Sexual dysfunction in male schizophrenia: influence of antipsychotic drugs, prolactin and polymorphisms of the dopamine D2 receptor genes

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Aim: Sexual dysfunction induced by antipsychotic drug treatment is under investigated and under reported. This study aimed to determine the influence of genetic polymorphisms in the D2 dopamine receptor (*DRD2*) and endothelial nitric oxide synthase (*eNOS*) genes, and the possible role of blood prolactin concentrations on sexual function in schizophrenic patients. **Materials & methods:** Male remitted schizophrenic patients (n = 100), who were living with a sexual partner and receiving antipsychotic drug monotherapy for at least 6 months, were assessed for sexual and erectile dysfunction using the Arizona Sexual Experience Scale and the five-item version of the International Index of Erectile Function. Blood samples were taken for plasma prolactin determination and genotyped for four polymorphisms: *DRD2* (-141C Ins/Del and Taq1A) and *eNOS* gene (G894T and T-786C). **Results:** The -141C Ins/Del, but not Taq1A, polymorphism of the *DRD2* gene was significantly associated with sexual dysfunction with the del allele being less frequent in sexual dysfunction subjects. Neither of the *eNOS* polymorphisms, G894T or T-786C, was significantly associated with sexual or erectile dysfunction. Prolactin concentrations were significantly higher in patients with erectile dysfunction but did not reach significance in those with sexual dysfunction. Prolactin was also reduced in -141C Del allele carriers. The frequency and severity of sexual dysfunction in the patients receiving typical antipsychotics was significantly greater than those receiving risperidone or clozapine, while prolactin concentrations were significantly higher in subjects receiving risperidone compared with those receiving clozapine or typical antipsychotics. **Conclusion:** This is the first evidence indicating that antipsychotic drug treatment in men is associated with a variant in the *DRD2* gene in which the -141C Del allele might be a protective factor. While this may, in part, be mediated by effects on prolactin, other factors are likely to contribute to the greater sexual dysfunction in patients receiving typical antipsychotics.

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KEYWORDS: antipsychotic ■ *DRD2* ■ *eNOS* ■ genetic polymorphism ■ sexual dysfunction

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Antipsychotic-induced sexual dysfunction (AP-SD) is a common and serious clinical side effect that is under investigated and under reported. Epidemiological research has reported substantial variations in the general prevalence of AP-SD, which ranges from approximately 30 to 80% [1]. SD has important implications for satisfaction with sexual life and overall quality of life [2,3]; it has been demonstrated as one of the major reasons for treatment noncompliance and inevitably affects clinical outcome and treatment success [4–6]. The differences in individual liability indicate the possible importance of genetic factors in determining the emergence of AP-SD.

The mechanisms of AP-SD remain largely unclear, and current theories derive mainly from studies of general sex physiology and psycho–pharmacology. The responses of various sexual components are under the control of numerous central and peripheral neural systems [7,8]. It has been postulated that a direct dopamine D2 receptor antagonist effect of antipsychotics may be the primary central mechanism, along with some indirect neuroendocrine factors, such as elevated prolactin levels [9]. Typical antipsychotics (e.g., haloperidol and thioridazine) are generally considered to cause relatively more SD than atypical agents (e.g., clozapine, olanzapine and quetiapine) and this has been ascribed to differences in affinity at D2 receptors [1,10]. Increased prolactin following antipsychotics has been suggested to suppress every aspect of sexual function (i.e., desire, erection and orgasm) [11], although this proposal remains controversial [12].

Two well-studied polymorphisms of the dopamine D2 receptor gene (*DRD2*), -141C Ins/Del and Taq1A, have been reportedly associated with dopamine D2 receptor density in *in vitro* studies [13] and in human striatum [14,15], respectively. Decreased dopamine D2 receptor density could theoretically result in greater vulnerability to dopamine blockade and hence an increased

occurrence of significant side effects, possibly including SD. This is supported by the finding that patients with a *DRD2* Taq1 A1 allele, associated with decreased brain receptor densities, had relatively higher prolactin levels following antipsychotic drug treatment [16].

We recently demonstrated that the gene expression and activity of nitric oxide synthase (NOS) isoforms are differentially affected by chronic antipsychotic treatment in rat penile tissues, indicating that peripheral mechanisms involving nitric oxide activity might also be involved in the pathogenesis of sexual side effects [17]. Interestingly, the *eNOS* G894T polymorphism was the first SNP shown to be associated with an increased risk of erectile dysfunction (ED) in two different racial populations [18,19]. The *eNOS* T-786C polymorphism, a functional promoter SNP [20], has been linked to an increased risk of developing coronary artery disease [21,22], which might also be relevant to the hemodynamics of penile erection.

The paucity of reports exploring the pharmacogenetics of AP-SD has prompted us to investigate the possible association with male AP-SD of these four potentially functional SNPs in two strong candidate genes, in order to better understand the mechanisms contributing to individual variability in SD in patients with schizophrenia.

Materials & methods

Subjects

The subjects were Chinese Han outpatients recruited from the psychiatric outpatient unit and four community psychiatric centers. All subjects provided written informed consent for participation in the study, which had been approved by the Hospital Ethical Committee, in accordance with the Declaration of Helsinki. Eligibility criteria for inclusion into the study were as follows:

- A married remitted male schizophrenia outpatient living with a stable sexual partner for the previous 6 months;
- Aged between 25 and 45 years;
- Medication with a single antipsychotic drug for at least 6 months.

Remitted schizophrenia was defined by two components: a Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of schizophrenia as established by the clinic physician, coupled with a current state of remission defined by the symptomatic criteria proposed by the Remission in Schizophrenia Working Group [23], excepting the requirement for continuous state of remission over 6 months. Patients were excluded if they had one or more of the following:

- Any reported history of SD before antipsychotic treatment;
- A general medical condition or history of a surgical procedure known to cause SD, for example prostatectomy, diabetes, hypertension or neurological disease;
- Any other side effect of antipsychotics, for example, tardive dyskinesia, which might indirectly influence sexual function or its reporting;
- Receiving other psychotropic drugs known to cause SD, for example antidepressants, although patients taking other adjunctive medications, such as anticholinergics and benzodiazepines, were not excluded;
- Any history of substance or alcohol abuse.

Clinical features & sexual function

Subjects were told they would participate in a brief survey to evaluate their experiences with their current psychiatric medications. A medical history was obtained, including:

- Demographic information;
- History of past illness and treatment;
- Currently prescribed psychotropic medications and duration of treatment.

The antipsychotic dose was calculated as chlorpromazine equivalent in mg/day. All patients were then rated using the Positive and Negative Syndrome Scale (PANSS) on the day of recruitment by the senior psychiatrists. The patient's psychiatric symptom severity over the previous 6 months was obtained from their treating clinical psychiatrist in the psychiatric outpatient unit and community psychiatric centers.

After obtaining demographic and medication/treatment information, sexual function was evaluated with a one-time rating of two five-item self-administered questionnaires: the Arizona Sexual Experience Scale (ASEX) [24] and the abridged five-item version of the International Index of Erectile Function (IIEF-5) [25]. The ASEX, assessing the severity of overall SD, has established psychometric properties (internal reliability and construct and convergent validity) in outpatients with schizophrenia or

schizoaffective disorder [26]. The criterion for SD, according to the ASEX, is a total score of 19 or above, any one item with an individual score of 5, or any three items with individual score of 4 [24]. The IIEF-5 focused on ED and intercourse satisfaction, while each item is scored on a five-point ordinal scale, where lower values represent poorer sexual function. A score of above 21 is considered normal erectile function and, at or below this threshold, is considered as ED [25]. Validated versions for China were used in the present study. The participants undertook this in an individual room with a total guarantee of confidentiality. If needed, the psychiatrist provided any necessary explanation to ensure the questionnaires were understood.

Prolactin measurement

Blood was collected after an overnight fast in a 5-ml EDTA vacuum tube from each patient and then centrifuged at 3000 rpm for 5 min to separate the plasma from cells; these were frozen and stored at -70°C until prolactin measurement and genotyping, respectively. Plasma prolactin was assayed in duplicate by double antibody radioimmunoassay. The reagents were provided in kits from Jiuding Biological Corporation, China. The inter- and intra-assay coefficients of variation were 5.6 and 5.9%.

Genotyping

After extraction of genomic DNA from blood cells, genotyping was performed by PCR–restriction fragment length polymorphism technique, using methods as previously described: *DRD2* Taq1A [27,28], *DRD2* -141C Ins/Del [13,29], *eNOS* G894T [30] and *eNOS* T-786C [31]. The resulting segments were digested with the restriction endonuclease TaqI for Taq1A, BstNI for -141C Ins/Del, BanII for G894T and MspI for T-786C (New England BioLabs, UK) and products separated by electrophoresis on 3% agarose gel stained with ethidium bromide.

Statistical analysis

All statistical analyses were performed using SPSS 11.5 for Windows employing two-tailed tests. Values of demographic characteristics and questionnaire scores are given as mean ± standard deviation. Differences in clinical variables or in PANSS scores between patient subgroups were evaluated by t-test or analysis of variance. Differences in sexual function between allele and genotype groups were evaluated with Mann–Whitney U and Kruskal–Wallis H tests as the ASEX and IIEF-5 scores were not normally distributed, while prolactin measures were log-transformed prior to analysis of variance. Chi-square tests were used to compare allele and genotype frequencies, and drug treatments, between the different sexual function subgroups. Power analysis demonstrated that the sample size had 80% power to identify significant frequency differences in SD with odds ratios of approximately 1.75.

Results

Clinical demographic characteristics & blood prolactin in male schizophrenic patients

A total of 176 psychiatric outpatients meeting the inclusion criteria were initially identified, of whom, 100 subjects finally provided written informed consent and participated in the study. Those patients received antipsychotic monotherapy with clozapine (n = 37), risperidone (n = 30), chlorpromazine (n = 21), haloperidol (n = 9) and olanzapine (n = 3). Using the cut-off level of the ASEX questionnaire, the patients were divided into two groups, the SD group (n = 47) with a mean ASEX score of 23.57 (± 3.02) and the normal sexual functioning group (n = 53) with a mean ASEX score of 13.19 (± 2.36). The clinical features of the SD and non-SD groups demonstrated no significant differences in age (40.6 ± 5.4 years and 41.0 ± 4.6 years, respectively), length of current drug treatment (8.32 ± 3.9 years and 6.91 ± 3.2 years, respectively), age of onset, chlorpromazine equivalent dosage or PANSS score. According to the IIEF-5 score, 45 patients were in the ED group. Again, there were no significant differences found in any socio–demographic and clinical variables between the erectile function groups divided according to IIEF-5 criteria.

Genetic association with sexual dysfunction

The genetic association of alleles and genotypes of the *DRD2* and *eNOS* polymorphisms with sexual and erectile function are shown in Tables 1 & 2. Where a single homozygous subject was found in the sample studied (for *DRD2* -141C Del/Del, and for *eNOS* 894TT), these samples were included in the heterozygote groups for further analysis. For *eNOS* -786 there were no CC homozygotes within the sample. The distribution of genotypes in each polymorphism did not differ significantly from Hardy–Weinberg equilibrium. There were no significant associations found for either of the *eNOS* polymorphisms or the *DRD2* Taq1A polymorphism

Table 1. Distributions of genotypes and alleles between sexual dysfunction and normal sexual function groups of schizophrenic patients determined by the Arizona Sexual Experience Scale.

	Genotypes	SD	Normal	χ^2	Alleles	SD	Normal	χ^2
DRD2 -141C Ins/Del	Del/Ins + Del/Del	3	11	$\chi^2 = 4.273$	Del	3	12	$\chi^2 = 4.746$
	Ins/Ins	44	42	df = 1; p = 0.046	Ins	91	94	df = 1; p = 0.003
DRD2 Taq1A	A1A1	9	8	$\chi^2 = 0.463$	A1	40	40	$\chi^2 = 0.482$
	A1A2	22	24	df = 2; p = 0.793	A2	54	66	df = 1; p = 0.488
	A2A2	16	21					
eNOS T-786C	TC	12	8	$\chi^2 = 1.696$	C	12	8	$\chi^2 = 1.508$
	TT	35	45	df = 1; p = 0.193	T	82	98	df = 1; p = 0.219
eNOS G894T	GG	39	45	$\chi^2 = 0.069$	G	86	97	$\chi^2 < 0.001$
	GT + TT	8	8	df = 1; p = 0.793	T	8	9	df = 1; p = 0.996

The different sexual function groups were divided according to the cut-off level of Arizona Sexual Experience Scale.
Comparisons between groups were made using χ^2 tests.
Del: Deletion; df: Degrees of freedom; DRD2: D2 dopamine receptor; eNOS: Endothelial nitric oxide synthase; Ins: Insertion; SD: Sexual dysfunction.

with either SD or ED. Analysis of the Taq1A polymorphism using dominant or recessive models also showed no significant association. These polymorphisms also showed no significant associations with clinical features of the patients studied, or with prolactin measurements (data not shown).

Significant association with SD determined by ASEX criteria was found for the -141C Ins/Del polymorphism in the *DRD2* gene (Table 1). The *DRD2* -141C Del allele was found to be significantly less frequent in SD patients than non-SD group (odds ratio: 0.258; 95% CI: 0.071–0.945; p = 0.003). The genotype distribution reflected this effect, with a significantly lower frequency of Del allele carriers in the SD group (odds ratio: 0.260; 95% CI: 0.068–0.999; p = 0.046). The same trend towards genotype and allelic associations was apparent for ED determined by IIEF-5 criteria, although results did not quite reach statistical significance (Table 2). The difference between the two measures was due to two subjects meeting SD criteria but not reporting ED.

Comparison of ASEX outcomes showed worse sexual function in the Ins/Ins genotype patient group than the -141C Del carriers (Table 3). The analyses also revealed a significant genotype association with three of the five ASEX individual subitems. Although the IIEF-5 total score did not differ significantly between -141C Del carriers and Ins/Ins homozygotes, a significant difference was found in two IIEF-5 individual subitems (3 and 4; p = 0.016 and 0.011, respectively). The -141C Del carriers had a longer duration of illness than the -141C Ins/Ins genotype group, but no other significant differences in socio–demographic and PANSS scores were found between the two genotype groups.

Prolactin & sexual dysfunction

The difference in blood prolactin between the SD (22.4 ± 18.9 ng/ml) and non-SD (17.9 ± 16.5 ng/ml) groups did not reach significance (p = 0.058). A significant difference in blood prolactin was found between the ED (23.4 ± 19.2 ng/ml) and non-ED (17.0 ± 16.0 ng/ml) groups (p = 0.017). Correlation analysis showed significant or

Table 2. Distributions of genotypes and alleles between erectile dysfunction and normal erectile function groups of schizophrenic patients determined by the International Index of Erectile Function-5.

	Genotypes	ED	Normal	χ^2	Alleles	ED	Normal	χ^2
DRD2 -141C Ins/Del	Del/Ins + Del/Del	3	11	$\chi^2 = 3.654$	Del	3	12	$\chi^2 = 4.095$
	Ins/Ins	42	44	df = 1; p = 0.082	Ins	87	98	df = 1; p = 0.058
DRD2 Taq1A	A1A1	9	8	$\chi^2 = 0.738$	A1	39	41	$\chi^2 = 0.758$
	A1A2	21	25	df = 2; p = 0.691	A2	51	69	df = 1; p = 0.384
	A2A2	15	22					
eNOS T-786C	TC	11	9	$\chi^2 = 1.01$	C	11	9	$\chi^2 = 0.898$
	TT	34	46	df = 1; p = 0.315	T	79	101	df = 1; p = 0.343
eNOS G894T	GG	36	48	$\chi^2 = 0.974$	G	81	102	$\chi^2 = 0.491$
	GT + TT	9	7	df = 1; p = 0.324	T	9	8	df = 1; p = 0.706

The different erectile function groups were divided according to the cut-off level of the International Index of Erectile Function-5.
Comparisons between groups were made using χ^2 tests.
Del: Deletion; df: Degrees of freedom; DRD2: D2 dopamine receptor; ED: Erectile dysfunction; eNOS: Endothelial nitric oxide synthase; Ins: Insertion.

near-significant effects between prolactin concentrations and IIEF-5 and ASEX scores (p = -0.191, p = 0.028 and p = 0.157, p = 0.059, respectively; Spearman's test, one-tailed).

Prolactin concentrations were found to be highly significantly associated with the *DRD2* -141C polymorphism, with the Ins/Ins genotype associated with significantly higher values than Del allele carriers (Table 3). No significant association of prolactin concentrations with any other polymorphism studied was apparent (data not shown).

Effect of antipsychotic drugs on severity of sexual dysfunction & blood prolactin

To assess whether the drug treatments differentially influenced SD, the sample was divided into three subgroups: those receiving clozapine, risperidone or typical antipsychotic drugs (chlorpromazine and haloperidol). Comparison of ASEX and IIEF-5 scores between antipsychotic drug groups revealed a significant treatment effect on severity of SD, as measured by ASEX total scores (p = 0.016) but not by IIEF-5 (p = 0.207). Posthoc tests showed that the ASEX total scores were higher in the typical antipsychotic drug group (20.73 ± 5.56) than in the clozapine (17.24 ± 6.08; p = 0.018) or risperidone (17.06 ± 5.17; p = 0.007) groups, indicating worse sexual function in the typical antipsychotic drug group than the other two subgroups. These findings were reflected in the greater proportion of subjects receiving typical antipsychotics reaching threshold criteria for SD and ED (66.7 and 60.7%, respectively) than in the clozapine (40.5 and 37.8%) and risperidone (40.0 and 43.3%) groups.

Prolactin showed significant differences between the drug groups, in which blood concentrations in the risperidone group (31.9 ± 22.3 ng/ml) were substantially and significantly higher than either the typical (17.8 ± 13.0 ng/ml; p = 0.042) or the clozapine (12.1 ± 10.1 ng/ml; p < 0.001) groups. The effect of prolactin on sexual function was explored further within the three drug groups. An effect was only apparent in the risperidone group where correlations between prolactin concentrations and IIEF-5 and ASEX scores showed significant or near-significant correlations (p = -0.384, p = 0.018 and p = 0.304, p = 0.051; Spearman's test, one-tailed).

Table 3. Comparison of sexual function and clinical features in the *DRD2* -141C Ins/Del genotype group.

Outcome measure	Del/Ins + Del/Del (n = 14)	Ins/Ins (n = 86)	p-value
Total ASEX score	14.9 ± 4.0	18.6 ± 6.0	0.021
– Sex drive	3.6 ± 0.9	4.0 ± 1.1	0.129
– Arousal	3.1 ± 1.1	3.8 ± 1.2	0.032
– Penile erection	2.5 ± 0.8	3.4 ± 1.3	0.007
– Orgasm (ability)	2.6 ± 0.7	3.7 ± 1.4	0.013
– Orgasm (satisfaction)	3.1 ± 1.1	2.7 ± 1.4	0.117
Total IIEF-5 score	22.0 ± 1.9	18.5 ± 6.0	0.171
– Erection confidence	3.9 ± 0.5	3.4 ± 1.1	0.177
– Erection firmness	4.4 ± 0.6	3.9 ± 1.3	0.535
– Maintenance frequency	4.9 ± 0.4	3.9 ± 1.4	0.016
– Maintenance ability	4.7 ± 0.5	3.7 ± 1.4	0.011
– Intercourse satisfaction	4.2 ± 0.7	3.6 ± 1.4	0.166
Age (years)	41.1 ± 4.6	40.7 ± 5.0	0.976
Age of onset (years)	24.2 ± 4.6	26.8 ± 4.8	0.069
Duration of schizophrenia	16.9 ± 4.9	14.0 ± 5.2	0.027
Dose	300.0 ± 123.6	336.0 ± 125.3	0.434
Total Positive and Negative Syndrome Scale	46.8 ± 6.1	47.5 ± 5.2	0.62
Positive subscore	12.2 ± 2.6	12.6 ± 2.2	0.514
Negative subscore	11.5 ± 2.2	11.9 ± 2.3	0.53
General subscore	23.1 ± 2.7	23.0 ± 2.6	0.936
Prolactin (ng/ml)	12.2 ± 13.6	21.3 ± 18.1	0.004

Data are expressed as mean ± standard deviation.
ASEX: Arizona Sexual Experience Scale; Del: Deletion; DRD2: D2 dopamine receptor; IIEF-5: International Index of Erectile Function-5; Ins: Insertion.

Discussion

In the present study, the severity and prevalence of SD in response to antipsychotic agents was evaluated in remitted male schizophrenia patients based on ASEX and IIEF-5 rating scales. The main findings of our study were in keeping with most previous reports that SD is common in male schizophrenia patients on antipsychotic medication [32], with 47 and 45% reaching threshold criteria for SD and ED, respectively, higher than the rate of such dysfunction in the general population (10–31%) [33–35].

Results are, on the whole, generally consistent between the IIEF-5 (ED) and ASEX (SD) measures. As mentioned, the difference between those in the ED and SD groups reflects two subjects reaching criteria for SD but not ED. Greater differences are seen in statistical tests of the scores from each questionnaire, reflecting substantial differences between the two measures. Thus SD, determined by the ASEX questionnaire, provides a far broader assessment of sexual function than IIEF-5, which focuses solely on erectile function.

To our knowledge, this is the first study to investigate genetic mechanisms of AP-SD in remitted male patients with schizophrenia. Our findings indicate a significant involvement of the *DRD2* -141C Ins/Del polymorphism in SD, following antipsychotic drug treatment. In this

Chinese Han population, the prevalence of SD in Del allele carriers (Del/Ins + Del/Del) was significantly lower than in Ins/Ins homozygotes with relatively better rating scale scores. Blood prolactin was also lower in Del allele carriers. Our findings suggested a protective effect of the *DRD2* -141C Del allele on sexual function following antipsychotic drug administration.

The -141C Ins/Del polymorphism has been reported to influence dopamine D2 receptor availability, with the Del allele being associated with a reduction of D2 receptor expression [13]. However, a PET study performed in healthy individuals revealed a higher striatal density of D2 receptors in -141C Del allele carriers [36]. This *in vivo* study provided the neuroimaging evidence for the -141C Del allele being a possible indicator of resistant response to antipsychotic medication. There have been several recent studies supporting this hypothesis. A study on Chinese Han population reported that schizophrenia patients carrying the Del allele showed less improvement following chlorpromazine treatment than those who did not; the frequency of the Del allele was also higher in nonresponders than in responders [37]. Another study on patients with first-episode schizophrenia, further indicated that relative to Ins/Ins homozygotes, -141C Del carriers took a significantly longer time to respond to olanzapine or risperidone treatment [38]. Taken together, these findings indicate that antipsychotics may be associated with a relative lower pharmacological efficacy in -141C Del alleles carriers and further suggest the possibility of the -141C Del allele as a protective factor for AP-SD.

It has been reported that the TaqA1 allele of the *DRD2* gene is associated with significantly decreased D2 receptor density, which may influence D2 receptor antagonism [14]. Patients with the *DRD2* A1 allele receiving antipsychotic medications were reported to have higher prolactin levels than patients without this allele [16], which indicated a possible link between the Taq1A polymorphism and AP-SD. However, we found no significant association of the Taq1A polymorphism of the *DRD2* gene with susceptibility to sexual side effects in our study. A recent report indicated a possible racial effect for the Taq1A polymorphism in its association with the overall level of side effects (i.e., including SD) due to antipsychotic medication [39]. This association was found in Caucasian subgroups, but disappeared if three subjects with Asian ethnicity were included in the statistical analysis [39].

The hormone prolactin has been also regarded as a causative factor underlying AP-SD [9]. The present study demonstrated elevations of blood prolactin in patients with SD, especially ED. Previous studies have shown that prolactin can suppress sexual behavior in both male patients [40,41] and rodents [42], although it is still not fully understood how this hormone affects the sexual capacity of male subjects. Several studies have found a significant correlation between prolactin and male sexual side effects [43–45], while others have failed to confirm these findings [12,46,47]. Interestingly, it has been suggested that only severe hyperprolactinemia is associated with human SD [48]. Given that prolactin elevation following antipsychotic drug treatment is primarily due to dopamine D2 receptor antagonism, it seems possible that the effect of the *DRD2* genotype on SD may be mediated through its effects on prolactin concentration. However, we found that prolactin concentrations correlated with ED only within the risperidone group, in which blood prolactin was substantially higher than in the clozapine or typical antipsychotic groups. Moreover, the risperidone group, despite having a higher mean level of prolactin, had less SD compared with patients receiving typical antipsychotic drugs. This is in keeping with a previous report indicating that the increased prolactin associated with risperidone treatment does not seem to be decisive for SD [47]. These observations strongly suggest that a *DRD2*-mediated prolactin elevation is not the only factor contributing to AP-SD in male patients with schizophrenia.

It is worth noting that both severity and prevalence of SD are generally lower with atypical antipsychotics than typical antipsychotics [49,50]. While some have reported that the frequency of SD induced by risperidone was higher than the other atypical antipsychotics, such as clozapine [51] and olanzapine [52], other studies, along with the present finding, suggest that risperidone is associated with a degree of SD similar to clozapine [53], olanzapine [54] and quetiapine [49]. The inconsistencies between these various reports might be attributed to a variety of influences and confounders, including, clinical factors of schizophrenia (e.g., psychiatric symptoms, comorbid conditions and comedication regimes) [55] and methodological factors including different assessment tools for sexual behavior and differences in study samples (e.g., subjects' sex and trial design) [10]. Attempting to address some of these limitations, the present study evaluated sexual function in

remitted schizophrenia patients within a stable sexual relationship, using questionnaires that had been tested for their reliability and validity in schizophrenia.

Apart from *DRD2* and prolactin, other mechanisms, including effects at the serotonin (5-HT) 2A receptor, might also contribute to the observed differences in SD between risperidone and typical antipsychotics, counteracting the effects of elevated prolactin. Both risperidone and clozapine have higher affinities for the 5-HT2A than the D2 receptor [56]. 5-HT2A antagonism has been demonstrated to have a strong stimulating effect on male sexual behavior in several animal studies [57,58]. However, further pharmacological mechanisms, or indirect effects via the elevation of other risk factors for SD, may well contribute to AP-SD.

The relationship between two SNPs (G987T and T-786C) of the *eNOS* gene and AP-SD was also determined. The G894T polymorphism had been reported to be a genetic susceptibility factor for ED in Mexican and Taiwanese populations [18,19]. However, a study in the German population did not find the association of this SNP with ED, but reported association of the G894 allele with response to sildenafil, a drug acting on the NO-cGMP pathway in erectile tissues [59]. In the present study, we did not detect any association between either SNP of the *eNOS* gene and AP-SD. However, given the evidence implicating *eNOS* in antipsychotic-induced sexual function, it would be premature to rule it out as a candidate gene for susceptibility to sexual side effects. An important role of *eNOS* in AP-SD has been established by the results of our animal study [17]. Moreover, sildenafil has also been found to be a safe and effective drug in the treatment of antipsychotic-induced ED [60,61]. Therefore, further functional polymorphisms of *eNOS* or other genes involved in the NO-cGMP pathway might still be risk factors for antipsychotic-induced SD.

This study had several limitations; as a cross-sectional study, it was not possible to determine the direct effect of antipsychotic treatment on the extent and severity of SD because of the absence of baseline ASEX and IIEF-5 ratings prior to treatment. Furthermore, while the study was powered to identify robust effects of genetic subgroups on SD, further investigation of subgroups, or interaction between treatment and genetic effects for example, was not justified with the sample size. The effects of four polymorphisms in two different genes have been tested for their association with measures of SD. While a separate valid hypothesis justifies the investigation of each gene, there is an element of multiple testing in this study that has not been corrected for by adjustment of p-values. However, even with the most conservative correction, it is clear that the association of the D2 -141C allele with SD would remain statistically significant. Nevertheless, the results of any small study such as this, needs to be considered as preliminary and awaiting replication in further cohorts before robust conclusions can be drawn. In addition, larger samples would be required to ascertain more precisely, the genetic effect on sexual function following specific medications, or to determine the interactions between D2 receptor genotype, prolactin and drug in contributing to AP-SD. Given the differences between drugs in D2 receptor affinity and effects on prolactin, it may be that receptor genotype would differentially influence SD following different drug treatments.

Nevertheless, our findings indicate that the typical antipsychotics are more likely to be associated with SD in men than the atypical drugs, including risperidone and clozapine, despite the higher blood prolactin concentrations associated with risperidone. In addition to pharmacological mechanisms of antipsychotic medication, genetic factors may also be important in determining AP-SD. The present genetic finding may help to predict the possible influence of antipsychotic treatment on sexual function, which has implications in the improvement of treatment compliance and the quality of life of patients with schizophrenia.

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Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Antipsychotic drug treatment is associated with sexual dysfunction, a poorly understood and under investigated but problematic side effect.
- This study aimed to determine the association of genetic polymorphisms in two candidate genes and sexual dysfunction in male subjects with schizophrenia receiving antipsychotic drugs, who were also in a stable sexual relationship.
- Two polymorphisms in each of the genes for the dopamine D2 receptor (*DRD2*) and for endothelia nitric oxide synthase (*eNOS*) were investigated for their association with scores on questionnaires for sexual and erectile dysfunction. Prolactin blood concentrations and their relationship to genotype and drug treatment were also studied.
- A significant genetic association with sexual dysfunction was found with the functional -141Ins/Del promoter region polymorphism of *DRD2*. Prolactin concentrations were also significantly associated with this polymorphism.
- There was a discrepancy between prolactin and sexual dysfunction related to drug type; prolactin was greatest in those patients receiving risperidone, but sexual dysfunction was greatest in those receiving typical antipsychotic drugs.
- This study identifies one genetic risk factor that may influence antipsychotic-induced sexual dysfunction partly via effects on prolactin secretion.
- Other genetic factors independent of the dopamine system and prolactin secretion are likely to contribute to antipsychotic-induced sexual dysfunction; further systematic search for such factors is needed.
- Identification of genetic polymorphisms influencing the emergence of this problematic side effect is an important step towards the eventual use of genetic testing in identifying at risk subjects, providing valuable information that will inform therapeutic practice.

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