male outpatients with schizophrenia or schizoaffective disorder, who experience antipsychotic-associated sexual dysfunction (while taking an antipsychotic with prolactin-elevating effects), this pilot study suggests that prolactin levels of ≥17 ng/mL may identify male patients likely to experience improved sexual functioning when switched to an antipsychotic with neutral prolactin effects.

Key Words: Antipsychotic, Endocrine, Neuroendocrine, Side Effect

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Introduction

Sexual dysfunction is common among antipsychotic-treated patients with schizophrenia (1, 2). Prior research suggests that the prolactin-elevating effect of many antipsychotics is an important mechanism of antipsychotic-associated sexual dysfunction among men with schizophrenia. In fact, previous clinical studies, which involved males with schizophrenia, have found a relationship between higher prolactin levels and greater impairment in sexual functioning (3-7).

Theoretically, switching from antipsychotics with marked prolactin-elevating effects (e.g., risperidone, tradi-

Clinical Implications

This pilot study, among male outpatients with schizophrenia or schizoaffective disorder who had sexual dysfunction while taking a prolactin-elevating antipsychotic, examined if there is a prolactin threshold that identifies male patients who experience improvement in sexual functioning when switched to an antipsychotic with neutral effects on prolactin. Findings suggest (among the range of prolactin levels) that the cutpoint or "threshold" of ≥17 ng/mL is a sensitive and specific threshold, with good negative predictive value and moderate positive predictive value, for identifying male outpatients who experience improvement in sexual functioning (≥20% reduction in ASEX total scores from baseline to exit for individual participants) when switched from an antipsychotic with prolactin-elevating effects to prolactin-neutral effects. Future research that employs larger sample sizes, both genders, lengthier study periods, and complete blinding to treatment assignment is needed, however, to more fully evaluate the switch combination used in the current study and to investigate whether prolactin thresholds exist for other switch combinations of antipsychotic medications. Future research is also needed to clarify the clinical value of prolactin thresholds for sexual functioning and antipsychotic switch treatment in schizophrenia. But the current pilot study is a first step at empirically evaluating this potential value and if a signal for such a threshold could be identified.

tional antipsychotics) (1-8) to antipsychotics with prolactin-neutral effects (e.g., quetiapine) (9) or prolactin-lowering effects (e.g., aripiprazole) (10) could lead to improved sexual functioning among men with antipsychotic-associated sexual dysfunction. There are, however, no existing studies to suggest if there is a particular prolactin level or prolactin "threshold" that identifies male patients who will experience improvement in sexual functioning when switched from antipsychotics with prolactin-elevating effects to antipsychotics with prolactin-sparing effects. If identified, such a prolactin "threshold" could guide clinicians in targeting male patients who are likely to benefit from switching antipsychotic medication. The purpose of the current pilot study was to examine if a signal for such a threshold could be identified.

Method

Participants

Twenty male outpatients with antipsychotic-associated sexual dysfunction (while taking an antipsychotic with prolactin-elevating effects) were recruited from five Dallas County public mental health outpatient clinics. Eligibility criteria for inclusion into the study included: 1) *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder as determined by the study physician and confirmed by the study coordinator using a symptom checklist; 2) minimum age requirement of 18 years; and, 3) sexual dysfunction (Arizona Sexual Experience Scale [ASEX]) (11) total score of ≥15 while taking risperidone as the only antipsychotic medication. The choice to operationally define sexual dysfunction as an ASEX total score of ≥15 is supported by two empirical sources of evidence. First, two previous studies which used the ASEX found that the optimal cutoff for discriminating patients' sexual dysfunction was an ASEX total score of ≥11 in the one study (12) and ≥19 in the other study (11). Thus, the ASEX total score of ≥15 that was used in the current pilot study represents the midpoint between these two established ASEX cutoffs. Second, we have been consistent in our use of the ASEX total score of ≥15 as an inclusion criterion in our prior treatment trials of sexual dysfunction, including a recent trial in which we found a significant difference in sexual functioning among patients switched from risperidone or haloperidol to quetiapine (i.e., demonstrating sensitivity to antipsychotic treatment effects) (13).

To prevent the entry of participants taking unnecessarily high doses of risperidone, only patients taking a risperidone dose of ≤4 mg/day were enrolled (unless they had a treatment history that clearly justified the need for higher dosing). Participants diagnosed with schizoaffective disorder must have received a stable dose of antimanic and/or antidepressant medication for ≥30 days prior to study entry and have experienced stability of mood symptoms for >2 weeks prior to baseline assessments. Participants were excluded if they: 1) received a long-acting injectable antipsychotic within one dosing interval of intended study entry; 2) had a medical cause for hyperprolactinemia (e.g., pregnancy/breast feeding, pituitary prolactinoma); or, 3) were taking medications known to raise prolactin (other than risperidone).

Data were collected over a three-year period from May, 2002 to October, 2005. The study protocol was approved by the Institutional Review Board of The University of Texas Southwestern Medical Center at Dallas, and written informed consent was obtained from all participants.

Procedures and Measures

The subjects of the current pilot study were the male participants of a larger six-week, randomized, double-blind trial that evaluated the effect of quetiapine switch versus risperidone continuation on sexual functioning (14). During the first six weeks of the larger parent study, patients were randomized to double-blind quetiapine switch versus

risperidone continuation. To provide a trial of quetiapine treatment for all patients, those randomized to double-blind risperidone continuation during weeks 1–6 of the larger parent study were switched to open-label quetiapine treatment during study weeks 7–12. Thus, all patients received six weeks of quetiapine switch treatment in the larger parent trial either as an initial double-blind assignment or, if initially randomized to double-blind risperidone continuation, as an open-label crossover treatment. We note here that in the larger parent trial we found no significant difference in sexual functioning between the quetiapine switch and risperidone continuation treatment groups (14).

The current pilot study examined, among the male participants of the parent study, whether there was an antipsychotic-associated prolactin threshold (while taking an antipsychotic with prolactin-elevating effects) that identified patients who experienced improvement in sexual functioning when switched to six weeks of treatment with a prolactin-neutral antipsychotic (quetiapine).

Antipsychotic Medication and Randomization

As indicated above, participants were randomized to six weeks of either double-blind quetiapine switch treatment (n=10) or double-blind risperidone continuation treatment, and then switched to six weeks of open-label quetiapine treatment (n=10). The current study, however, focused on risperidone-associated prolactin levels and sexual functioning when patients were switched to six weeks of quetiapine treatment (double-blind or open-label). Randomization was further stratified by antidepressant medications known to cause sexual dysfunction (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, and venlafaxine). During the first week of double-blind treatment, the cross-taper period, pre-study risperidone was gradually discontinued in patients who were randomized to double-blind quetiapine switch (with quetiapine titrated to a dose of 300 mg/day as tolerated during week 1 and maintained at this dose until the end of week 2). Dosing of double-blind quetiapine during the final four weeks of treatment was flexible, however, with maximum allowable doses of 800 mg/day. Participants who were randomized to six weeks of double-blind risperidone continuation treatment, and then switched to six weeks of open-label quetiapine, received risperidone in doses identical to their pre-study regimen and then received open-label quetiapine in doses similar to those in the double-blind quetiapine group. Blinding of treatment groups in the double-blind phase was maintained through the use of identically appearing capsules.

Sexual Functioning and ASEX Response

Participants' sexual functioning was evaluated using the five-item Arizona Sexual Experience Scale (ASEX) (11). ASEX ratings used in the current study were obtained at baseline and at exit (the final visit). To mitigate the discomfort of discussing the sensitive topic of sexual functioning, the study utilized self-administered questionnaire cards that participants read silently to themselves. The participants then reported only the scale number that corresponded to their experience for each ASEX item. The five items included: strength of sex drive (Item 1), ease of sexual arousal (Item 2), penile erection (Item 3), ability to reach orgasm (Item 4), and satisfaction with orgasm (Item 5). The ASEX measured each item using a six-point Likert-type scale that ranged from 1 (*little to no impairment*) to 6 (*complete dysfunction*). ASEX total scores (which equaled the sum of all five items) ranged from 5 to 30. Higher ASEX scores reflect greater impairment of sexual functioning. The ASEX has established psychometric properties (internal reliability and construct and convergent validity) in outpatients with schizophrenia and schizoaffective disorder (15). The ASEX ratings were conducted by raters who were blinded to patients' prolactin level results.

ASEX response was a binomial variable operationally defined as ≥20% reduction (improvement) in ASEX total score from baseline to exit for individual participants—these participants were, thus, considered responders to quetiapine switch treatment—and <20% reduction in ASEX total score (these participants were, thus, considered nonresponders to quetiapine switch treatment). We chose *a priori* to employ a response definition of ≥20% improvement (reduction) in ASEX total score because: 1) a similar degree of scale score improvement (≥20% reduction) in the Positive and Negative Syndrome Scale (PANSS) total score is commonly used to define psychotic disorder symptom response in medication trials of patients with schizophrenia or schizoaffective disorder; and, 2) previous clinical research (13, 14) suggests that only a modest change (improvement) in sexual functioning can be expected when switching from antipsychotics with a greater degree of sexual side effects to antipsychotics with a lesser degree of sexual side effects. To clarify the clinical meaning of the ASEX response definition, a 20% improvement in ASEX total scores translated, on average, into an approximately 4-point improvement from baseline, since the mean baseline ASEX total score was around 20. Examples of ASEX response would, thus, include a 1-point improvement/change in 4 of 5 ASEX subscales/items (e.g., change from somewhat weak/difficult/unsatisfying to somewhat strong/easily/satisfying on 4 of 5 scales) or a 4-point improvement/change in a single ASEX subscale/item (e.g., change from very weak/difficult/unsatisfying to extremely strong/easily/satisfying).

Psychotic Disorder Symptoms

The severity of psychotic disorder symptoms was

assessed with the Positive and Negative Syndrome Scale (PANSS) (16). PANSS ratings used in the current study were obtained at baseline and at exit (the final visit). The PANSS ratings were conducted by raters who were blinded to patients' prolactin level results.

Prolactin Levels and Prolactin Cutpoints

Blood serum samples were collected at baseline and subsequently at exit (the final visit). Blood serum samples were collected between 9:30 a.m. and 4:00 p.m. to mitigate the potential confound effect of circadian rhythm on prolactin secretion. Blood serum samples at baseline were measured for risperidone-associated prolactin levels and blood serum samples at exit (the final visit) were measured for quetiapine-associated prolactin levels. Blood serum samples were measured for prolactin levels (ng/mL) at a local clinical laboratory, with a normal prolactin reference range of 2.1 to 17.7ng/mL for males.

Each prolactin cutpoint was a binomial variable operationally defined as the proportion of patients who were ≥ the risperidone-associated baseline prolactin level (cutpoint) and the proportion of patients who were < the risperidone-associated baseline prolactin level (cutpoint). All observed prolactin levels were used as cutpoints (≥5, 8, 11, 14, 17, 22, 24, 25, 34, 48, 52, 61 ng/mL).

Participant Characteristics

Various participant characteristics were collected to describe the sample and test for group differences (double-blind quetiapine versus open-label quetiapine and responders versus nonresponders): age, diagnosis (schizophrenia or schizoaffective disorder), drug dose, presence/absence of concurrently prescribed antidepressant known to cause sexual dysfunction (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, and venlafaxine), baseline and exit prolactin levels, baseline and exit ASEX scores, and baseline and exit PANSS total scores. Participant characteristics ratings, as well as ASEX and PANSS clinical ratings, were conducted by raters who were blinded to patients' prolactin level results.

Data Analysis

Receiver Operating Characteristic (ROC) analysis was carried out (for the range of observed prolactin cutpoints mentioned above) to determine the optimal antipsychotic-associated prolactin threshold (while taking an antipsychotic with prolactin-elevating effects) that best identified male outpatients who experienced improvement in sexual functioning when switched to an antipsychotic with neutral prolactin effects. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC) were assessed between each risperidone-associated prolactin cutpoint and ASEX response to quetiapine switch treatment. The AUC was tested against a nominal area of 0.50 using the Z statistic. The area under the ROC curve is a parameter used to quantify the ability or accuracy of the test (which, in our case, was the antipsychotic-associated prolactin threshold) to correctly classify or discriminate ASEX responders versus nonresponders to quetiapine switch treatment. Mathematically, an AUC can range from 0.50 to 1. Thus, an AUC of 1 represents a perfect test (cutpoint)—perfect discrimination of ASEX responders versus nonresponders. An AUC of 0.50, however, represents a useless test (cutpoint)—the inability to discriminate between ASEX responders versus nonresponders. In practice, an AUC generally falls somewhere between 0.50 and 1. Odds Ratios were estimated (using Logistic Regression) from the corresponding two independent proportions (prolactin cutpoint versus ASEX response). A Wald Chi-Square was used to test for a significant association between each risperidone-associated prolactin cutpoint and ASEX response to quetiapine switch treatment. The level of significance for all tests was set at α=.05 and, because of the pilot nature of the current study, p values were left unadjusted for multiple testing.

Results

Participant Characteristics

The sample in this pilot study consisted of twenty male participants. The age range was 24 to 57 years (with an average age of 40.7 years, standard deviation [SD]=9.3). The diagnosis included 14 (70.0%) participants with schizophrenia and 6 (30.0%) with schizoaffective disorder. Seven of the twenty (35.0%) participants were concurrently taking an antidepressant known to cause sexual dysfunction (3 participants in the quetiapine double-blind group and 4 in the quetiapine open-label group). However, the point-biserial correlations, r_{pb} revealed no significant relationship between the presence (coded as 1) or absence (coded as 0) of concurrently prescribed antidepressant and the total continuous ASEX score at baseline (r_{pb}=0.35, p=.12) and the total continuous ASEX score at exit (r_{pb}=0.40, p=.08). The average baseline ASEX total score was 20.5 (SD=6.0) and the average exit ASEX total score was 18.3 (SD=5.5). The average baseline and exit PANSS total scores were 77.6 (SD=12.4) and 73.9 (SD=14.0), respectively. The average risperidone-associated prolactin level (ng/mL) at baseline was 21.5 (SD=18.5, range=6.8 to 61) and the average quetiapine-associated prolactin level (ng/mL) at exit was 8.0 (SD=4.8, range=5.6 to 18). The average risperidone dose (mg/day) at baseline was 4.3 (SD=1.0) and the average quetiapine dose (mg/day) at exit was 295.0 (SD=51.0).

Responders (those experiencing ≥20% reduction in ASEX total scores from baseline to exit, which comprised 8 out of the 20 participants) and nonresponders (those experiencing <20% reduction in ASEX total scores from baseline to exit, which comprised 12 out of the 20 participants), did not differ statistically on any of the participant characteristics (p's>0.23), including the proportion of responders and nonresponders switched to double-blind quetiapine treatment versus open-label quetiapine treatment, p=0.65. Further, the double-blind quetiapine and open-label quetiapine treatment groups did not differ statistically on any of the participant characteristics (p's>0.24). Participant characteristics are reported in Table 1.

With respect to dosing, additional analyses revealed no significant relationship between risperidone dose at baseline and ASEX total scores at baseline (p=.75). Further, there was no significant omnibus quetiapine group (double-blind versus open-label) × dose interaction on ASEX total scores at exit (p=.91) and no significant relationship between quetiapine dose at exit and ASEX total scores at exit within each respective quetiapine group (p's>.73).

Table 1 Participant Characteristics of the Male Schizophrenia Outpatients

Participant Characteristic	Patient Sample (n=20)
Age in years, M (SD)	40.7 (9.3)
Diagnosis, n (%)	
Schizophrenia	14 (70.0)
Schizoaffective	6 (30.0)
Antidepressant, n (%)*	
No	13 (65.0)
Yes	7 (35.0)
ASEX total at baseline, M (SD)†	20.5 (6.0)
ASEX total at exit, M (SD)‡	18.3 (5.5)
PANSS total at baseline, M (SD)†	77.6 (12.4)
PANSS total at exit, M (SD)‡	73.9 (14.0)
Prolactin at baseline, ng/mL, M (SD)†	21.5 (18.5)
Prolactin at exit, ng/mL, M (SD)‡	8.0 (4.8)
Risperidone dose at baseline, mg/day, M (SD)	4.3 (1.0)
Quetiapine dose at exit, mg/day, M (SD)	295.0 (51.0)

M=sample mean; SD=standard deviation; n=sample size
*Antidepressant known to cause sexual dysfunction
†Risperidone-associated
‡Quetiapine-associated

Prolactin Level and ASEX Response

The ROC analysis determined that the antipsychotic-associated prolactin cutpoint of ≥17 ng/mL (while taking an antipsychotic with prolactin-elevating effects) best identified male outpatients who experienced improvement in sexual functioning (≥20% reduction in ASEX total scores from baseline to exit) when switched to treatment with a neutral effect on prolactin (quetiapine). As shown in Table 2, the antipsychotic-associated prolactin cutpoint of ≥17 ng/mL vis-à-vis ASEX response represented the best combination of sensitivity (75.0%) and specificity (75.0%), with good negative predictive value (81.8%) and moderate positive predictive value (66.7%). The ROC curve (Figure 1), with an AUC of .714 (95% CI: .47 to .89), also supports ≥17 ng/mL as the optimal antipsychotic-associated prolactin cutpoint (from among the various prolactin cutpoints). Thus, an AUC of .714 means that 71.4% of the time a randomly selected male outpatient from the ASEX responder group had an antipsychotic-associated prolactin cutpoint of ≥17 ng/mL (while taking an antipsychotic with prolactin-elevating effects), whereas a randomly selected male outpatient from the ASEX nonresponder group had an antipsychotic-associated prolactin cutpoint of <17 ng/mL (while taking an antipsychotic with prolactin-elevating effects). The logistic regression revealed that the odds of responding to a switch to an antipsychotic treatment (quetiapine) with a neutral prolactin effect (≥20% reduction in ASEX total score from baseline to exit) was nine times higher in male outpatients with an antipsychotic-associated prolactin level of ≥17 ng/mL (while taking an antipsychotic with prolactin-elevating effects) than those with an antipsychotic-associated prolactin level of <17 ng/mL (which were the greatest odds of responding to quetiapine switch treatment from among the various prolactin cutpoints, χ^2=4.34, p<.03). Results are reported in Table 2.

Discussion

The current pilot study, among male outpatients with schizophrenia or schizoaffective disorder who had sexual dysfunction while taking a prolactin-elevating antipsychotic, examined if there is a prolactin threshold that identifies male patients who experience improvement in sexual functioning when switched to an antipsychotic with neutral effects on prolactin. Findings suggest (among the range of prolactin levels) that the cutpoint or "threshold" of ≥17 ng/mL is a sensitive and specific threshold, with good negative predictive value and moderate positive predictive value, for identifying male outpatients who experience improvement in sexual functioning (≥20% reduction in ASEX total scores from baseline to exit for individual participants) when switched from an antipsychotic with prolactin-elevating effects to prolactin-neutral effects.

Table 2 ROC Results of the Risperidone-Associated Baseline Prolactin Cutpoints for ASEX Response to Quetiapine Switch Treatment

Prolactin Cutpoint (ng/mL)†	ASEX Response*						
	Sensitivity	Specificity	PPV	NPV	Odds Ratio‡	χ^2	p Value§
5	100	16.7	44.4	100	||	0.001	0.97
8	87.5	33.3	46.7	80.0	3.50	1.03	0.31
11	75.0	41.7	46.2	71.4	2.14	0.57	0.45
14	75.0	50.0	50.0	75.0	3.00	1.21	0.27
17	75.0	75.0	66.7	81.8	9.00	4.34	0.03
22	62.5	75.0	62.5	75.0	5.00	2.65	0.10
24	50.0	75.0	57.1	69.2	3.00	1.28	0.26
25	50.0	83.3	66.7	71.4	5.00	2.35	0.12
34	37.5	83.3	60.0	66.7	3.00	1.06	0.30
48	25.0	83.3	50.0	62.5	1.67	0.21	0.65
52	25.0	91.7	66.7	64.7	3.67	0.96	0.33
61	0.0	91.7	0.0	57.9	¶	0.001	0.98

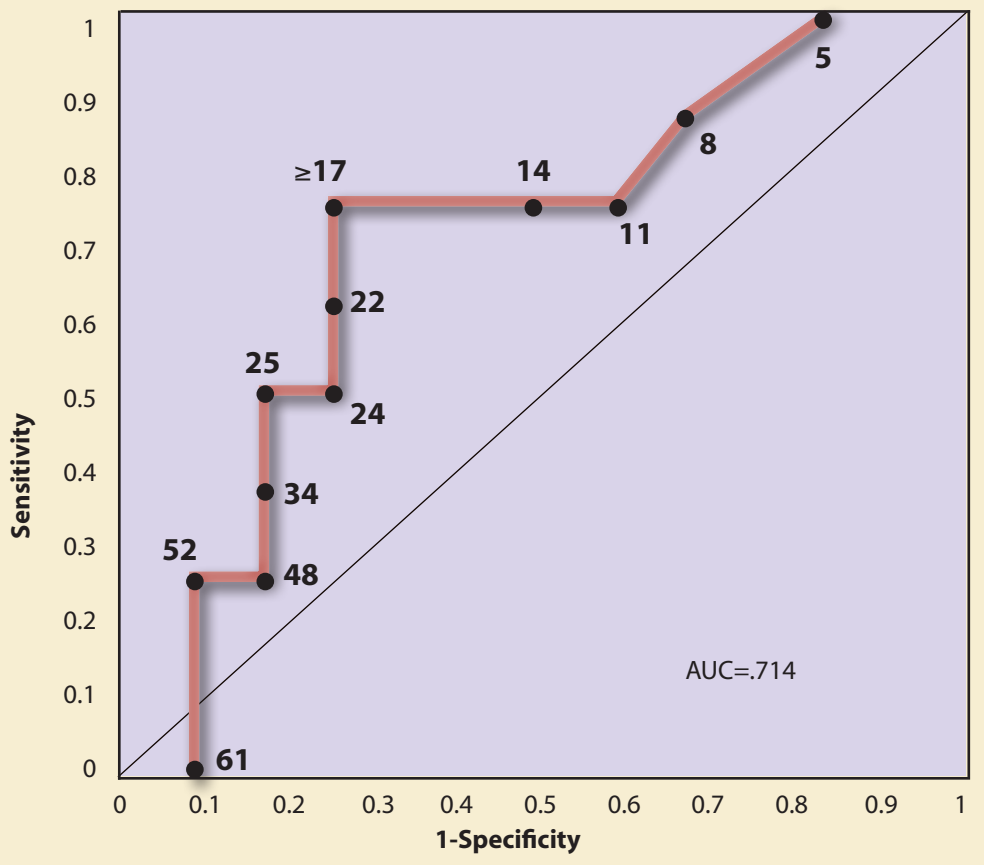
PPV=positive predictive value; NPV=negative predictive value; χ^2=Wald Chi-Square statistic was used to test the relationship between the prolactin cutpoint and ASEX response; p value=one-tailed p value; n=20. *ASEX response was a binomial variable operationally defined as ≥20% reduction in ASEX total score from baseline to exit for individual participants who were responders to quetiapine switch treatment and <20% reduction in ASEX total score for those who were nonresponders. †Prolactin cutpoint was a binomial variable operationally defined as the proportion of patients who were ≥ the risperidone-associated baseline prolactin level (cutpoint) and the proportion of patients who were < the risperidone-associated baseline prolactin level (cutpoint). ‡The odds ratio was calculated from the corresponding two independent proportions (prolactin cutpoint vs. ASEX response). The general interpretation of the odds ratio of 9.00 presented in this table is: those persons with a risperidone-associated baseline prolactin level of ≥17 have 9.00 times higher odds of responding to quetiapine switch treatment (≥20% reduction in ASEX total score from baseline to exit) than those with a risperidone-associated baseline prolactin level of <17. § Because of the pilot nature of the current study, p values were left unadjusted for multiple testing. ||Odds ratio not calculated because there were no patients who were < the prolactin cutpoint and who were responders to quetiapine switch treatment (≥20% reduction in ASEX total score from baseline to exit). ¶Odds ratio not calculated because there were no patients who were ≥ the prolactin cutpoint and who were responders to quetiapine switch treatment (≥20% reduction in ASEX total score from baseline to exit).

This basic finding is consistent with the pharmacodynamic actions of the particular antipsychotics studied (17), but may also have relevance when switching from other prolactin-elevating antipsychotics (e.g., first-generation antipsychotics) to quetiapine or other prolactin-neutral agents (e.g., aripiprazole). Of particular interest, the prolactin threshold of ≥17 ng/mL (vis-à-vis ASEX response) is nearly identical to the upper limit of the "normal" prolactin range for men as determined by the local clinical laboratory employed in the study (17.7 ng/mL) and by literature reports of the general population (18.8 ng/mL) (18).

The current study is also relevant for understanding the mechanisms of antipsychotic-associated sexual dysfunction. These findings build on prior studies demonstrating a relationship between higher prolactin levels and greater impairment in sexual functioning of antipsychotic-treated men with schizophrenia (3-7). This pilot study suggests that an antipsychotic medication switch that corrects hyperprolactinemia can result in improved sexual functioning. The current findings, however, may not be generalizable to females and to other combinations of antipsychotic medication switches that reduce hyperprolactinemia to normal levels. Preclinical investigations suggest that antipsychotics may produce sexual dysfunction by mechanisms other than prolactin elevation, including direct dopamine type 2 (D2) blockade and antagonism at α_1 adrenergic receptors (19).

The current pilot study may be tempered by a few limitations. In particular, the current study had a relatively small sample size of twenty participants. Thus, the relatively small sample size limited the range of observed prolactin levels (cutpoints) to those of the twenty male participants (sample) in the current study. We note, however, that the range of observed prolactin levels (5 to 61 ng/mL) in the current study is fairly encompassing and covers most of (and exceeds) the "normal" prolactin range for men in the general population (18). Another potential limitation of the study arises from the use of both open-label and double-blind quetiapine treatment in the same study sample. That is, ten of the twenty study participants received open-label quetiapine treatment (and the remaining ten patients received double-blind quetiapine treatment), which could have introduced bias into the clinical ratings, including the assessment of sexual

Figure 1 ROC Curve of the Risperidone-Associated Prolactin Cutpoints for ASEX Response to Quetiapine Switch Treatment (AUC=.714)



functioning (via the ASEX). The blinding of clinical raters to prolactin levels, however, should have mitigated potential rater bias for the primary outcome (sexual functioning as assessed by the ASEX). We also note that the results of our significance tests presented earlier suggest that the double-blind quetiapine and open-label quetiapine treatment groups did not differ statistically on any of the participant characteristics (as listed in Table 1). Nonetheless, the findings of this pilot study should be considered preliminary until confirmed by a larger trial in which treatments are blinded for all patients. The inclusion of patients taking antidepressant medications known to cause sexual dysfunction could have moderated (in part) the relationship between serum prolactin level and sexual functioning. We note, however, that our point-biserial correlation analysis only found a modest magnitude of association between the presence/absence of such antidepressant medications and ASEX total scores (at baseline and at exit). In addition, a brief six-week study period may have limited the number of patients responding to quetiapine switch and may have limited the generalizability of the findings regarding patients who are treated for longer durations. Further, using a convenience sample coupled within a university (research) medical setting might have limited the generalizability of the study results.

The current pilot study has strengths that could provide guidance on the design of future trials. Ratings of sexual functioning were conducted with an instrument—the original version of the five-item ASEX—which has established psychometric properties in measuring sexual functioning of outpatients with schizophrenia and schizoaffective disorder (15). ASEX ratings were also carried out blind to prolactin status. The current study employed risperidone and quetiapine dosing that were near the minimal effective doses, which mitigated the potential confound that ASEX response to quetiapine switch was a result of dosing of the agents.

Finally, we believe it is beyond the scope of this pilot study to broadly generalize our results to female schizophrenia patient populations and to patients with nonpsychotic disorders. The breadth of our results is limited to the antipsychotics and ASEX ratings and response among male outpatients with schizophrenia or schizoaffective disorder who appear similar to those in the current study. It is this context in which our results should be interpreted.

Conclusions

This pilot study is the first trial to our knowledge to show that, among male outpatients with schizophrenia or schizoaffective disorder who had sexual dysfunction associated with a prolactin-elevating antipsychotic, a prolactin threshold may exist that is sensitive and specific in identifying male patients who are likely to experience improvement in sexual functioning when switched to a prolactin-neutral antipsychotic. Future research that employs larger sample sizes, both genders, lengthier study periods, and complete blinding to treatment assignment is needed, however, to more fully evaluate the switch combination used in the current study and to investigate whether prolactin thresholds exist for other switch combinations of antipsychotic medications. Future research is also needed to clarify the clinical value of prolactin thresholds for sexual functioning and antipsychotic switch treatment in schizophrenia. But the current pilot study is a first step at empirically evaluating this potential value and if a signal for such a threshold could be identified.

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