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Systematic Review

Sex Selection Bias in Schizophrenia Antipsychotic Trials—An Update Systematic Review

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Abstract: The lack of female participation in antipsychotic trials for schizophrenia poses an important issue regarding its applicability, with direct and real-life repercussions to clinical practice. Here, our aim is to systematically review the sampling sex bias among randomized clinical trials (RCTs) of second-generation antipsychotics—namely risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole—as an update to a previous 2005 review. We searched MEDLINE and the Cochrane database for studies published through 7 September 2020 that assessed adult samples of at least 50 subjects with a diagnosis of schizophrenia, schizophrenia spectrum disorder, or broad psychosis, in order to investigate the percentage of women recruited and associated factors. Our review included 148 RCTs, published from 1993 to 2020, encompassing 43,961 subjects. Overall, the mean proportion of women was 34%, but only 17 trials included 50% or more females. Younger samples, studies conducted in North America, pharmaceutical funding and presence of specific exclusion criteria for women (i.e., pregnancy, breast-feeding or lack of reliable contraceptive) were associated with a lower prevalence of women in the trials. Considering the possible different effects of antipsychotics in both sexes, and our lack of knowledge on the subject due to sampling bias, it is imperative to expand actions aimed at bridging this gap.

Keywords: second generation antipsychotics; clinical trials; schizophrenia; sex bias

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1. Introduction

Sampling bias regarding female participation in clinical trials has been a longstanding issue, mainly because it raises concerns about the applicability of findings for women [1]. Such sex bias is a consequence of researchers' erroneous assumption that female individuals present too much data variability due to their reproductive cycle and that men can adequately serve as representatives for both sexes. However, studies [2] have shown that men exhibit hormonal variability equal to or even greater than women and, more importantly, robust findings point out that pharmacokinetics and pharmacodynamics differ between sexes, increasing the need to further investigate drug effects, specifically in women.

Several research funding centers and peer-review journals have defined sex and gender analysis as a prerequisite of scientific validity. The objective was to improve reproducibility and validation of research findings and to promote inclusion and transparency [3]. More recently, a National Institutes of Health (NIH) initiative established the equal representation of sexes for all grant proposals as a requirement, which represented a further step towards the reduction of sex bias [4–6].

This review aims to investigate sex bias, specifically in antipsychotic trials for schizophrenia patients. Schizophrenia is a mental illness that affects both men and women similarly in terms of prevalence [7] and, although antipsychotics represent the only pharmacological

treatment supported by scientific evidence, there is a broad gap concerning the recruitment of women in antipsychotic trials [8,9].

Chaves and Seeman (2006) [8] performed a systematic review of 67 randomized clinical trials testing second generation antipsychotics and found the median proportion of women was 33% among the samples. Overall, the study included 21,190 individuals, out of which less than a third were women (N = 6825, 32.2%). Several factors were associated to relative paucity of females in these trials: (1) strict inclusion criteria for women, especially in studies with ziprasidone (i.e., use of reliable contraception or surgical sterilization, post-menopause for 2 years minimum, or exclusion of pregnancy or lactation); (2) selection of inpatients exclusively; (3) studies performed in North America, when compared to other continents; and (4) younger samples.

A more recent review investigated participation of women in long-acting antipsychotic trials, and reached similar results [9]. Females were again underrepresented, as part of 36% of the total sample. Furthermore, Santos-Casado et al. identified that, out of the 40 trials included in the review, six studies analyzed the main outcomes of interest divided by sex, and only three of those discussed the results separately for women.

Such lack of attention to women represents an even larger issue in light of the sex differences in schizophrenia, which are consistently reported in the literature. One of the most well-described regards illness onset: although the first psychotic episode generally occurs in young adults, women present a higher age of onset and a second peak of incidence in the perimenopause period [10–12]. This means that estrogen might play an important role in the pathogenesis of schizophrenia; in fact, previous studies suggest that estrogen may exert neuroprotective effects in the brain and reduce inflammatory responses [13].

There are findings suggesting that clinical presentation may vary, too, with women manifesting more affective symptoms and men more negative symptoms [14,15]. Additionally, there might be differences related to prognosis, as studies often report that women's premorbid functioning and outcomes in schizophrenia are better than men's, with lower rates of hospitalization, suicide and social impairment [16].

Response to antipsychotic treatment appears to differ between sexes as well. The effective dose of antipsychotic is significantly lower for woman and the influence of sex hormones on psychotropics' metabolism and mechanism of action could explain such differences [17]. The cytochrome (CYP) system involved in the metabolism of antipsychotics is influenced by sex hormones; for instance, premenopausal women, due to the higher estrogen levels, present lower activity of the isoenzyme CYP1A2, responsible for olanzapine and clozapine metabolization, resulting in increased plasma concentrations of these antipsychotics when compared to men [18]. Differences in dopamine transmission [19] can also influence the response to antipsychotics. This was reported in a recent investigation about how D_2 receptor occupancy varies between sexes [20], which showed that men required twice the dose of olanzapine to achieve the same D_2 occupancy as women. Lastly, the female body has more subcutaneous fat, that slows the absorption of drugs, thus increasing the accumulation of lipophilic medications, such as antipsychotics, extending their half-life. This possibly also explains why women can be more vulnerable than men to metabolic syndrome and cardiovascular complications during antipsychotic treatment. On the other hand, such contrast appears to fade after menopause, suggesting that pharmacokinetic and pharmacodynamic properties probably vary across reproductive periods [21]—but far too little data is available on antipsychotic treatments in postmenopausal women.

Finally, the exclusion of pregnant or breast-feeding women from trials is also a problem, although there are ethical reasons for this as well. Recommendations of monotherapy treatment with the lowest effective dose and individualized risk–benefit analyses are widely spread [22]. However, during pregnancy and postpartum, psychotic symptoms frequently oscillate [23] and represent an important burden to perinatal women, but research on psychiatric illnesses during this period are still lacking [22]. Consequently, it is still unclear how symptoms are set off by pregnancy and childbirth, and improved, evidence-based treatment for these women are much needed.

Regardless of the evidence suggesting considerable differences between female and male metabolisms when both therapeutical and side effects are reported, studies rarely acknowledge the distinctions between gender. These characteristics could be important to determine more appropriate posology for women, the lack of which might directly influence the effect of medications [24]. Yet, recent treatment guidelines for schizophrenia do not differentiate antipsychotic treatment by sex [15,25].

Despite international recommendations to boost female inclusion and attempts to reduce sex bias in research, the relative lack of women in clinical trials may still represent a matter of concern. Thus, to investigate if the ratio of men to women in antipsychotic trials remains improperly high, we conducted an update to the review carried out by Chaves and Seeman (2006) [8].

2. Results

In total, 148 studies, published between 1993 and 2020, were included in our review—67 from the original review performed by Chaves and Seeman (2006) [8] and 81 retrieved in this update, published from 2005 onwards (see Figure 1 for details on search results and Table S1 for information on included studies). Table 1 presents the general characteristics of the studies. The entire sample encompassed 43,961 subjects, 28,956 (66%) men and 15,005 (34%) women, with a mean age of 36.7 years (SD = 7, ranging from 21.5 to 72) and mean trial duration of 146.5 days (SD = 196, median = 56 days, ranging from 1 to 1095). Most studies received pharmaceutical funding (N = 109, 73.6%).

Overall, women represented 34% of the whole sample, with a mean proportion (number of women/all participants) of 34.1% (SD = 0.1), ranging from 0 (one study) to 100% (also a single study), although only 17 (11.4%) trials provided a sample composed of 50% or more females.

Table 2 shows how the proportion of women recruited in the studies differed according to trial and sample characteristics, taking the categorical variables into account. Full results regarding the multiple comparisons can be found in Table S2. Trials published before the year 2000 enrolled a lower proportion of women than those from the next two decades ($F = 3.6$, $p = 0.03$). The studies financed by the pharmaceutical industry also presented lower participation of women when compared to the studies with non-pharmaceutical funding ($F = 9.31$, $p < 0.01$). Regarding location, we found trials in North America had the lowest mean proportion of women when compared to Asia, Europe, Latin America and Oceania, as well as the ones conducted in more than one continent ($F = 12.1$, $p < 0.01$), but no differences emerged among these five categories.

Table 1. General characteristics of included studies.

	N	Mean (SD)	Median	Range
Total sample	43,961	297 (277.5)	248.5	50–1995
Men	28,956	195.7 (183.8)	154.5	0–1295
Women	15,005	101.4 (102.9)	78.5	0–700
Proportion of women	-	34.1% (0.1)	34.4%	0–100%
Duration of trial (days)	-	146.5 (196)	56	1–1095
Age (years) †	-	36.7 (7)	37	21.5–72

† Data from 144 studies.

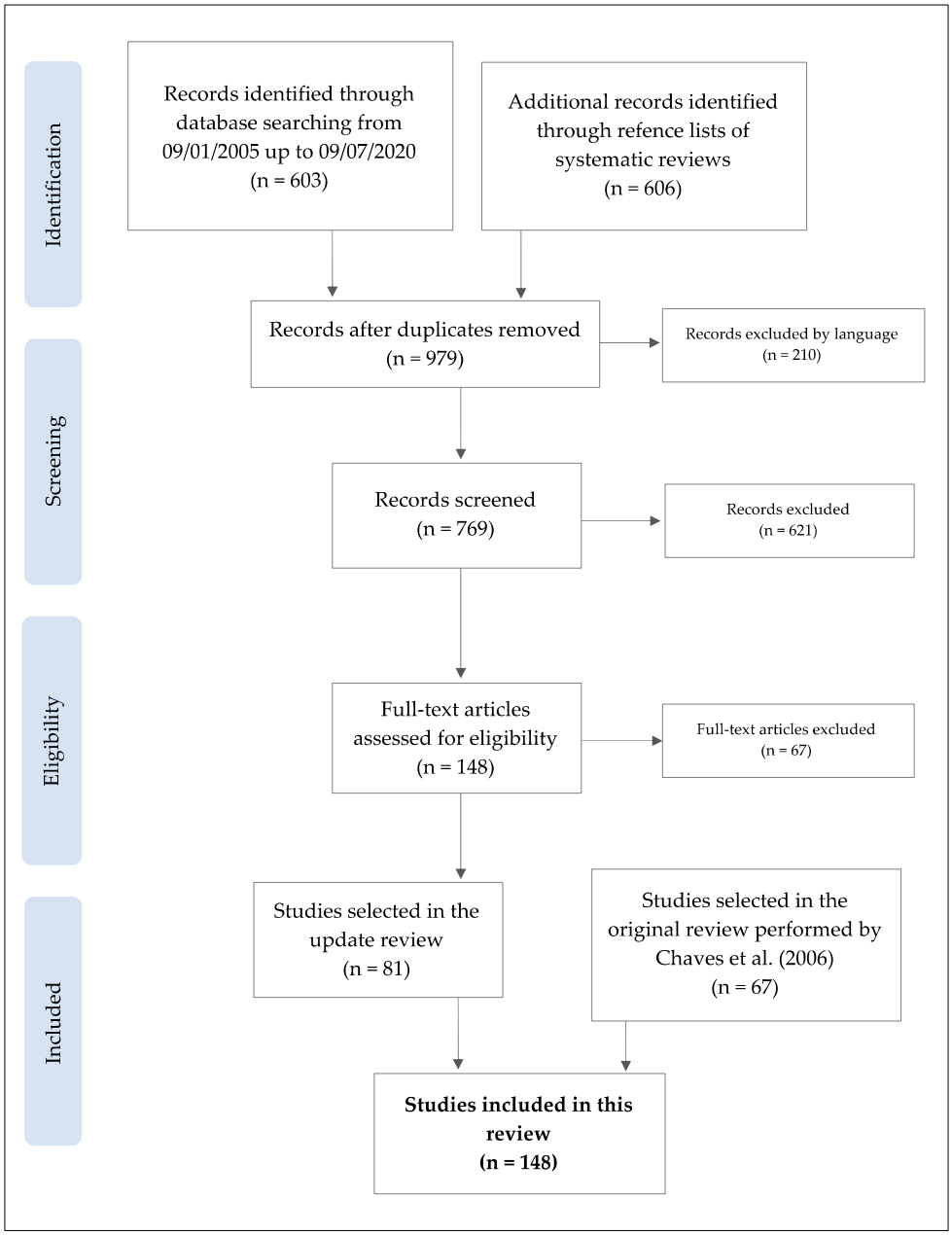

Figure 1. PRISMA flowchart.

Eighty-five studies stipulated inclusion criteria for women, excluding, for example, pregnancy, breast-feeding or lack of reliable contraception. Such studies presented lower female participation than the trials that did not explicitly report such a requirement ($F = 5.41$, $p = 0.02$). Trials conducted with inpatients also had lower means ($F = 3.83$, $p = 0.02$). No significant differences between the categories were found concerning sample size ($F = 1.32$, $p = 0.27$), number of study centers ($F = 2.12$, $p = 0.15$), symptom presentation ($F = 1.59$, $p = 0.21$), number of episodes ($F = 1.11$, $p = 0.33$) and diagnosis included ($F = 1.5$, $p = 0.23$).

When evaluating the antipsychotic treatments individually, results showed that trials testing olanzapine presented a higher proportion of women ($F = 7.95$, $p < 0.01$), and a trend value emerged for risperidone ($F = 3.83$, $p = 0.06$) and ziprasidone ($F = 3.57$, $p = 0.06$), but with a lower mean in the ziprasidone group. Trials in which an FGA ($F = 4.65$, $p = 0.03$) or placebo ($F = 12.21$, $p < 0.01$) were used in the comparator arm also had lower female participation, although the difference for the FGA variable was no longer significant after year of publishing was added as a covariate in the model ($F = 1.57$, $p = 0.21$).

Table 2. Proportion of women by trial characteristics and one-way analysis of variance (ANOVA).

	Number of Trials N (%)	Total Sample N (%)	Proportion of Women Mean (SD)	Sig.	Post hoc Comparisons †
Decade of publication					
≤2000	28 (18.9%)	9188 (20.9%)	28.7% (0.11)	$p = 0.03$ *	≤2000 vs. 2001–2010: $p = 0.02$ ≤2000 vs. ≥2011: $p = 0.02$
2001–2010	73 (49.3%)	23,034 (52.4%)	36% (0.11)		
≥2011	47 (31.8%)	11,739 (26.7%)	36.4% (0.17)		
Funding					
Pharmaceutical	109 (73.6%)	35,015 (79.7%)	33.6% (0.12)	$p = 0.01$ *	Pharm. vs. Non-pharm.: $p < 0.01$
Non-pharmaceutical	25 (16.9%)	6605 (15.0%)	42.4% (0.17)		
Not reported	14 (9.5%)	2341 (5.3%)	30.2% (0.14)		
Sample size					
50–100	31 (20.9%)	2313 (5.3%)	38% (0.19)	$p = 0.27$	
101–200	35 (23.6%)	5092 (11.6%)	35.3% (0.14)		
201–500	65 (43.9%)	21,796 (49.6%)	32.5% (0.10)		
>501	17 (11.5%)	14,760 (33.6%)	36.4% (0.08)		
Location					
Asia	28 (21.4%)	5116 (11.6%)	44.3% (0.18)	$p = 0.01$ *	N. America vs. Asia: $p < 0.01$ N. America vs. Europe: $p < 0.01$ N. America vs. Other: $p < 0.01$ N. America vs. Multiple: $p < 0.01$ Asia vs. Multiple: $p < 0.01$
Europe	23 (17.6%)	3820 (8.7%)	38.6% (0.10)		
Other	4 (3.1%)	427 (1.0%)	45% (0.20)		
North America	34 (26.0%)	9854 (22.4%)	24.9% (0.07)		
Multiple continents	42 (32.1%)	20,937 (47.6%)	33.7% (0.09)		
Number of study centers					
Single center	17 (11.5%)	1630 (3.7%)	38.9% (0.21)	$p = 0.15$	
Multicenter	123 (83.1%)	40,684 (92.5%)	33.9% (0.12)		
Not reported	8 (5.4%)	1647 (3.7%)	39.6% (0.15)		
Inclusion criteria for women					
Yes	85 (57.4%)	26,174 (59.5%)	32.2% (0.13)	$p = 0.02$ *	Yes vs. Not specified: $p = 0.02$
Not specified	63 (42.6%)	17,787 (40.5%)	38.2% (0.14)		
Symptom presentation					
Stable	22 (14.9%)	5557 (12.6%)	38.8% (0.09)	$p = 0.21$	
Acute	98 (66.2%)	29,516 (67.1%)	33.5% (0.14)		
Both	18 (12.2%)	6889 (15.7%)	36.6% (0.16)		
Not reported	10 (6.8%)	1999 (4.5%)	34.5% (0.15)		
Setting					
Inpatient	63 (42.3%)	15,194 (34.6%)	31.1% (0.15)	$p = 0.02$ *	Inpatient vs. Outpatient: $p = 0.04$ Inpatient vs. Both: $p = 0.02$
Outpatient	26 (17.4%)	7566 (17.2%)	36.5% (0.11)		
Both	37 (24.8%)	15,282 (34.8%)	38% (0.13)		
Not reported	23 (15.4%)	5919 (13.5%)	36.4% (0.12)		
Number of psychotic episodes					
First episode	16 (10.8%)	2922 (6.6%)	32.7% (0.13)	$p = 0.33$	
Multiple episode	56 (37.8%)	17,294 (39.3%)	36.4% (0.16)		
Both	38 (25.7%)	12,786 (29.1%)	32.3% (0.11)		
Not reported	38 (25.7%)	10,959 (24.9%)	35.6% (0.12)		
Diagnosis included					
Only SCZ	84 (56.8%)	27,733 (63.1%)	35.1% (0.14)	$p = 0.23$	
SCZ spectrum	50 (33.8%)	13,875 (31.6%)	35.8% (0.12)		
Broad psychosis	14 (9.5%)	23,53 (5.4%)	28.9% (0.13)		
Use of risperidone					
Yes	66 (44.9%)	18,732 (42.6%)	37.2% (0.15)	$p = 0.06$	
No	81 (55.1%)	24,740 (56.3%)	32.9% (0.11)		
Use of olanzapine					
Yes	69 (46.9%)	19,016 (43.3%)	38.1% (0.14)	$p = 0.01$ *	Yes vs. No: $p < 0.01$
No	78 (53.1%)	24,456 (55.6%)	31.9% (0.12)		
Use of quetiapine					
Yes	29 (19.7%)	8523 (19.4%)	35% (0.12)	$p = 0.94$	
No	118 (80.3%)	34,949 (79.5%)	34.8% (0.14)		
Use of ziprasidone					
Yes	27 (18.4%)	7895 (18.0%)	30.4% (0.12)	$p = 0.06$	
No	120 (81.6%)	35,577 (80.9%)	35.8% (0.14)		
Use of aripiprazole					
Yes	29 (19.6%)	10,448 (23.8%)	37.5% (0.10)	$p = 0.22$	
No	119 (80.4%)	33,513 (76.2%)	34.1% (0.14)		
Use of FGA					
Yes	52 (35.4%)	16,550 (37.6%)	31.6% (0.12)	$p = 0.03$ *	Yes vs. No: $p = 0.03$
No	95 (64.6%)	26,922 (61.2%)	36.6% (0.14)		
Use of additional SGAs ††					
Yes	29 (19.7%)	9372 (21.3%)	36.8% (0.11)	$p = 0.38$	
No	118 (80.3%)	34,100 (77.6%)	34.3% (0.14)		

Table 2. *Cont.*

	Number of Trials N (%)	Total Sample N (%)	Proportion of Women Mean (SD)	Sig.	Post hoc Comparisons †
Use of placebo					
Yes	37 (25.0%)	13,070 (29.7%)	28.3% (0.11)	$p = 0.01$ *	Yes vs. No: $p < 0.01$
No	111 (75.0%)	30891 (70.3%)	36.9% (0.14)		
Type of administration					
Oral	121 (81.8%)	34,361 (78.2%)	35.3% (0.14)		
Injectable	13 (8.8%)	5320 (12.1%)	34% (0.11)	$p = 0.49$	
Both	14 (9.5%)	4280 (9.7%)	30.8% (0.14)		
Antipsychotic of interest					
Multiple SGAs	77 (52.0%)	21,687 (49.3%)	38.5% (0.14)	$p = 0.01$ *	Single SGA vs. Mult. SGAs: $p < 0.01$
Single SGA	71 (48.0%)	22,274 (50.7%)	30.7% (0.12)		
Comparator arm					
Only SGA	66 (44.6%)	16,555 (37.7%)	40% (0.14)	$p = 0.01$ *	FGA vs. Only SGAs: $p < 0.01$ Placebo vs. Only SGAs: $p < 0.01$ FGA + placebo vs. Only SGAs: $p < 0.01$
FGA	45 (54.9%)	14,336 (32.6%)	32.4% (0.12)		
Placebo	21 (25.6%)	6862 (15.6%)	28.9% (0.11)		
FGA + placebo	16 (19.5%)	6208 (14.1%)	27.5% (0.10)		

† For post hoc analysis, studies with missing data (category "not reported") were not included. Only significant comparisons presented here. For full results, see Table S2. †† Additional SGAs included trials with: amisulpride, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, paliperidone, sertindole and vabicaserin. * The mean difference is significant at the 0.05 level. SCZ: schizophrenia, FGA: first generation antipsychotics, SGA: second generation antipsychotic.

We also analyzed the antipsychotics as groups and found that studies with multiple SGAs as the medications of interested had a higher proportion of women than studies with a single SGA as main treatment ($F = 13.31$, $p < 0.01$). This difference, however, could be explained by the use of FGA or placebo in these trials, as seen by the loss of statistical significance when FGA and placebo were added in the models as covariates ($F = 2.14$, $p = 0.15$). Within the comparator arm, the mean proportion of women was higher for the SGA category than all others ($F = 7.48$, $p < 0.01$)—as expected, considering the previous analysis –, but there were no significant differences between FGA, placebo or FGA in addition to placebo.

In the linear regression models used to analyze continuous variables (Table 3), we found that year of publication ($\beta = 0.18$, $t = 2.25$, $p = 0.03$) and mean age of the sample ($\beta = 0.23$, $t = 2.788$, $p < 0.01$) were directly associated with the proportion of women recruited, but sample size ($\beta = -0.05$, $t = -0.59$, $p = 0.56$) and duration of trial ($\beta = 0.06$, $t = 0.69$, $p = 0.49$) were not.

Table 3. Linear regressions models.

	B	*SE*	*β*	*t*	*p*
Year of publication	0.004	0.002	0.183	2.251	0.026
Sample size	0.000	0.000	−0.049	−0.588	0.557
Duration of trial	0.000	0.000	0.057	0.685	0.494
Mean age	0.004	0.002	0.228	2.788	0.006

Tests were conducted independently for each continuous variable.

Considering the lower prevalence of women in North American studies, we conducted χ^2 tests to assess if relevant trial characteristics differed between locations. Compared to all other continents, we found that a larger number of trials in North America received pharmaceutical support ($\chi^2 = 7.30$, $p < 0.01$), specified additional inclusion criteria for women ($\chi^2 = 4.33$, $p = 0.03$) and used placebo ($\chi^2 = 17.35$, $p < 0.01$), but distributions were proportional regarding decade of publication ($\chi^2 = 3.63$, $p = 0.06$), setting ($\chi^2 = 2.01$, $p = 15$) and use of FGA ($\chi^2 = 0.40$, $p = 0.51$).

Last, we performed a stepwise multiple regression analysis including all variables that proved statistically significant in the previous models, to investigate their independent effects on the proportion of women. Summary results can be found in Table 4. Year of publication, setting, use of olanzapine and comparator arm were automatically excluded

from the model due to the lack of a significant effect, but location, funding, inclusion criteria for women and mean age had a significant influence on the frequency of women. So, despite our findings concerning the features of North American trials, this analysis shows that studies conducted in North America (vs. all other locations), funded by pharmaceutical companies (vs. non-pharmaceutical funding), requiring specific inclusion criteria for women and assessing younger samples were associated with a lower enrollment of women, as independent characteristics.

Table 4. Stepwise multiple regression analysis.

	B	*SE*	*β*	*t*	*p*
Constant	0.302	0.074		4.057	0.000
Location	−0.025	0.004	−0.494	−5.848	0.000
Funding	−0.002	0.000	−0.398	−4.656	0.000
Inclusion criteria for women	0.001	0.000	0.221	2.691	0.008
Mean age	0.004	0.002	0.166	2.017	0.046

R^2 = 0.337, adjusted R^2 = 0.310, F change = 4.067.

3. Discussion

In line with the review conducted by Chaves and Seeman (2006) [8], our study found that women's enrollment in antipsychotic trials for schizophrenia remains low, as they represent merely 34% of the subjects assessed here. Although our analyses suggest this gap might be decreasing over time, it appears to be moving in a slow pace—17 of the 148 trials retrieved in this review gathered samples in which at least half of the participants were women, and only 8 from the past decade.

We identified a few independent variables that influenced the proportion of women recruited in these studies. Younger samples were associated with a higher number of men, which was not surprising, as women tend to manifest the first symptoms later than men. Financial support also emerged as an independent factor in our review: studies that received pharmaceutical funding recruited 33% of women on average, opposed to 42% in trials without any pharmaceutical support. RCTs are costly and require major financial investment; so, when a trial receives pharmaceutical support, the pressure to achieve significant results, especially in terms of efficacy and safety, might encourage the recruitment of a more homogeneous sample, which is attained through more stringent eligibility criteria. The selection criteria are designed to enroll a specific population of interest whose chances of yielding effects with clinical importance are higher, thus justifying the financial investment, confirmed by more robust findings. However, from a scientific point of view, such motives should not substantiate selection bias [26].

Studies that included specific requirements for female participation, i.e., no pregnant or lactating women or reliable contraceptive, showed a lower percentage of women, as expected. Although we understand that ethical reasons play an important role due to safety concerns, such exclusion criteria can be often disproportional to the actual risks imposed by the medication or to an individual's actual risk of pregnancy [27]. Additionally, a general rule requiring "reliable" contraceptive, e.g., intake of exogenous hormones, can represent an additional confounding variable. Last, there is justifiably concern about potentially generating fetal harm, but the exclusion of pregnancy also leads to setbacks, especially if we consider that schizophrenia is an illness that affects young populations and that psychotic symptoms occur relatively often in perinatal women [23,28]. This highlights the need for research on specific treatments based on pregnancy exposure, and not a complete exclusion of pregnant women. Therefore, these requirements should be individualized to each study's design and antipsychotic of interest.

Finally, our review showed that trials conducted in North America appear to recruit less women when individually compared to Asia, Europe, Latin America and Oceania,

with an overall mean difference of −17% regarding the percentage of female subjects (North America vs. all other continents pulled together). Chaves and Seeman (2006) found the same results, and argued that, in North America, women might be more reluctant to provide consent [29] and contraception prerequisites are possibly more rigid, making women less eligible [29], which, in fact, is in accordance with our findings, as more North American studies in our review presented such a feature. Additionally, trials in North America were more often funded by the pharmaceutical industry. However, these variables emerged as independent factors in our multivariate analysis and center location produced the highest effect in the model.

One of the main problems induced by sex selection bias in antipsychotic trials regards applicability. Pharmacokinetic and pharmacodynamic properties can differ across genders [21]. Factors that may contribute for this include body size and composition, diet, exercise, use of substance, smoking status, comorbid disease, and differences between male and female metabolism. The higher percentage of adipose tissue in the female body composition tends to provide greater bioavailability and slower elimination of lipophilic drugs, generating higher plasma concentration of antipsychotics. Consequently, side effects are potentially more distressing for women, especially metabolic side effects. It may also explain why studies have reported better antipsychotic response with lower doses of medication among women [30]. Additionally, it seems that this difference ceases to exist in postmenopausal women, indicating that effective doses probably vary in distinct reproductive periods [21].

There are consistent findings indicating differences in medication response and tolerability between pre and postmenopausal women [31,32]. The latter, in fact, may require higher maintenance doses than men, possibly as a result of estrogen's antidopaminergic effect on antipsychotic response [33,34]. The post menopause period can also intensify side effects of antipsychotics [35], such as weight gain—which increases metabolic and cardiovascular risks [36]—and hyperprolactinemia—which is associated with osteoporosis, sexual and urogenital dysfunctions [37], leading to a worse subjective experience of the treatment.

As such, we highlight the consequences of sex bias in antipsychotic clinical trials, as the lack of knowledge it generates has an important impact on how drugs are prescribed and marketed. How the therapeutic and side effects of antipsychotics differ between men and women continues mostly to be disregarded in treatment guidelines for schizophrenia [15,25]. As a result, clinical decisions which should consider such differences end up dependent of each practitioner's judgement.

Furthermore, as pointed out by the recent review conducted by Santos-Casado et al. (2019) [9], antipsychotic trials rarely analyze or discuss results taking sex or gender differences into account separately. Integrating sex and gender analysis into study design has already brought innovation to other fields and signaled new directions for targeted therapies (for example, the use of immunotherapies for cancer [38] and improvement of pain and depression treatments [39]). It can also promote improvements in research methodology, experimental efficiency, bias reduction, social inclusion and foster discovery and novel drug development in humans [3].

Conversely, several studies have reported low representation of women in clinical trials for drug development. Female participation is estimated at 30.6% [40], and only 35% conduct proper subgroup analyzes and half of clinical trials do not show sex-based analysis [41]. Moreover, sex bias is present even in studies conducted with animal models, seeing as 80% of them work exclusively with males [42]. As a result, the lack of data on male and female differences at baseline, response to treatment and sex factors interferences are not clearly described, leading to biased recommendations that are not adapted to either women nor men and cannot be generalized [3].

The objective of this update review was to evaluate if participation of women in antipsychotic trials for schizophrenia has been improved, but in fact, the results showed that the sex bias has not changed. It is worth mentioning one limitation of our review, namely

SGAs developed more recently, such as paliperidone, lurasidone, sertindole, asenapine and brexpiprazole, were not included in our study. These SGA trials were only included if the original antipsychotics determined by Chaves and Seeman (2006)—risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, which are among the most commonly prescribed SGAs [43–45]—were also being tested. A recent systematic review and network meta-analysis conducted by Huhn et al. (2019) [46] encompassed 402 RCTs to compare the efficacy of 32 oral antipsychotics. Although not their focus, the authors made available data regarding the sex of participants. We found that the studies using amisulpride (N = 16), asenapine (N = 8), brexpiprazole (N = 6), cariprazine (N = 4), lurasidone (N = 7), paliperidone (N = 12) and sertindole (N = 7)—half of which were included in our review, approximately—recruited, on average, 38% of women, but less than 30% when the sole comparator was a placebo (which would represent trials excluded in our study). Such exclusion might have provided an overestimation regarding female enrollment, as women are usually more recruited only after the safety of new drugs are better established. Likewise, we have excluded studies with treatment-resistant populations and those performed in veteran centers, which also would engage a considerably lower proportion of women.

In conclusion, sampling bias continues to hinder women representativeness in clinical trials for the treatment of schizophrenia. We feel it is vital to call further attention to this issue and, more importantly, to implement additional efforts. Accordingly, research entities—such as ethical committees, government health agencies and scientific journals—should implement more stringent measures to bridge this gap.

For this reason, we suggest that studies should include an equivalent or, at least, not so dissimilar gender proportion. Some steps towards this goal include implementing protocols to individually assess pregnancy risk and provide contraceptive methods to women of childbearing potential when necessary. As maintaining the use of regular oral antipsychotic medications is already difficult enough, adding the maintenance of oral contraception might increase the complexity of the task, so it may be also feasible to select women who are allowed to use intrauterine devices or intramuscular progesterone, for instance; nonetheless, it is likely that this could, too, lead to a small number of eligible female patients. As there is no simple design solution to masking recruitment, authors should at least provide sufficient information to enable readers to know when this bias has taken place.

It would also be important to encourage "real life" trials, with less focus on general efficacy as the main outcome, in order to increase knowledge regarding antipsychotics specific effects on premenopausal, perinatal and postmenopausal women. So, in addition to further including women, it is imperative to better analyze data and report findings individually for both sexes and account for differences within subgroups as well, considering women's reproductive cycles, instead of excluding or ignoring this variable.

4. Materials and Methods

4.1. Search Strategy

This is an update to the Chaves and Seeman (2006) [8] systematic review, following the same procedures in order to retrieve more recent studies. Briefly, we performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA guidelines [47] (the PRISMA checklist can be found in Table S3). We searched MEDLINE from 2005 to 7 September 2020 for randomized clinical trials (RCTs) testing risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole, either as the main drug or as the comparator, using the terms "risperidone", "aripiprazole", "olanzapine", "quetiapine", "ziprasidone", "schizophrenia", and "psychosis", and, as subject headings, "clinical trials", "controlled clinical trials", and "randomized clinical trials". We also conducted a search on the Cochrane database, and additional trials were assessed manually among reference lists of major systematic reviews.

4.2. Selection Criteria

The inclusion criteria were: (1) assessment of one or more of the mentioned antipsychotics; (2) group placement had to be random; (3) a control group was required, using either a placebo, a different second generation antipsychotic (SGA), a first generation antipsychotic (FGA), or distinct dosages or administration forms of the same antipsychotic; 3) adult patients diagnosed with schizophrenia, schizophrenia spectrum disorder, or broad psychosis, although no specific instrument or criteria was necessary; (4) publication in full in an English language academic journal; and (5) the total sample (subjects + controls) had to exceed 50. Trials assessing SGAs developed more recently, such as paliperidone, lurasidone or brexpiprazole, were only included in our study if the comparator drug was one of the five antipsychotics of interested. Blindness was not a requirement. We excluded trials that: (1) included treatment-resistant patients because these are more often men; (2) tested clozapine, because it is mainly prescribed for treatment-resistant patients; (3) investigated mood disorders exclusively, even if they were psychotic; and (4) enrolled patients in Veteran Affairs Centers (where mainly male selection would be expected).

4.3. Screening and Data Extraction

Each study was screened independently by two investigators, first by title and abstract and, afterwards, with a full-text evaluation. Conflicts were resolved by consensus. The data extraction for the selected studies was also performed by two investigators, including the following information: source of financial support (pharmaceutical, non-pharmaceutical), pharmacotherapy characteristics (antipsychotics and type of administration), control arm information (other SGA, FGA, placebo, different dose or different administration), number and localization of the study sites (divided by continent), setting (inpatient, outpatient, or both), diagnosis (only schizophrenia, schizophrenia spectrum disorder, and broad psychosis), symptom presentation (acute, stable, or both), number of the psychotic episodes (first episode only, multiple episodes, or both), duration of the study (in days), number of the total sample, number of men and number of women, mean age of the sample, and if the study stipulated further inclusion criteria for women (such as exclusion of pregnant and lactating women and/or reliable contraception required).

4.4. Statistical Analysis

All analyses were performed on SPSS version 26 [48]. The proportion of women in each study was weighted based on sample size. We investigated how the percentage of women varied according to the studies characteristics, using one-way analysis of variance (ANOVA) for categorical variables and linear regression models for continuous ones. In addition, analysis of covariance (ANCOVA) was used to add covariables to the latter when indicated, to test possible interactions. We also used chi-squared (χ^2) tests to evaluate if trial characteristics varied between locations. Afterwards, we performed a stepwise multiple regression analysis employing the variables that provided statistically significant results in the first tests to evaluate their individual effects on the proportion of women. Differences were considered significant if $p < 0.05$.

5. Conclusions

This update systematic review found that female recruitment in clinical trials for the treatment of schizophrenia remains insufficient—less than 35% of samples overall. In light of the possible different effects of antipsychotics in both sexes, and our lack of knowledge on the subject due to sampling bias, it is vital to actively encourage additional efforts aimed at bridging this gap.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/women1020009/s1, Table S1: Studies included in the review, Table S2: Post hoc analysis/Multiple comparisons—Differences on proportion of women recruited according to trial characteristics, Table S3: PRISMA Checklist.

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References

1. Lally, J.; Watkins, R.; Nash, S.; Shetty, H.; Gardner-Sood, P.; Smith, S.; Murray, R.M.; Gaughran, F. The Representativeness of Participants with Severe Mental Illness in a Psychosocial Clinical Trial. *Front. Psychiatry* **2018**, *9*, 654. [CrossRef] [PubMed]
2. Itoh, Y.; Arnold, A.P. Are Females More Variable than Males in Gene Expression? Meta-Analysis of Microarray Datasets. *Biol. Sex Differ.* **2015**, *6*, 18. [CrossRef]
3. Tannenbaum, C.; Ellis, R.P.; Eyssel, F.; Zou, J.; Schiebinger, L. Sex and Gender Analysis Improves Science and Engineering. *Nature* **2019**. [CrossRef]
4. Clayton, J.A.; Collins, F.S. NIH to Balance Sex in Cell and Animal Studies. *Nature* **2014**. [CrossRef]
5. Clayton, J.A.; Tannenbaum, C. Reporting Sex, Gender, or Both in Clinical Research? *JAMA J. Am. Med. Assoc.* **2016**, *316*, 1863–1864. [CrossRef] [PubMed]
6. Zakiniaeiz, Y.; Cosgrove, K.P.; Potenza, M.N.; Mazure, C.M. Balance of the Sexes: Addressing Sex Differences in Preclinical Research. *Yale J. Biol. Med.* **2016**, *89*, 255–259.
7. Saha, S.; Chant, D.; Welham, J.; McGrath, J. A Systematic Review of the Prevalence of Schizophrenia. *PLoS Med.* **2005**, *2*, 0413–0433. [CrossRef] [PubMed]
8. Chaves, A.C.; Seeman, M.V. Sex Selection Bias in Schizophrenia Antipsychotic Trials. *J. Clin. Psychopharmacol.* **2006**, *26*, 489–494. [CrossRef]
9. Santos-Casado, M.; García-Avello, A. Systematic Review of Gender Bias in the Clinical Trials of New Long-Acting Antipsychotic Drugs. *J. Clin. Psychopharmacol.* **2019**, *39*, 264–272. [CrossRef] [PubMed]
10. Cotton, S.M.; Lambert, M.; Schimmelmann, B.G.; Foley, D.L.; Morley, K.I.; McGorry, P.D.; Conus, P. Gender Differences in Premorbid, Entry, Treatment, and Outcome Characteristics in a Treated Epidemiological Sample of 661 Patients with First Episode Psychosis. *Schizophr. Res.* **2009**, *114*, 17–24. [CrossRef]
11. Varma, V.K.; Wig, N.N.; Phookun, H.R.; Misra, A.K.; Khare, C.B.; Tripathi, B.M.; Behere, P.B.; Yoo, E.S.; Susser, E.S. First-Onset Schizophrenia in the Community: Relationship of Urbanization with Onset, Early Manifestations and Typology. *Acta Psychiatr. Scand.* **1997**, *96*, 431–438. [CrossRef]
12. Kirkbride, J.B.; Errazuriz, A.; Croudace, T.J.; Morgan, C.; Jackson, D.; Boydell, J.; Murray, R.M.; Jones, P.B. Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses. *PLoS ONE* **2012**, *7*, e31660. [CrossRef]
13. Cersosimo, M.G.; Benarroch, E.E. Estrogen Actions in the Nervous System: Complexity and Clinical Implications. *Neurology* **2015**. [CrossRef]
14. Køster, A.; Lajer, M.; Lindhardt, A.; Rosenbaum, B. Gender Differences in First Episode Psychosis. *Soc. Psychiatry Psychiatr. Epidemiol.* **2008**, *43*, 940–946. [CrossRef] [PubMed]
15. Ochoa, S.; Usall, J.; Cobo, J.; Labad, X.; Kulkarni, J. Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review. *Schizophr. Res. Treat.* **2012**. [CrossRef] [PubMed]
16. Seeman, M.V. Does Gender Influence Outcome in Schizophrenia? *Psychiatr. Q.* **2019**, *90*, 173–184. [CrossRef] [PubMed]
17. Crawford, M.B.; DeLisi, L.E. Issues Related to Sex Differences in Antipsychotic Treatment. *Curr. Opin. Psychiatry* **2016**, *29*, 211–217. [CrossRef]
18. Seeman, M.V. Are There Gender Differences in the Response to Antipsychotic Drugs? *Neuropharmacology* **2019**. [CrossRef]
19. Gillies, G.E.; Virdee, K.; McArthur, S.; Dalley, J.W. Sex-Dependent Diversity in Ventral Tegmental Dopaminergic Neurons and Developmental Programing: A Molecular, Cellular and Behavioral Analysis. *Neuroscience* **2014**, *282*, 69–85. [CrossRef]
20. Eugene, A.R.; Masiak, J. A Pharmacodynamic Modelling and Simulation Study Identifying Gender Differences of Daily Olanzapine Dose and Dopamine D2-Receptor Occupancy. *Nord. J. Psychiatry* **2017**, *71*, 417–424. [CrossRef]
21. Seeman, M.V. Men and Women Respond Differently to Antipsychotic Drugs. *Neuropharmacology* **2020**, *163*, 107631. [CrossRef]
22. Jones, I.; Chandra, P.S.; Dazzan, P.; Howard, L.M. Bipolar Disorder, Affective Psychosis, and Schizophrenia in Pregnancy and the Post-Partum Period. *Lancet* **2014**, *384*, 1789–1799. [CrossRef]
23. Grigoriadis, S.; Seeman, M.V. The Role of Estrogen in Schizophrenia: Implications for Schizophrenia Practice Guidelines for Women. *Can. J. Psychiatry* **2002**, *47*, 437–442. [CrossRef] [PubMed]

24. Soldin, O.P.; Chung, S.H.; Mattison, D.R. Sex Differences in Drug Disposition. *J. Biomed. Biotechnol.* **2011**, *2011*, 7–9. [CrossRef] [PubMed]
25. Abel, K.M.; Drake, R.; Goldstein, J.M. Sex Differences in Schizophrenia. *Int. Rev. Psychiatry* **2010**, *22*, 417–428. [CrossRef]
26. Van Spall, H.G.C.; Toren, A.; Kiss, A.; Fowler, R.A. Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals: A Systematic Sampling Review. *J. Am. Med. Assoc.* **2007**, *297*, 1233–1240. [CrossRef]
27. American College of Obstetricians and Gynecologists. *Ethical Considerations for Including Women as Research Participants*; American College of Obstetricians and Gynecologists: Washington, DC, USA, 2016; Volume 127.
28. González-Rodríguez, A.; Seeman, M.V. The Association between Hormones and Antipsychotic Use: A Focus on Postpartum and Menopausal Women. *Ther. Adv. Psychopharmacol.* **2019**, *9*, 204512531985997. [CrossRef]
29. Robinson, D.; Woerner, M.G.; Pollack, S.; Lerner, G. Subject Selection Biases in Clinical Trials: Data from a Multicenter Schizophrenia Treatment Study. *J. Clin. Psychopharmacol.* **1996**, *16*, 170–176. [CrossRef]
30. Lange, B.; Mueller, J.K.; Leweke, F.M.; Bumb, J.M. How Gender Affects the Pharmacotherapeutic Approach to Treating Psychosis—A Systematic Review. *Expert Opin. Pharmacother.* **2017**, *18*, 351–362. [CrossRef]
31. Goldstein, J.M.; Cohen, L.S.; Horton, N.J.; Lee, H.; Andersen, S.; Tohen, M.; Crawford, A.M.K.; Tollefson, G. Sex Differences in Clinical Response to Olanzapine Compared with Haloperidol. *Psychiatry Res.* **2002**, *110*, 27–37. [CrossRef]
32. González-Rodríguez, A.; Catalán, R.; Penadés, R.; Ruiz Cortés, V.; Torra, M.; Seeman, M.V.; Bernardo, M. Antipsychotic Response Worsens With Postmenopausal Duration in Women With Schizophrenia. *J. Clin. Psychopharmacol.* **2016**, *36*, 580–587. [CrossRef] [PubMed]
33. Riecher-Rössler, A.; Häfner, H. Schizophrenia and Oestrogens—Is There an Association? *Eur. Arch. Psychiatry Clin. Neurosci.* **1993**, *242*, 323–328. [CrossRef]
34. Seeman, M. Neuroleptic Prescription for Men and Women. *J. Soc. Pharmacol.* **1989**, *3*, 219–236.
35. Olten, B.; Bloch, M.H. Meta Regression: Relationship between Antipsychotic Receptor Binding Profiles and Side-Effects. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2018**, *84*, 272–281. [CrossRef] [PubMed]
36. Newcomer, J.W. Antipsychotic Medications: Metabolic and Cardiovascular Risk. *J. Clin. Psychiatry* **2007**, *68* (Suppl. 4), 8–13.
37. Li, L.; Wang, Z. Ovarian aging and osteoporosis. In *Advances in Experimental Medicine and Biology*; Springer: Singapore, 2018; Volume 1086, pp. 199–215.
38. Conforti, F.; Pala, L.; Bagnardi, V.; De Pas, T.; Martinetti, M.; Viale, G.; Gelber, R.D.; Goldhirsch, A. Cancer Immunotherapy Efficacy and Patients' Sex: A Systematic Review and Meta-Analysis. *Lancet Oncol.* **2018**. [CrossRef]
39. Labonté, B.; Engmann, O.; Purushothaman, I.; Menard, C.; Wang, J.; Tan, C.; Scarpa, J.R.; Moy, G.; Loh, Y.H.E.; Cahill, M.; et al. Sex-Specific Transcriptional Signatures in Human Depression. *Nat. Med.* **2017**. [CrossRef] [PubMed]
40. Pinnow, E.; Sharma, P.; Parekh, A.; Gevorkian, N.; Uhl, K. Increasing Participation of Women in Early Phase Clinical Trials Approved by the FDA. *Women's Health Issues* **2009**. [CrossRef]
41. Benjeaa, Y.; Geysels, Y. Gender Bias in the Clinical Evaluation of Effectiveness in Therapies. *Appl. Clin. Trials* **2020**, *29*, 30–33.
42. Beery, A.K.; Zucker, I. Sex Bias in Neuroscience and Biomedical Research. *Neurosci. Biobehav. Rev.* **2011**, *35*, 565–572. [CrossRef]
43. Taipale, H.; Puranen, A.; Mittendorfer-Rutz, E.; Tiihonen, J.; Tanskanen, A.; Cervenka, S.; Lähteenvuo, M. Antipsychotic Use among Persons with Schizophrenia in Sweden and Finland, Trends and Differences. *Nord. J. Psychiatry* **2020**, 1–8. [CrossRef] [PubMed]
44. Roberts, R.; Neasham, A.; Lambrinudi, C.; Khan, A. A Quantitative Analysis of Antipsychotic Prescribing Trends for the Treatment of Schizophrenia in England and Wales. *JRSM Open* **2018**, *9*, 205427041875857. [CrossRef] [PubMed]
45. Yazici, E.; Cilli, A.S.; Yazici, A.B.; Baysan, H.; Ince, M.; Bosgelmez, S.; Bilgic, S.; Aslan, B.; Erol, A. Antipsychotic Use Pattern in Schizophrenia Outpatients: Correlates of Polypharmacy. *Clin. Pract. Epidemiol. Ment. Heal.* **2017**, *13*, 92–103. [CrossRef]
46. Huhn, M.; Nikolakopoulou, A.; Schneider-Thoma, J.; Krause, M.; Samara, M.; Peter, N.; Arndt, T.; Bäckers, L.; Rothe, P.; Cipriani, A.; et al. Comparative Efficacy and Tolerability of 32 Oral Antipsychotics for the Acute Treatment of Adults with Multi-Episode Schizophrenia: A Systematic Review and Network Meta-Analysis. *Lancet* **2019**, *394*, 939–951. [CrossRef]
47. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions: Explanation and Elaboration. *BMJ* **2009**, *339*, b2700. [CrossRef] [PubMed]
48. IBM Corp. *IBM SPSS Statistics for Macintosh*; Version 26.0; IBM Corp: Armonk, NY, USA, 2019.