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ORIGINAL RESEARCH ARTICLE

Sex Differences Between Female and Male Individuals in Antipsychotic Efficacy and Adverse Effects in the Treatment of Schizophrenia

Megan Galbally[1,2] · Karen Wynter[1,3] · Dan Siskind[4,5] · Christoph U. Correll[6,7,8,9] · Korinne Northwood[4,5] · Susanna Every-Palmer[10]

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Abstract

Background and Objective Antipsychotics are core treatments for people living with psychotic disorders. Understanding individualised factors that influence both efficacy and adverse responses will improve outcomes. The objective of this study was to examine sex differences in antipsychotic-related efficacy and tolerability.

Methods This was a secondary analysis of data from phase 1 and 1a of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE); participants with schizophrenia were randomly assigned to double-blinded treatment with oral olanzapine, quetiapine, risperidone, ziprasidone or perphenazine. Measures included Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions (CGI) scale and Calgary Depression Rating Scale, as well as self-reported side effects, medication compliance, dosage, weight measurements and various blood parameters.

Results There were 1460 participants including 380 female and 1080 male individuals. Very few differences existed between male and female participants in response, adverse reactions, compliance or antipsychotic dosage. However, significantly more female participants than male participants reported constipation (28% vs 16%), dry mouth (50% vs 38%), gynecomastia/galactorrhea (11% vs 3%), incontinence/nocturia (16% vs 8%) and self reported weight gain (37% vs 24%) [all $p < 0.001$]. Within the risperidone treatment group, there was a significantly greater increase in prolactin levels ($p < 0.001$) among female participants ($n = 61$) than male participants ($n = 159$). No overall differences in clinician-rated measures, weight gain or other laboratory indicators were found.

Conclusions While overall sex differences were limited across efficacy and tolerability for antipsychotic treatment, there were some specific findings with risperidone. Further examination of sex differences within antipsychotic trials will be important to improve efficacy and reduce adverse responses across as well as individualising care for people with schizophrenia.

1 Background

As recommended in guidelines, as well as common clinical practice, antipsychotics are a core component for both the treatment as well as ongoing relapse prevention management of psychotic disorders including schizophrenia [1–4]. While psychotic disorders have approximate equivalence in prevalence across the sexes, there are evident differences in the patterns of onset, presentation and course of illness as well as the associated psychosocial impacts [5–7]. These differences include female individuals' later average age of illness onset, heightened vulnerability to the development of a new psychotic disorder or relapse in the early postpartum period, and the exploration of oestrogen as a potential adjunctive treatment to enhance antipsychotic efficacy [5,

Key Points

There is only limited research into sex differences for efficacy of and adverse reactions to antipsychotic treatment for schizophrenia, yet this is an important potential aspect of improving individualised care.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) remains an important, large and comprehensive trial of antipsychotic treatment of schizophrenia. However, the data collected have not been examined for sex differences.

Female participants were found to have higher levels of self-reported adverse effects overall and specifically from risperidone as well as higher prolactin levels associated with risperidone.

Extended author information available on the last page of the article

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6]. This combined evidence suggests potential biological sexual dimorphic differences, as well as the role of sex and gender experiences (including poverty, sexual risk in treatment settings, domestic violence and discrimination) as determinants of the presentation and course of schizophrenia in female individuals [8–11]. While there has been now a consistent call from researchers to consider sex and gender differences in health-related research, the response in the psychopharmacological field has been slow, with a persisting sex/gender-neutral approach adopted by most new studies [12–14]. Yet, while there is evidence to suggest the likelihood of sexual dimorphic biological differences in psychotic disorders, it is also critical to treatment planning to understand if these differences extend to the response to, and safety of antipsychotics.

To date, there has only been limited research on efficacy and sex differences in antipsychotics, with most studies focusing on dose response [15–17]. Findings suggest female individuals may respond to lower antipsychotic doses, although greater adherence to treatment may at least partially account for this association [18]. However, there is evidence to support differences in pharmacodynamics, including the role of hormonal changes over the lifespan, with research showing antipsychotics become less efficacious during menopause [19, 20]. There is also evidence that female individuals are more susceptible to adverse drug reactions, with many of the known antipsychotic adverse effects, such as prolactin induction, osteoporosis and metabolic syndrome, also having specific implications for female individuals [21–24]. These effects include conditions such as risks of developing gestational diabetes in pregnancy, osteopenia in perimenopause, hyperprolactinaemia and infertility, and potential drug interactions between antipsychotics and contraceptives and hormonal replacement treatment, which are both commonly used by female individuals across their adult life. This situation has led to a call to consider sex differences in mental health research and indeed in the development of clinical practice guidelines as part of aspiring to improved individualised precision treatment practices [12, 25].

There are significant challenges in incorporating the consideration of sex differences for both schizophrenia and antipsychotics into research, given the low prevalence and difficulties in recruiting and retaining cohorts; however, one way to address this is the use of secondary analyses of existing trial data. The BeST inTro pragmatic trial [15] included 144 patients with 93 male and 51 female individuals taking aripiprazole, amisulpride and olanzapine and followed participants to 52 weeks with the primary outcome being scores on the Positive and Negative Symptom Scale (PANSS) [26], and a subsequent secondary analysis of sex differences of the collected data was undertaken [15]. In this recent paper that undertook this secondary analysis focusing on examining sex differences in data collected as part of BeST inTro, clear sex differences were identified in both the efficacy and tolerability of specific antipsychotics [15]. Amisulpride, for example, was more efficacious in male participants, dose-corrected levels were higher in female participants, and this antipsychotic caused more adverse effects in female participants including increased prolactin levels and body mass index (BMI) [15, 26].

While there have been many antipsychotic trials, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) undertaken two decades ago remains a seminal study trial into the antipsychotic management of people with schizophrenia [27]. CATIE was carefully designed to ensure relevance to clinical practice and hence the trial period of 18 months was far longer than the standard 4- to 6-week medication trials and longer than the BeST inTro. Recruitment occurred across the USA and the study was funded by the National Institute of Mental Health in contrast to many trials that are sponsored by pharmaceutical companies. The longer trial period enabled the collection of important data on efficacy, adverse reactions and in particular the co-morbid physical health of participants with some similar measures used in BeST inTRo; however, CATIE included a broader and more comprehensive data collection. CATIE included 1460 participants from 57 sites across the USA, in contrast to 144 participants recruited across four academic sites with three in Norway and one in Austria in BeST inTRo [26]. While CATIE data have been examined in numerous nested studies, there has been limited focus on utilising these data to examine sex differences [28, 29]. Unlike shorter duration trials with more limited measures and few participants, these data are ideal for examining potential differences in efficacy and adverse reactions between female and male individuals. Indeed, a recent systematic review found most studies examining data for sex differences are limited to a small array of short-term measures of potential adverse reactions and they rarely include self-report, blood parameters and clinician-rated measures collected over an extended period as reported in CATIE [17].

This study first aimed to investigate the differences in efficacy of, and response to antipsychotics between female and male individuals, and their relative efficacy among female individuals. Second, we aimed to investigate the differences in commonly reported and measured antipsychotic-related adverse reactions between female and male individuals.

2 Methods

2.1 Study Description

CATIE was a randomised controlled trial and studied 1460 participants with chronic schizophrenia enrolled across

57 sites across the USA. The trial protocol details randomisation and the methodology including inclusion and exclusion criteria [27]. Table 1 summarises the sample description.

We report data from phase 1 and 1a of CATIE. During phase 1 of the trial, patients (aged 18–65 years who currently or had in the past met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [30] criteria for schizophrenia) were randomly assigned to double-blinded treatment with oral olanzapine, quetiapine, risperidone, ziprasidone and perphenazine. Participants with tardive dyskinesia bypassed phase 1 owing to the additional risks from being assigned to perphenazine, and they were assigned to treatment with one of the other four medications (phase 1a). Participants who responded to treatment to which they were assigned, remained on that treatment for the duration of the 18-month treatment period. Participants who discontinued phase 1/1a participated in subsequent phases; these data are not reported here. The dosage and assessment schedule is also reported in the study protocol [27].

Participants attended monthly assessments during which data were collected by clinical and functional assessments, patient self-report, pill counts, laboratory tests and assessment of patients' pulse, blood pressure and weight. Not all assessments occurred at all visits. We report on data from baseline and end-of-phase (final visit) assessments. Average and modal dosage data over all visits are also reported.

2.2 Measures

Efficacy outcomes included changes in scores on the PANSS [31], the Clinical Global Impressions (CGI) scale [32] and the Calgary Depression Rating Scale [33]. The PANSS is a 30-item clinician-administered rating scale [31]. PANSS scores can range from 30 to 210, with higher scores indicating more severe psychopathology. Subscales include the Positive Scale (excess or distortion of normal functions such as hallucinations, range 7–49), the Negative Scale (diminution or loss of normal functions, range 7–49) and the General Psychopathology Scale (range 16–112).

The CGI provides an overall clinician-determined summary measure, the CGI-Severity (CGI-S), that considers all available information: patient history, psychosocial circumstances, symptoms, behaviour and the impact of the symptoms on the patient's ability to function [32, 34]. Scores range from 1 to 7 with higher scores indicating a greater severity of illness.

The Calgary Depression Rating Scale-Severity is a clinician-rated measure of the severity of depression among people with schizophrenia [33]. Scores range from 0 to 27 with higher scores indicating a greater severity of depression symptoms.

To assess neurological side effects, we report on treatment-emergent symptoms meeting clinical thresholds in the following scales: Barnes Akathisia Scale (BRS) [35]; Simpson-Angus Extrapyramidal Side Effect Scale (EPS) [36] and Abnormal Involuntary Movement Rating Scale (AIMS) [34].

Table 1 Baseline demographic and clinical characteristics by sex

	Female participants ($n = 380$)	Male participants ($n = 1080$)	p^a	d or ϕ
Age, mean (SD)	42.23 (10.32)	39.96 (11.31)	0.001	0.205
Diagnosis, *n* (%)				
Schizophrenia	344 (90.5)	1026 (95.0)		
Schizoaffective disorder	30 (7.9)	48 (4.4)		
Schizophreniform disorder	1 (0.3)	1 (0.1)		
Bipolar disorder	1 (0.3)	1 (0.1)		
Major depression	1 (0.3)	1 (0.1)		
Psychosis NOS	0 (0.0)	3 (0.3)		
Other specify	3 (0.8)	0 (0.0)		
Abuse/dependence, *n* (%)				
Alcohol	32 (8.4)	220 (20.4)	< 0.001	0.139
Drugs	42 (11.1)	258 (23.9)	< 0.001	0.139
PANSS scores, baseline mean (SD)				
Total	75.14 (18.43)	75.84 (17.25)	0.516	0.017
Positive	18.12 (5.56)	18.59 (5.66)	0.280	0.028
Negative	19.60 (6.69)	20.37 (6.30)	0.039	0.054
General psychopathology	37.41 (9.70)	36.88 (9.17)	0.381	−0.023

NOS Not Otherwise Specified, *PANSS* Positive and Negative Syndrome Scale, *SD* standard deviation

[a] *p*-Values and effect sizes associated with Mann–Whitney *U* tests (age) and χ^2 tests (all other variables)

These are all clinician-rated scales that assessed the severity of medication-induced akathisia, parkinsonism symptoms and dyskinesias, respectively.

An 'Adverse Events/Side Effects Form' was used to collect data about participants' perceptions of whether they experienced 18 well-established adverse effects commonly associated with at least one of the study antipsychotics (see Table 8). Given the focus on sex differences, we report on all of these, except menstrual irregularities, at end-of-phase.

Cardiometabolic effects of the drugs were monitored from baseline to end-of-phase. This included recording of weight and height to calculate changes in BMI. Laboratory tests described previously within the study protocol included a range of tests including blood testing for glucose, triglycerides, total cholesterol and prolactin [27]. As previously identified, the blood parameters were not uniformly collected in the fasting state, so they are regarded as random levels for both lipids and glucose [37].

2.3 Statistical Analysis

We report baseline demographic, clinical characteristics and medication compliance by sex. Dosage compliance is indicated first by final visit clinician-rated frequency: never/almost never [0–25% of the time]; sometimes [26–50% of the time]; usually [51–75% of the time] or always/almost always [76–100% of the time]. Second, means and standard deviations are presented for the proportion of capsules (%) taken at the final visit, based on the pill count in the returned bottle.

To compare efficacy and response between female and male participants, we compared change values, baseline to end-of-phase, for PANSS scores that had been calculated for participants in whom less than 20% of items were missing for total and subscale scores. Similarly, we compared change scores for the CGI-S and Calgary Depression Inventory. We also report differences in the following binary variable, which is available in the CATIE dataset: CGI-S response (Yes/No), which indicates whether patients met the criteria "CGI-S ≤ 3, or CGI-S $= 4$ and Change from Phase 1/1A baseline is at least -2".

To investigate the relative efficacy of treatment groups among female and male participants, we compared PANSS change scores among the five treatment groups, within each sample separately. To compare adverse reactions between female and male participants, we first report on the proportion of female and male participants meeting criteria for treatment-emergent severity indices for the AIMS, BRS and EPS. These variables are provided in the CATIE data, as treatment-emergent AIMS severity index value of ≥ 2; treatment-emergent AIMS severity index value of ≥ 1; treatment-emergent BRS global clinical assessment value of ≥ 3 and treatment-emergent EPS scale mean score value of ≥ 1. We also report changes (baseline to end-of-phase) in weight, % weight gain and BMI, patient-reported presence of side effects at end-of-phase, and changes (baseline to end-of-phase) in laboratory indicators, by sex.

We compared differences in continuous variables between female and male participants using Mann–Whitney U tests, as distributions were significantly non-normal. We report means and standard deviations for ease of interpretation. Effect sizes represent Cohen's d (z/sqrt(n)) where z is the standardised test statistics; effect sizes of 0.2, 0.5 and 0.8 or greater are considered small, medium and large, respectively [38]. For statistically significant differences, we report the standardised test statistic for the Mann–Whitney U test.

For categorical variables, we generated crosstabulations by sex. We report the statistical significance value associated with the χ^2 test. Continuity corrections were applied in the case of binary variables. Effect sizes for these results reflect Cohen's ϕ (effect sizes of 0.1, 0.3 and 0.5 or greater are considered small, medium and large, respectively). For statistically significant differences, we report the χ^2 value.

To compare PANSS change scores between the five treatment groups within the sample of female participants only, we used the Kruskal–Wallis test. We report means and standard deviations for ease of interpretation. Effect sizes represent $\eta^2[H] = (H - k + 1)/(n - k)$ where H is the test statistic and k is the number of groups; effect sizes of 0.01, 0.06 and 0.14 or greater are considered small, medium and large, respectively. For statistically significant differences, we report the standardised test statistic for the Kruskal–Wallis test.

Comparisons by sex were also conducted within each treatment group. These results are presented in the Electronic Supplementary Material (ESM).

To account for multiple tests, we applied the Bonferroni correction. We provide exact p-values and interpret only results with $p < 0.001$ as statistically significant. Where any crosstabulation has expected cell counts of less than 5, a footnote indicating this is included under the relevant table.

3 Results

In total, there were 1460 participants, 1080 were male and 380 were female, with female participants making up 26% of the sample. Baseline demographic and clinical characteristics by sex are shown in Table 1. A significantly higher proportion of male participants (220/1080) than female participants (32/380) reported alcohol ($\chi^2 = 27.27$, $p < 0.001$) abuse/dependence; the same was true for drug abuse/dependence (258/1080 vs 42/380; $\chi^2 = 27.59$, $p < 0.001$). At baseline, there were no significant differences between male and female participants in PANSS scores (Table 1) or

the proportion of participants in PANSS score categories (Table 1 of the ESM).

There was no significant difference between female and male participants in terms of compliance to medication dosage in the overall sample (Table 2) or in each treatment group (Table 2 of the ESM). There was also no significant difference between female and male participants in each treatment group, in terms of dosage compliance at final visit, or average and modal dose over the course of the trial (Table 2 of the ESM).

3.1 Efficacy and Response Differences Between Female and Male Participants

Changes in PANSS scores from baseline to end-of-phase by sex are shown in Table 3. The overall trend was for a greater reduction in PANSS scores in female participants, although this difference was not significant. There were also no significant differences in PANSS change scores between female and male participants in any of the treatment groups (Table 3 of the ESM).

There were no significant differences between male and female participants in terms of changes in CGI-S or Calgary Depression Scale scores overall (Table 4) or within treatment groups (Table 4 of the ESM). Using CGI-S ≤ 3 or CGI-S $= 4$ and Change from Phase 1/1A baseline is at least -2 as an indicator of CGI-S response, there were no significant differences in the proportion of female participants (101/274, 36.9%) and male participants (269/781, 34.4%) who met these criteria ($p = 0.517$). No significant differences in proportions were identified in any of the treatment groups when analysed separately.

3.2 Relative Efficacy Across Antipsychotics

No significant differences (adjusted $p < 0.001$) across different antipsychotics were observed among female participants. Among male participants, the only significant difference was that a greater improvement in PANSS positive scores was reported in the olanzapine group than in the quetiapine group ($p < 0.001$) (Table 5).

3.3 Differences in Adverse Reactions by Sex

There were no significant differences in the proportion of male and female participants who showed treatment-emergent severity indices for AIMS, BRS and EPS, in the overall sample (Table 6) or in any of the treatment groups (Table 5 of the ESM). Changes in weight, percentage weight gain and changes in BMI by sex are shown in Table 7. There were no significant differences overall (Table 7) or in any of the treatment groups (Table 6 of the ESM).

The presence of patient-reported side effects at end-of-phase are shown in Table 8. A significantly higher proportion of female than male participants reported the following side effects at end-of-phase: constipation (77/280 vs 121/783, $\chi^2 = 18.960$, $p < 0.001$), dry mouth (140/280 vs 299/784, $\chi^2 = 11.494$, $p < 0.001$), gynecomastia/galactorrhea (30/280 vs 26/784, $\chi^2 = 21.187$, $p < 0.001$), incontinence/nocturia (44/280 vs 59/784, $\chi^2 = 14.900$, $p < 0.001$), and weight gain (104/280 vs 185/783, $\chi^2 = 18.356$, $p < 0.001$).

Within the risperidone treatment group, a significantly higher proportion of female than male participants reported the following side effects at end-of-phase: gynecomastia/galactorrhea (13/69 vs 5/183, $\chi^2 = 17.249$, $p < 0.001$) and incontinence/nocturia (19/68, vs 14/183, $\chi^2 = 16.143$, $p < 0.001$). No significant differences were identified within the other treatment groups (see Table 7 of the ESM).

Finally, in Table 9, we show changes in laboratory results by sex, from baseline to end-of-phase. None of these changes was significant overall (Table 8) or within individual treatment groups (Table 8 of the ESM) except for within the risperidone treatment group, which showed a significantly greater increase in prolactin levels ($z = -3.949$, $p < 0.001$)

Table 2 Dosage compliance by sex: mean (SD)

	Total *n*	Female participants	Male participants	p[a]	ϕ/d
Clinician-rated compliance at final visit, *n* (%)	1046			0.901	0.024
Never/almost never [0–25% of the time]		22 (8.1)	65 (8.4)		
Sometimes [26–50% of the time]		16 (5.9)	54 (7.0)		
Usually [51–75% of the time]		25 (9.2)	64 (8.3)		
Always/almost always [76–100% of the time]		208 (76.8)	592 (76.4)		
Proportion of capsules (%) taken (based on pill count in returned bottle) at final visit Mean (SD)	988	84.76 (25.87)	84.93 (25.87)	0.634	0.013

SD standard deviation

[a] *p*-Values and effect sizes associated with Mann–Whitney *U* tests

among female participants ($n = 61$) than male participants ($n = 159$).

4 Discussion

While there has been much speculation on likely sex differences for antipsychotics, in this study, we did not find any significant evidence for overall group differences for antipsychotics and sex differences in efficacy and response within a trial of antipsychotics in the context of treatment of schizophrenia. This study did find that adverse reactions and when individual antipsychotics were examined there were limited notable sex differences. In self-reported adverse reactions, there were higher rates of dry mouth, constipation, incontinence/nocturia, self reported weight gain, and gynaecomastia/galactorrhea in female participants, and then also gynaecomastia/galactorrhea and incontinence/nocturia specifically in those female participants randomised to risperidone. There were no sex differences found in common laboratory

Table 3 Change in PANSS scores (baseline to end-of-phase) by sex

	Total *n*	Female participants Mean (SD)	Male participants Mean (SD)	p^a	*d*
Total score	1066	− 3.81 (18.2)	− 1.74 (17.76)	0.179	0.041
Positive Scale	1068	− 0.8 (6.08)	− 0.68 (5.91)	0.919	−0.003
Negative Scale	1068	− 1.18 (6.31)	− 0.36 (60.3)	0.032	0.066
General Psychopathology Scale	1066	− 1.67 (9.28)	− 0.71 (9.29)	0.219	0.038

PANSS Positive and Negative Syndrome Scale, *SD* standard deviation

[a]*p*-Values and effect sizes associated with Mann–Whitney *U* tests

Table 4 Changes in CGI-S and Calgary Depression rating scale scores (baseline to end-of-phase) by sex

	Total *n*	Female participants Mean (SD)	Male participants Mean (SD)	p^a	*d*
CGI-S score change	1050	− 0.11 (1.18)	− 0.07 (1.1)	0.363	0.028
Calgary Depression Rating Scale score change	1063	− 0.31 (4.39)	− 0.28 (4.18)	0.677	− 0.013

CGI-S Clinical Global Impression Severity scale, *SD* standard deviation

[a]*p*-Values and effect sizes associated with Mann–Whitney *U* tests

Table 5 Relative efficacy of treatments as reflected by differences in PANSS change scores, by sex

PANSS scores	Olanzapine Mean (SD)	Perphenazine Mean (SD)	Quetiapine Mean (SD)	Risperidone Mean (SD)	Ziprasidone Mean (SD)	p^a	η^2
Female participants							
Total	− 8.39 (18.12)	− 9.33 (18.90)	− 1.74 (14.86)	0.88 (17.84)	0.13 (19.67)	0.001	0.052
Positive	− 2.66 (5.11)	− 2.04 (6.80)	− 0.63 (4.02)	0.76 (6.03)	1.11 (8.04)	0.003	0.043
Negative	− 2.14 (6.65)	− 2.65 (6.25)	− 0.56 (5.85)	− 0.03 (6.40)	− 0.55 (5.94)	0.052	0.019
General psychopathology	− 3.59 (9.14)	− 4.63 (9.50)	− 0.54 (8.05)	0.77 (10.02)	− 0.42 (8.21)	0.005	0.039
Male participants							
Total	− 5.93 (15.81)	− 0.13 (16.89)	0.15 (17.90)	− 2.71 (19.87)	1.41 (16.53)	0.007	0.013
Positive	− 2.33 (4.89)	− 0.36 (5.94)	0.44 (6.34)	− 0.80 (6.07)	− 0.20 (5.73)	< 0.001	0.020
Negative	− 1.15 (6.29)	− 0.23 (5.28)	− 0.31 (6.01)	− 0.22 (6.65)	0.54 (5.34)	0.471	− 0.001
General psychopathology	− 2.44 (8.10)	0.46 (9.11)	0.02 (9.36)	− 1.68 (10.28)	1.07 (8.81)	0.012	0.011

PANSS Positive and Negative Syndrome Scale, *SD* standard deviation

[a]*p*-Values and effect sizes associated with Kruskal–Wallis tests. Significant differences in post-hoc pairwise comparisons are reported in the text where adjusted $p < 0.001$

Table 6 Proportion of female and male participants meeting criteria for treatment-emergent severity indices for validated movement side-effect indicators (baseline to end-of-phase) by sex

	Total *n*	Female participants *n* (%)	Male participants *n* (%)	p^a	ϕ
Treatment-emergent AIMS severity index value of ≥ 2	1452	47 (12.5)	128 (11.9)	0.845	−0.008
Treatment-emergent AIMS severity index value of ≥ 1	1452	67 (17.8)	192 (17.9)	1.000	0.001
Treatment-emergent BRS global clinical assessment value of ≥ 3	1452	27 (7.2)	54 (5.2)	0.154	−0.041
Treatment-emergent EPS scale mean score value of ≥ 1	1452	15 (4.0)	64 (6.0)	0.186	0.038

AIMS Abnormal Involuntary Movement Scale, *BRS* Barnes Rating Scale for Akathisia, *EPS* Simpson–Angus Extrapyramidal Side Effects Scale

[a]*p*-Values and effect sizes associated with χ^2 tests

Table 7 Changes in weight/BMI (baseline to end-of-phase) by sex

	Total *n*	Female participants Mean (SD)	Male participants Mean (SD)	p^a	*d*
Change in weight from baseline (kg)	1028	2.58 (17.03)	2.27 (17.03)	0.700	−0.012
% weight gain from baseline	1028	1.83 (9.33)	1.57 (7.88)	0.675	−0.013
Change in BMI from baseline	1023	0.49 (2.87)	0.35 (2.49)	0.453	−0.023

BMI body mass index, *SD* standard deviation

[a]*p*-Values and effect sizes associated with Mann–Whitney *U* tests

Table 8 Self-reported presence of side effects at end-of-phase by sex ($n = 1062$)

	Female participants *n* (%)	Male participants *n* (%)	p^a	ϕ
Akathisia	95 (34.1)	241 (30.8)	0.350	0.313
Akinesia	81 (29.0)	204 (26.1)	0.382	−0.029
Constipation	77 (27.5)	121 (15.5)	< 0.001	−0.136
Dry mouth	140 (50.0)	299 (38.1)	< 0.001	−0.106
Gynecomastia/galactorrhea	30 (10.7)	26 (3.3)	< 0.001	−0.146
Hypersomnia	46 (16.4)	122 (15.6)	0.806	−0.010
Incontinence/nocturia	44 (15.7)	59 (7.5)	< 0.001	−0.122
Insomnia	103 (36.9)	244 (31.2)	0.094	−0.054
Orthostatic faintness	85 (28.9)	211 (26.9)	0.568	−0.020
Sex drive	53 (19.0)	163 (20.8)	0.574	0.020
Sexual arousal	44 (15.8)	162 (20.7)	0.093	0.054
Sexual orgasm	40 (14.4)	130 (16.7)	0.419	0.028
Sialorrhea	46 (16.4)	102 (13.0)	0.187	−0.043
Skin rash	34 (12.1)	67 (8.5)	0.100	−0.054
Sleepiness	138 (49.5)	133 (42.4)	0.050	−0.062
Urinary hesitancy	24 (8.6)	79 (10.1)	0.540	0.022
Weight gain	104 (37.1)	185 (23.6)	< 0.001	−0.134

[a]*p*-Values and effect sizes associated with χ^2 tests

parameters at the end of the trial of antipsychotics, including metabolic markers as well as in objective measures of weight gain and clinician-rated movement measures. When individual antipsychotics were examined, however, female participants taking risperidone had significantly higher prolactin levels than male participants.

A recent systematic review examined evidence for sex differences in adverse drug reactions for a number of agents,

including olanzapine, clozapine, aripiprazole, risperidone and amisulpride [17]. This review found sex differences in adverse reactions for amisulpride, clozapine and olanzapine but limited evidence for sex differences for either aripiprazole or risperidone [17]. For olanzapine, there was less weight gain in female participants than male participants. However, the adverse reactions reported in the included studies were limited, for example, risperidone studies were limited to reports of weight gain, parkinsonism and dystonia. In addition to this systematic review, a secondary analysis was undertaken of a recent clinical trial, finding sex differences in adverse reactions to amisulpride, with higher prolactin levels and BMI increases in female individuals versus male individuals, but female individuals also had 72% higher dose-corrected serum levels than male individuals for amisulpride ($p = 0.019$) [15]. Our study reports on olanzapine, quetiapine, risperidone, ziprasidone and perphenazine and finds significant differences in self-reported adverse reactions and then specifically for risperidone in female participants and a trend towards improved efficacy for olanzapine and perphenazine for female participants. Overall, this suggests the importance of ongoing replication and reporting of sex differences as part of clinical trials undertaken for antipsychotics. Nevertheless, the higher self-reported adverse effect rates in female versus male individuals may be one explanation why two independent database studies, one in Finland [39] and one in the UK [40], found significantly higher non-adherence rates to antipsychotics in female than male individuals. A reason why this adverse effect difference did not translate into observable adherence differences in the CATIE sample could well be that patients in the clinical trial had more surveillance and knew that their adherence was being assessed, whereas the database studies used passively monitored medication dispensation data. Moreover, both these database studies followed patients from a first episode of illness, while the CATIE sample had more chronic illness. More research is needed into the relationship between disease stage, adverse effects and non-adherence as well as their effect on treatment effectiveness.

There has been consideration of possible sex differences in both the course and treatment of schizophrenia and other psychotic disorders, in response to: evidence of later onset of illness in female individuals, emerging evidence that oestrogen may reduce the response to antipsychotics during menopause as well as increasing the likelihood of psychotic symptoms, and the overall increased burden of adverse reactions in female individuals for many pharmacological agents [5, 6, 41, 42]. Managing schizophrenia in female individuals is also complicated by differences across the lifespan including adrenarche, menstruation, menopause, and the possibility of pregnancy and potential impacts on pregnancy outcomes, making the choice of agent a more complex risk-benefit analysis [43, 44]. Overall, it is likely clinical care can be improved by understanding any potential differences in treatment response, adverse reactions, and risks for female individuals as part of everyday clinical practice. Yet research into sex differences in efficacy and adverse reactions for antipsychotics, as well as evidence to inform understanding the risks associated with their use in pregnancy and also in menopause is limited. One path to building an improved evidence base is to utilise data collected as part of a large clinical trial such as this study has done, to inform this ongoing area of research.

In previous studies of risperidone, while sex differences in treatment efficacy have not consistently been identified [45], there has been evidence suggesting female individuals have differences in prolactin and other adverse effects, which may be influenced by the interaction between sex and pharmacogenetics [46]. Our study does not have data that can explain any potential pharmacokinetic or pharmacodynamic sex differences that might underpin our findings for risperidone. However, it is well established that female individuals have key differences in drug absorption, protein binding, volume of distribution and metabolism [42] as well as sex-related differences in cytochrome P450 [47]. Hepatic enzyme activity is indeed influenced by sex differences and also critical to understanding the efficacy and

Table 9 Changes in laboratory indicators from baseline to end-of-phase by sex

	Total *n*	Female participants Mean (SD)	Male participants Mean (SD)	p^a	*d*
Glucose (mg/dL)*	970	5.16 (45.06)	−0.17 (41.86)	0.281	0.037
Triglycerides (mg/dL)*	974	2.13 (126.41)	−12.28 (166.51)	0.064	−0.059
Total cholesterol*(mg/dL)	974	−4.71 (45.31)	−6.18 (43.71)	0.355	−0.030
Prolactin (ng/mL)	949	−4.32 (38.54)	−1.52 (16.04)	0.103	0.053

SD standard deviation

*Random levels

[a] *p*-values and effect sizes associated with Mann–Whitney *U* tests

adverse reactions of many psychopharmacological agents including antipsychotics [42, 47].

A limitation of this study was the lack of information on the perimenopausal and menopausal status of participants. A recent review identified that changes in oestrogen during menopause are associated with reduced synthesis of specific enzymes that metabolise antipsychotics, with evidence of reduced antipsychotic efficacy occurring during menopause [41]. As the average age of female participants in our sample was 42 years, it is likely a number of participants were perimenopausal. A further limitation is that blood parameters for lipids and glucose were not necessarily taken in the fasting state and are therefore limited in interpretation, as previous authors have noted [37]. Additionally, a number of previous limitations have been commented on with CATIE data [29, 48], including the study sample was not representative of all subgroups of schizophrenia, a lack of clarity of inclusion criteria and dosage scheduling, inadequate statistical power for certain subgroup comparisons, diversity in study settings and a relatively short mean duration of staying in the trial that was originally designed to last for 18 months, which limits the identification of delayed adverse effects.

5 Conclusions

While our findings demonstrate only limited sex differences in therapeutic response and adverse reactions to antipsychotics as measured within CATIE, the ongoing need remains for investment into understanding whether any sex differences exist, and if so, what these may be. Other areas of research examining sex differences in human health suggest these differences are likely to be complex. Data are limited, with female individuals only relatively recently included in pharmacological trials, as well as the use of female animal models of human health, suggesting there is still much to discover [13, 49]. Moreover, to better understand antipsychotic use in female individuals requires study of their interactions with endogenous and exogenous sex steroid hormones, which change during adrenarche, menarche, pregnancy and menopause, as well as with hormonal contraceptives and hormone replacement therapy for female individuals [5, 50]. Furthermore, recent research also supports the consideration of how genetics may also underpin sex differences in drug metabolism as an emerging important consideration in future drug research [51]. Moreover, sex differences in patient-reported outcomes, including regarding the experience and value that specific symptoms and their improvement or persistence for certain adverse effects in male and female individuals, should be explored further. Finally, studies investigating sex differences should also focus on the complex factors that lead to medication non-adherence, which needs to be measured objectively.

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Declarations

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Conflict of Interest Cristoph U. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax and Quantic. Megan Galbally, Karen Wynter, Dan Siskind, Korinne Northwood and Susanna Every-Palmer have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval As outlined in the protocol paper for CATIE, a CATIE Ethics Committee, chaired by Paul Appelbaum, reviewed all human subjects ethics considerations [27].

Consent to Participate As outlined in the protocol paper, all prospective research participants were screened for decisional capacity [27]. Those who demonstrated adequate decisional capacity to participate in this research study were allowed to decide whether to enter the study. Those who choose to participate signed a consent form and entered the screening phase.

Consent for Publication Not applicable.

Data Availability Data are available from a data repository.

Code Availability IBM SPSS Statistics syntax is available from the first author on request.

Author Contributions MG, DS and SE-P contributed to the study conception and design. Data access was provided by CC and DS. Material preparation and data analysis were performed by KW. The first draft of the manuscript was written by MG and KW and all authors commented on previous versions of the manuscript. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work.

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Authors and Affiliations

Megan Galbally[1,2] · Karen Wynter[1,3] · Dan Siskind[4,5] · Christoph U. Correll[6,7,8,9] · Korinne Northwood[4,5] · Susanna Every-Palmer[10]

✉ Megan Galbally
megan.galbally@monash.edu

[1] School of Clinical Sciences, Monash Medical Centre, Monash University, 246 Clayton Road, Clayton, VIC 3168, Australia

[2] Health Futures Institute, Murdoch University, Perth, WA, Australia

[3] Faculty of Health, Deakin University, Geelong, VIC, Australia

[4] Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

[5] Metro South Addiction and Mental Health Hospital and Health Service, Brisbane, QLD, Australia

[6] Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA

[7] Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

[8] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany

[9] German Center for Mental Health (DZPG), Partner Site Berlin, Berlin, Germany

[10] Department of Psychological Medicine, University of Otago, Wellington, New Zealand