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Gender differences in the response to antipsychotics or mood stabilizers in patients with acute mania: An individual patient data meta-analysis of placebo-controlled studies

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ABSTRACT

Evidence suggests a worse clinical course in women compared to men with bipolar disorder. However, little research has explored gender differences in the efficacy of anti-manic medication. We sought to determine whether there are gender differences in efficacy of drug treatment in acute manic episodes of bipolar I disorder, and the influence of dichotomized age as a proxy for menopausal status and baseline severity on gender differences. We performed an individual patient data meta-analysis of 10 short term placebo controlled registration trials for treatment of acute mania (N = 2199) performed between 1996 and 2007 using the (Young) Mania Rating Scale ((Y)MRS)) as outcome. We observed a difference in effect size in mean change and responder status between men and women (NNT = 6.3 vs. 5.3), with a small but significant effect of gender on treatment response (β = 0.031). The effect size was larger in women older than 47 compared to women aged 47 and under (NNT = 4.2 vs. 7.5), and to a lesser extent, larger in men over 47 years compared those aged 47 and under (NNT = 3.8 vs. 6). Results were mainly driven by differences in response in the placebo group and independent of baseline severity. These findings suggest that men and premenopausal women might have a clinically modest advantage over their women and postmenopausal counterparts in treatment with anti-manic medication. Our results were limited by our sample not including antimanic agents registered after 2007 and by the absence of direct biological information regarding sex and menopausal state. Future research should aim to replicate current findings utilizing biological confirmation on the menopausal status and test whether findings are generalizable to newer antimanic agents.

1. Introduction

Mania is the hallmark of bipolar I disorder, characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood (The Diagnostical and Statistical manual, 2013). The prevalence of bipolar I disorder (BD) is consistent across cultures and ethnic groups, with a lifetime prevalence of 0,6%, affecting men and women equally (Morgan et al., 2005).

Despite equal lifetime prevalence, distinct gender differences in the course and prognosis of bipolar I disorder have been identified (Hendrick et al., 2000; Kennedy et al., 2005). Women have shown higher inpatient admission rates (Fellinger et al., 2018; Ragazan et al., 2019), increased rates of rapid cycling (Erol et al., 2015), and more mixed episodes (Diflorio and Jones, 2010), together, suggesting a worse clinical course and prognosis in women relative to men with bipolar I disorder. Antipsychotic drugs and mood stabilizers are the mainstay of treatment of bipolar I disorder, both in management of acute mood episodes as well as maintenance treatment and play a central role in

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determining the clinical course of bipolar disorder. One possible explanation for a more severe course of bipolar I disorder in women could be poorer efficacy of antipsychotic drugs and mood stabilizers in women relative to men. A potential pathway through which such gender differences in treatment efficacy could arise, is through effects of the primary female sex hormone estrogen. Higher levels of estrogen in premenstrual women could have a negative effect on treatment outcome, this effect is lost after menopause when estrogen levels (rapidly) decrease in women. Indeed, tamoxifen, a synthetic estrogen antagonist and inhibitor of protein kinase c activity, has shown efficacy both as monotherapy (Yildiz et al., 2008; Zarate et al., 2007) and as an add -on to lithium or valproate (Kulkarni et al., 2014, 2016).

In contrast to major depressive disorder, surprisingly little research has been published on gender differences and the role of estrogen in response to conventional pharmacotherapeutic treatments in bipolar disorder. One meta-analysis indicated similar clinical response to lithium in women and men (Viguera et al., 2001). However, to the best of our knowledge no such meta-analysis has been published for antipsychotic drugs and mood stabilizers. Moreover, previous pivotal randomized clinical trials in bipolar disorder have not been sufficiently powered to infer reliable gender-specific similarities or differences in efficacy.

The aim of the current study is to determine whether differences in efficacy (defined as a difference between drug effect and placebo response), in the treatment of patients with an acute manic episode are moderated by gender and dichotomized age as a proxy for menopausal status. Our hypotheses, based on the anti-manic, anti-estrogenic effects of Tamoxifen, are that women with acute mania show lower efficacy of treatment with anti-manic medication than men (Morgan et al., 2005), that women respond slower relative to men (Arnold, 2003), that women aged 47 or under (with a relatively higher level of estrogen) with acute mania have a poorer efficacy than women older than 47 and (Geoffroy et al., 2013) that these effects are independent of baseline symptom severity.

2. Methods

2.1. Selection of studies

We included all studies (n = 10) submitted to the Dutch Medicines Evaluation Board (MEB) during an 11-year period as part of market authorization applications in Europe for the indication acute manic episode of bipolar I disorder. Although data was retrieved from the Dutch MEB, these studies were part of international trials. All studies were short-term double-blind randomized, placebo-controlled trials involving patients diagnosed with DSM-IV bipolar I disorder. Pharmaceutical companies provided individual patient data to enable an individual patient data (IPD) meta-analysis. Restrictions apply to the availability of these data, which were used under license for this study, including disclosing individual names of included medications. Data are available from the authors with the permission of the pharmaceutical companies. The drugs investigated were antipsychotics and anticonvulsant mood stabilizers. Active comparators were included and analyzed as treatment. Studies that included less than ten men or women in either the active medication or placebo arm were excluded because correlations could not be properly calculated. We further restricted the analyses to subjects that were given a proven effective dose of the medication, as indicated in the Summary of Product Characteristics (SmPC). Risk of bias was assessed using the Cochrane RoB Tool. The guideline for the preferred reporting items for systematic reviews and meta-analyses (PRISMA) was followed except for items pertaining specifically to systematic reviews (Stewart et al., 2015). We pre-specified our methods and analysis plan in the PROSPERO database for systematic reviews (ID= CRD42022329785).

2.2. Instruments

The severity of the acute manic episode of bipolar I disorder at baseline and at study endpoint was assessed with two instruments. The Young Mania Rating Scale (YMRS) comprises 11 items: seven items are scored on a 0–4 scale and four are scored on a 0–8 scale. The total score ranges from 0 (no symptoms) to 60 (severe symptoms) (Young et al., 1978). The Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia – Change Version (MRS from SADS-C) also comprises 11 items: one item is scored on a 0–2 scale and ten items are scored on a 0–5 scale (higher score indicates higher severity). The total score ranges from 0 (no symptoms) to 52 (severe symptoms) (Endicott and Spitzer, 1978).

2.3. Measures for response, baseline severity, and menopausal state

We used two efficacy outcomes: the standardized difference in mean change score on the YMRS or the MRS from baseline to follow-up and the difference in percentage of responders. We considered patients a responder if their score on the YMRS or MRS decreased by 50% or more from baseline to follow-up (Tohen et al., 2009). As two different rating scales were used in the studies, we decided to use mean percentual improvement as primary outcome measure. The endpoint was defined at the three-week post-baseline assessment, since this is the time point recommended for establishing short-term efficacy in the EMA Committee for Proprietary Medicinal Products (CPMP) guideline on the clinical investigation of medicinal products for the treatment of mania (CPMP, 2001). For any missing individual (Y)MRS item(s), we used the average of the other (Y)MRS items for that patient for that visit. For patients who dropped out before week three, the last observation was carried forward (LOCF) to week three. The difference in mean improvement and the difference in percentage responders between active treatment and placebo at week three (LOCF) was considered as the main outcome measures.

No direct information was available on the menopausal status. Therefore, following earlier studies, we used age 47 as a proxy for the age of the menopause (Goldstein et al., 2002; Storosum et al., 2023). Women older than 47 were considered to be in the post-menopausal phase.

2.4. Statistical analysis

We used a two-step, random effects IPD meta-analysis. We used random effect rather than a fixed effect meta-analysis because the included studies had been performed by independently operating companies who examined different medications, tested at different times and in different populations and thus between-study heterogeneity in outcomes was to be expected (Riley et al., 2010).

First, we calculated the total scores on the respective questionnaires at baseline and week three, and used these scores to calculate percentual change from baseline. We also calculated response rate (RR), defined as at least 50% reduction of (Y)MRS score between baseline and week three. Next, in order to test our first hypothesis, the association between gender and effect size was evaluated in each included study, using a multivariate adjusted regression models using either mean percentual change from baseline on the (Y)MRS (linear), or response (logistic) as the dependent variable and the interaction of gender (men vs. women) by treatment (active medication vs. placebo) as the indicator for a modifier effect of gender on treatment effect. These analyses yield β coefficients and odds-ratio respectively. The β coefficients expresses the relation between gender and symptom reduction on the (Y)MRS scale.

In addition, to test hypothesis two, we tested the modifying effect of dichotomized age as a proxy for menopausal status by adding the interaction of age (dichotomized with cut-off point 47) and treatment (active medication vs. placebo). Both models were corrected for the main effects of the interactions and baseline severity.

To investigate the effect of baseline severity, we performed these analyses with and without correction for baseline severity.

Next, in order to obtain a pooled estimate of the β per study, we performed a meta-analysis on the outcomes of the previous step: β′s and corresponding standard errors yielded from the regression analyses were presented as input.

In the responder population, time to response was calculated for each individual patient. Subsequently, using this time to response as a dependent variable, a multivariate adjusted linear regression model was built for each study. As per the first research question, the interaction of gender (men vs. women) by treatment (active medication vs. placebo) was added as independent variable to examine a modifying effect of gender on the time to response. In addition, we tested the modifying effect of menopausal status by adding the interaction of age (dichotomized with cut-off point 47 years) and treatment (active medication vs. placebo). Both models were corrected for the main effects of the interaction variables and baseline severity.

For all above steps, sensitivity analyses were performed. In these analyses, the dichotomization in age that approximates the distinction between pre- and postmenopausal status was altered from 47 years to ages below 45 and above 50 years, in order to exclude women in perimenopause. Also, analyses were repeated excluding patients using mood stabilizers.

The regression analyses were performed using SPSS version 24 (SPSS24) and the meta-analysis was performed with Comprehensive Meta-Analysis, version two (CMA2).

3. Results

3.1. Study selection and baseline characteristics

Individual patient data from all 10 studies were provided by the pharmaceutical companies and included in the analyses. Enrolment had taken place between 1996 and 2007. Here, we present results from 2199 patients: 1280 (58.2%) on active medication and 919 (41.8 %) on placebo; 1021 (46.4%) women and 1178 (53.6%) men; 1661 with an age ≤47 years and 538 with an age >47 years.

Table 1 presents demographic- and baseline characteristics of the included patients. There were no significant differences in baseline characteristics between men and women in the included trials.

Supplementary Fig. 1 shows a low over-all risk of bias in the individual trials.

Table 1
Baseline characteristics.

	Women		men	
	Active compound	Placebo	Active compound	Placebo
N (%)	1021 (46.4)		1178 (53.6)	
N (%)	597 (58.5)	424 (41.5)	683 (58.0)	495 (42.0)
Age in years, mean (SD)	41.0 (12.7)	38.9 (12.3)	38.1 (12.2)	38.2 (11.8)
MRS				
N (%)	134 (13.1)		152 (12.9)	
N (%)	56 (5.5)	78 (7.6)	58 (5.0)	94 (8.0)
MRS score at baseline, mean (SD)	27.5 (6.7)	26.2 (7.3)	28.3 (6.6)	28.6 (6.1)
YMRS				
N (%)	887 (86.9)		1026 (87.1)	
N (%)	541 (61.0)	346 (39.0)	625 (60.9)	401 (39.1)
YMRS score at baseline, mean (SD)	31.3 (6.8)	30.9 (7.0)	31.4 (6.9)	31.9 (7.7)

3.2. Differences in efficacy between men and women

Table 2 shows that in men, difference in response rates between the active compound and placebo arm was higher compared to women (18.9% RR and a NNT of 5.3 for men vs. 15.8% RR and NNT of 6.3 for women. Furthermore, differences in average improvement of the MRS/YMRS scores were also higher in men (19.1 for men vs. 18.2 for women).

Fig. 1a presents the results of the IPD meta-analyses for mean percentual change and response. Antipsychotics and mood stabilizers have a statistically significant larger effect in men than in women after correction for baseline severity, age, and age dichotomized by cut-off point 47 years, both in terms of mean percentual change and response rate. This is represented by an aggregate β of 0.031 (95% Confidence interval: 0.014–0.048, p = <0.001) for the mean percentual YMRS/MRS change, and the aggregate adjusted OR of 1.136 (95% Confidence Interval: 1.011–1.277, p = 0.033) for response rate (see Fig. 2).

3.2.1. Differences in efficacy between premenopausal and postmenopausal women

Table 3 shows that compared to women aged 47 and under, older women had higher differences in response rates (13.3% RR and a NNT of 7.5 for women aged 47 and under) vs. 23.8% RR and NNT of 4.2 for women aged older than 47 and larger differences in average improvements in the percentage of (Y)MRS scores (15.2 for women aged 47 and under vs. 26.8 for women aged older than 47).

Table 3 also shows that compared to men aged 47 or under, men aged older than 47 had higher differences in response rate (RR of 16.8% and a NNT of 6 for men aged 47 or under vs. RR of 26.6% and a NNT of 3.8 for men aged older than 47 26.6% vs. 16.8%: NNT = 3.8 vs. NNT = 6) and larger differences in average improvement in the percentage change of (Y)MRS scores (18.6 in men aged 47 or under vs. 21 for men aged older than 47).

Fig. 1b shows the model when correction for menopausal status (dichotomized age interaction with gender) is removed from the model. The moderating effect of gender is magnified to a β of 0.057 (95% Confidence Interval: 0.043 – 0.071, p < 0.001) for the mean percentual YMRS/MRS change, and the aggregate adjusted OR to 1.257 (95% confidence interval: 1.153–1.370, p < 0.001) for response rate.

3.3. Role of baseline severity in effect size differences

Supplementary Fig. 2 shows the results of the modifying effect of gender after baseline severity is removed from the model. The modifying effect of gender is hardly effected by this step with an aggregate β of 0.054 (95% confidence interval 0.039–0.069, p < 0.001) and an adjusted OR of 1.131 (95% confidence interval 1.025–1.249, p = 0.014), indicating minimal modification by baseline severity of the gender by treatment effect.

Table 2
Efficacy outcomes by gender.

	Women		Men	
	Active compound	Placebo	Active Compound	Placebo
N (%)	597	424	683	495
Mean improvement on YMRS or MRS scores in % (SD)	45.2 (0.3)	27.0 (0.4)	45.3 (0.5)	26.2 (0.4)
Response rate in %	47.9	32.1	48.2	29.3
Responders N	286	136	329	145
Difference in response rate	15.8		18.9	
Number needed to treat	6,3		5,3	
Mean time to response in weeks (SD)	2.0 (0.7)	1.9 (0.8)	1.9 (0.8)	1.9 (0.8)

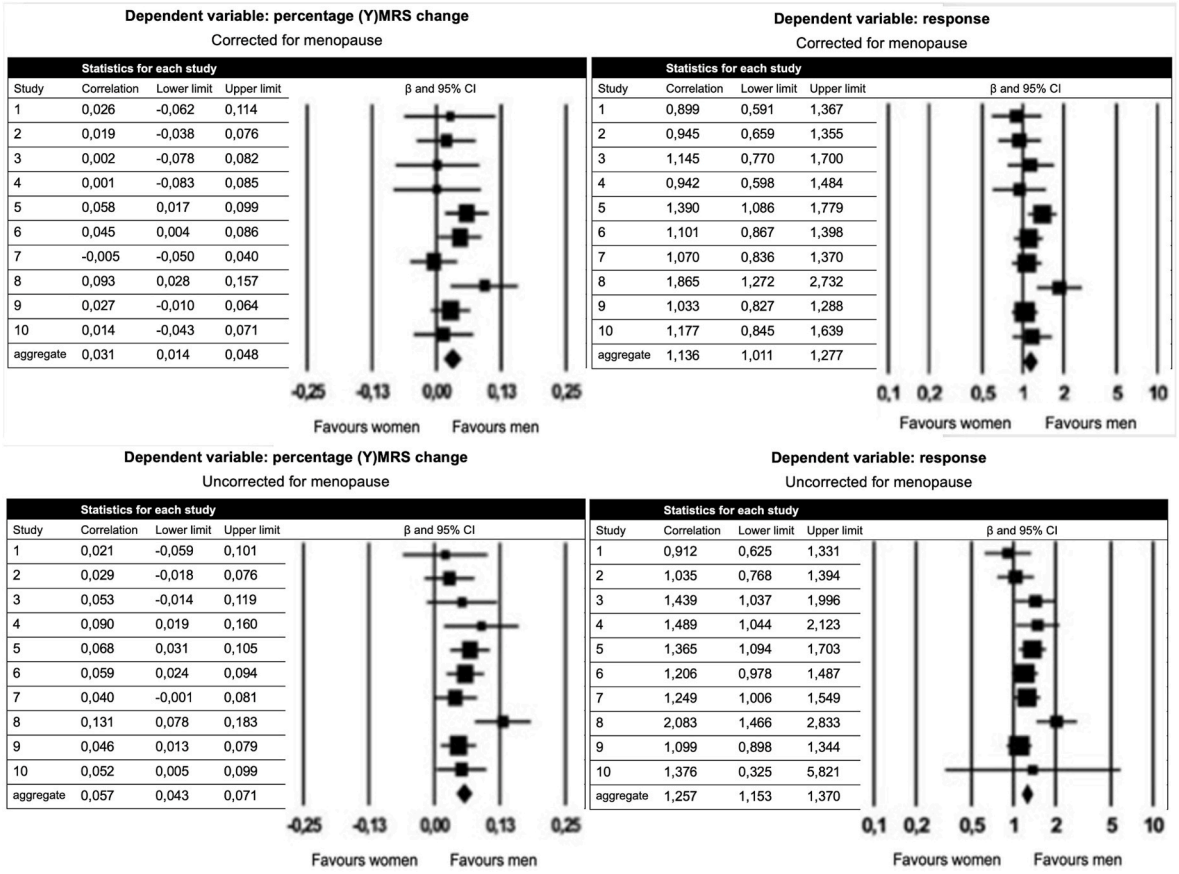

Fig. 1. Interaction of treatment and gender (with main effects) on relative decrease in the (Young) Mania Rating Scale (β), and on responserate (OR). and uncorrected for.

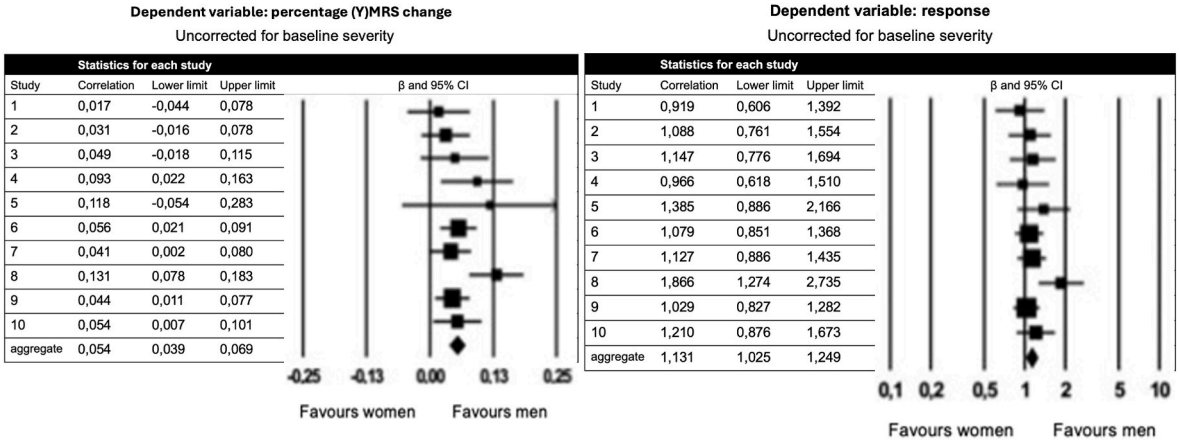

Fig. 2. Interaction of treatment and gender (with main effects) on relative decrease in the (Young) Mania Rating Scale (β), and on responserate (OR).

3.4. Gender differences in time to response

Table 2 also shows no numerical difference in time to response between men and women. This was confirmed by the IPD meta-analysis for time to response (shown in Fig. 3) with a non-significant aggregate β of 0.017 (−0.054 - 0.087, p = 0.650)

3.5. Sensitivity analyses

None of the abovementioned results differed significantly from the main analyses when separating by age and excluding patients aged between 45 and 50 years old. This is represented by an aggregate β of 0.035 (95% Confidence interval: 0.014–0.066) for the mean percentual YMRS/MRS change and the aggregate adjusted OR of 1.140 (95% Confidence Interval: 1.011–1.290) for response rate.

None of the abovementioned results differed significantly from the main analysis when excluding patients using moods-stabilizers. This is represented by an aggregate β of 0.041 (95% Confidence interval: 0.011–0.053 p = <0.001) for the mean percentual YMRS/MRS change, and the aggregate adjusted OR of 1.133 (95% Confidence Interval: 1.012–1.273, p = 0.038) for response rate for the main analysis comparing effect size between men and women.

Table 3
Efficacy outcomes by age.

	Men age ≤47		Men age >47	
	Active compound	Placebo	Active Compound	Placebo
N (%)	520	390	163	105
Mean improvement on YMRS or MRS scores in % (SD)	45.7 (0.4)	27.1 (0.4)	43.8 (0.4)	22.8 (0.4)
Response rate in %	48.1	31.3	48.5	21.9
Responders N	250	122	79	23
Difference in response rate	16,8		26,6	
Number needed to treat	6		3,8	
Mean time to response in weeks(SD)	1.9 (0.8)	1.9 (0.7)	1. (0.8)	1.8 (08)
	Women age ≤47		**Women age >47**	
	Active compound	**Placebo**	**Active Compound**	**Placebo**
N (%)	431	320	166	104
Mean improvement on YMRS or MRS scores in % (SD)	44.7 (0.4)	29.5 (0.4)	46.4 (0.3)	19.6 (0.4)
Response rate in %	48.0	34.7	47.6	24.0
Responders N	207	111	79	25
Difference in response rate	13.3		23.6	
Number needed to treat	7,5		4,2	
Mean time to response in weeks (SD)	2.1 (0.8)	1.9 (0.7)	1.9 (0.8)	2.0 (0.8)

4. Discussion

Our results indicate that anti-manic drugs are associated with larger mean symptom reduction and a larger response rate in men with an acute manic episode of bipolar-I-disorder compared to women, but not with a shorter time to response. Furthermore, gender differences in effect size were independent of baseline symptom severity. Although these findings are statistically significant, the gender differences in efficacy are small and of modest clinical significance. Age older than 47 was positively associated with treatment effect and treatment response in women, but not with time to response. Although response in older men was also larger than in younger men, the magnitude of this age effect was smaller than in older women vs. younger women. Although we lacked biological confirmation of menopausal status, the latter finding could suggest a positive association between treatment efficacy and post-menopausal status. Both gender difference and a potential moderating effect of menopausal state could suggest a negative, albeit small, role of estrogen in the efficacy of anti-manic drugs.

Although the effect of gender on mean symptom reduction and response is statistically significant in our IPD meta-analysis, the effect is modest, as demonstrated by an aggregate β of 0.031 and an OR of 1.136. At week three the number needed to treat (NNT) for response in women is 6.3 and 5.3 for men. This indicates that gender differences regarding the response to antipsychotic medication and mood stabilizers may be of modest clinical relevance. However, women aged 47 or younger with a NNT for response of 7.5 have a considerable smaller response to drug treatment than women aged older than 47 with a NNT of 4.2, indicating an association between older age and response to regular drug treatment in acute manic episode in women, with an almost doubled aggregate β (0.057) in older women. This age effect is also present in men, although to a lesser extent, where men younger than 47 have a response to drug treatment with a NNT of 6 compared to a NNT of 3.8 for their older counterparts. These findings might suggest a moderation effect of menopausal status and are consistent with the hypothesis that estrogen might play a (modest) role in effect-size of medication in the treatment of acute mania. However, these findings should be interpreted with caution as we had no direct measures of estrogen levels or biological confirmation of menopausal status available and these findings could be explained by factors other than differences in estrogen level such as gender and age differences in medication adherence.

Remarkably, current results are in contrast to earlier studies in patients with schizophrenia, where gender difference was found in favor of women (Storosum et al., 2023; Rabinowitz et al., 2014). Moreover, in contrast to the earlier studies, younger women and men with schizophrenia had a nominally larger response than older men and women.

Interestingly, our findings suggest that gender differences in efficacy were mainly driven by differences in response in the placebo group instead of differences in response in patients receiving active medication (Tables 2 and 3). Women in this study responded better in the placebo group than men. This is in line with the meta-analysis of Yildiz et al. (2011). Both in men and in younger patients, the larger separation between active medication and placebo was related to a lower response in

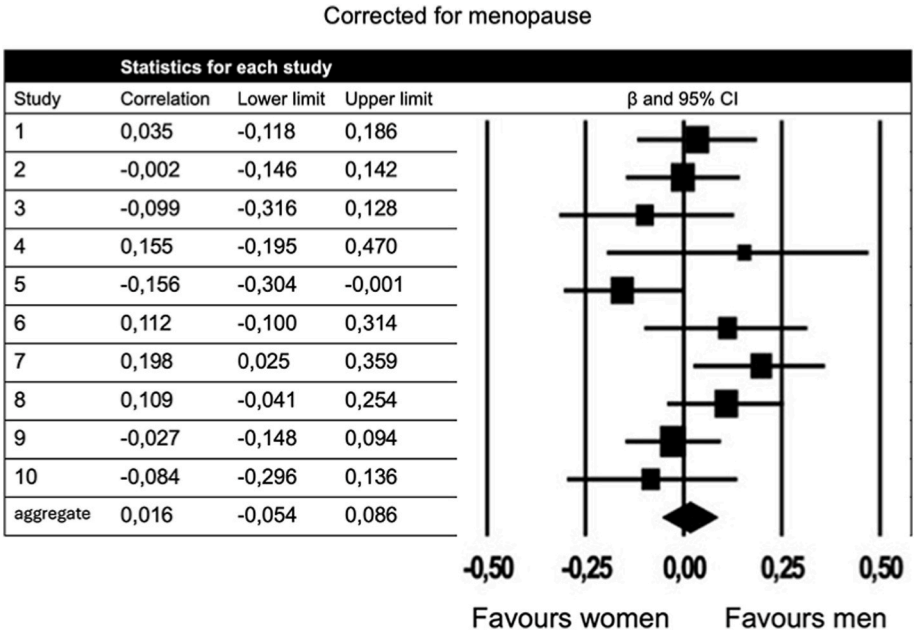

Fig. 3. Interaction of treatment and gender (with main effects) on time to response (β).

the placebo group and not due to a larger response in the active medication group. Indeed, the response in the active medication groups is similar in these trials, while the net benefit of administering antipsychotic medication over placebo is higher in men and younger patients (i.e. effectsize/separation). In clinical practice, this difference in net benefit of antipsychotic medicine over placebo holds true, while the response to active medication that was found in this study may vary, seeing as the latter is dependent on contextual effects relating to treatment-setting and spontaneous factors such as natural course of the disease. Both contextual factors and spontaneous factors may effect women and men differently (Vambheim and Flaten, 2017). This makes the similarity of the response to active medication in women and men less translatable to clinical practice, while the difference in effectsize between men and women holds true in clinical practice.

Our results do not suggest that the increased response in the placebo group in women can be attributed to baseline inflation, as correcting for baseline severity did not influence gender difference in efficacy, but there are other factors that might influence a higher response to placebo in women compared to men.

Our finding contrast the results of Viguera et al., where women and men receiving lithium maintenance therapy did not differ in treatment outcome (Viguera et al., 2001). One explanation of these divergent findings could be related to gender playing a different role in bipolar disorder during the acute phase, and the maintenance-phase. Another possible explanation could be related to the difference in methodology of the current IPD meta-analysis and the aggregate meta-analysis of Virueara et al. IPD meta-analyses are considered the gold standard to explore questions regarding the effect in specific subgroups of patients as it can explore patient-level variation in treatment response (Leboyer et al., 2005). This calls for future IPD meta-analysis of gender differences in bipolar maintenance treatment (and bipolar depression) to explore if gender differences are specific to the manic phase or whether they are also apparent in the maintenance phase.

The current study has both strengths and limitations. The main strengths include the use of a large number of randomized placebo-controlled trials and the use of individual patient data from these studies in the meta-analyses. An important limitation of the current study is that we did not have access to a biological confirmation on the menopausal status of the female subjects, such as estrogen levels. Age, dichotomized around the putative mean age of onset of menopause was thus chosen as a proxy variable for menopause as was done in an earlier study in patients with schizophrenia (Goldstein et al., 2002; Storosum et al., 2023). We also ran sensitivity analyses excluding ages between 45 and 50 to this end, which did not significantly alter results. Also, no data was available about the use of sex hormones at the individual patient level, which may increase estrogen levels in either the pre-menopausal or postmenstrual group. Another important limitation is that our meta-analysis only included a selection of studies, i.e. randomized double-blinded placebo controlled studies and are part of registration dossiers that were submitted to the MEB and were granted a license for registration. The enrolment in these studies took place between 1996 and 2007. These dossiers include all studies (and the individual patient data) that have been conducted before registration and contain positive studies (active treatment superior to placebo) as well as negative studies (active treatment not superior to placebo) making this database rather unique and sufficient for answering the research questions. However, although medications included in the current study are still among the most prescribed anti-manic drugs in current clinical practice, we were not able to include some of the newer anti-manic agents, therefore limiting the generalizability of current findings. Furthermore, although we did correct for baseline severity, the gender difference in response to antipsychotic medication and mood stabilizers might have been confounded by numerous genetic and environmental confounders that potentially influenced the relationship between gender and effect size. Since information regarding marital status, weight, socio-economic status and other environmental factors were not represented in our original data, we could not test their effect on response, which ultimately limits our findings. Additionally, although adherence to orally administered medication obviously influences responsiveness to drug medication, we could not test the effect of this potential confounder because the studies that were included in our meta-analysis did not provide data on repeated therapeutic drug monitoring (TDM) of medication blood concentrations. Including injectable antipsychotic medication for mood stabilization would ensure medication adherence, however our dataset only included oral medication. Therefore, treatment adherence could not be reliably and objectively measured, and we could not address the potential confounding effect of gender differences in treatment adherence. Future research, including trials with TDM or injectable antipsychotic medications, is necessary to investigate the role of treatment adherence in explaining gender differences in efficacy of drug treatment in patients with an acute manic episode. Finally, due to limitations in sample size (especially regarding mood stabilizers) we were not able to perform analyses for mood stabilizers and antipsychotic medications separately because with segregated analyses the number of patients in the gender groups within studies falls below the number of patients, which are necessary to obtain reliable results. Future research would therefore benefit from a larger proportion of patients treated with mood stabilizers, to enable separate analyses on gender differences in for antipsychotic medications and mood stabilizers.

In this individual patient meta-analysis of randomized controlled trials of drug treatment in acute mania for bipolar I disorder, we found a significant, albeit small, effect of gender on response rates and on mean symptom change after three weeks of treatment. Specifically, we showed that response in women patients is smaller compared to men. In both genders, age was positively associated with response, although this effect was higher in women than in men, specifically when dichotomized at age 47 as a proxy for menopause. In previous research, the modulating effect of estrogen on treatment response has often been discussed, especially in schizophrenia but also in acute mania. Although in need of replication studies employing direct measures of estrogen levels, our findings are in line with findings that suggest a negative albeit modest moderating effect of estrogen on drug efficacy.

CRediT authorship contribution statement

Bram W.C. Storosum: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sem E. Cohen:** Methodology, Formal analysis. **Taina K. Mattila:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Kit C.B. Roes:** Methodology, Formal analysis. **Carlijn Welten:** Writing – review & editing, Data curation, Conceptualization. **Wim van den Brink:** Writing – review & editing, Methodology. **Lieuwe de Haan:** Writing – review & editing, Methodology, Conceptualization. **Damiaan Denys:** Writing – review & editing. **Jasper B. Zantvoord:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors of this paper declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.11.014.

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