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RESEARCH

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Ethnic differences in efficacy of drug treatment in patients with an acute manic episode: an individual patient data meta-analysis of randomized placebo-controlled trials

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Abstract

Background Little is known about the effect of ethnicity on drug treatment in patients with an acute manic episode. The aim of this study is to determine whether ethnicity moderates the response to drug treatment in patients with an acute manic episode, and whether this moderation is independent of potential confounders.

Methods We analysed ten short-term placebo-controlled registration trials of atypical antipsychotics and anticonvulsive mood stabilizers in patients with an acute manic episode (n = 2199). A one-step random effects individual patient data meta-analysis (IPD) was applied to establish the moderating effect of ethnicity on symptom improvement on the Young Mania Rating Scale (Y)MRS and on response defined as 50% (Y)MRS symptom reduction. These analyses were corrected for baseline severity, age, and gender. A two-step IPD comparing these outcomes between White, Black and Asian patients. Additionally, a conventional meta-analysis was performed to determine the effect size of drug treatment separately for these ethnic groups.

Results In the complete dataset, 60.4% of the patients was White, 8.0% was Black, 12.7% was Asian, 33.7% was of other ethnicities. Ethnicity did not significantly moderate the efficacy of drug treatment: pooled beta-coefficient (β) for the interaction between treatment and the ethnicities White, Black and Asian, varying from 0.889 to 0.899 with overlapping confidence-intervals ranging from 2.356 to 2.430 in the main analysis. The drug treatment effects were significant in all three analysable ethnicity groups compared to placebo.

Discussion In White,Black, and Asian patients with an acute manic episode drug treatment is equally effective.

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Introduction

In the USA, Bipolar Disorder (BD) is characterized by mania, hypomania, depressive, and mixed episodes. The prevalence rates of BD are similar for White and Non-Hispanic Black populations(Blanco et al. 2017; Breslau et al. 2006; Merikangas et al. 2007), ranging from 2 to 4% (Merikangas et al. 2007; Kessler et al. 2007; Akiskal et al. 2000). Nevertheless, despite following the clearly outlined criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), Black patients with BD are often misdiagnosed as schizophrenia—a chronic vulnerability to non-affective psychoses—possibly due to clinician bias (Chen et al. 1998; Jones and Gray 1986; Kilbourne et al. 2004; Strakowski et al. 2003; Zhang and Snowden 1999). Mania, is characterised by a distinct period of abnormally and persistently elevated, expansive, or irritable mood and is the hallmark of a bipolar I disorder (Association 2013). Besides mood stabilizers and lithium, antipsychotic medications are an important mainstay in the treatment of patients with an acute manic episode. Black patients with BD are receiving antipsychotics more often than White BD patients (Fleck et al. 2002) with no ethnic differences in the use of atypical vs. typical antipsychotics (Szarek and Goethe 2003). Different clinical and demographic factors as well as trial characteristics have been associated with the effect sizes of drug treatment in an acute manic episode: a larger number of collaborating study sites is associated with a smaller treatment effect and the presence of higher baseline mania symptom ratings predicts greater improvement in the active medication arm but not in the placebo arm of studies (Yildiz et al. 2011). In an individual patient data (IPD) meta-analysis, we investigated the effect of gender on drug treatment response in patients with an acute manic episode and found a significant difference in effect size between men and women (Storosum et al. 2022a), with a higher response in men relative to women. In a recent IPD meta-analysis we have shown that atypical antipsychotic medication is equally effective in White and Black patients with schizophrenia (Storosum et al. 2022b). To the best of our knowledge, so far only two studies investigated the moderating effect of ethnicity on response to antipsychotic drug treatment in patients with an acute manic episode. One study compared Black patients (n = 41) to White patients (n = 190) treated with olanzapine. Post-hoc analysis showed similar symptom improvement for groups (Degenhardt et al. 2011). In the second study, treatment with olanzapine was compared between Latin American patients and White patients. Latin American patients treated with olanzapine (n = 51) or haloperidol (n = 48) had similar remission rates (64.7% vs. 68.8%) at week 6, whereas White patients treated with olanzapine (n = 120) had higher remission rates than White patients treated with haloperidol (n = 113): 49.2% vs. 32.7% (p = 0.012) (Tamayo et al. 2007) The relative paucity of research on ethnic differences in the response to drug treatment in acute mania is in contrast to other fields in medicine. For instance, regarding antihypertensives in which Black patients respond less to beta-blockers and ACE-inhibitors than White patients (Brewster et al. 2004).

The aim of the current individual patient data (IPD) meta-analysis is the first meta-analysis to test whether ethnicity moderates the response to drug treatment in patients with acute mania, and whether a potential moderating effect is independent on baseline severity, age, or gender.

Definitions

In the literature, the terms 'race' and 'ethnicity' are often used interchangeably. Due to the negative connotations to the term 'race', we will use the term 'ethnicity', even though 'race' was used in some of the quoted literature and in the databases. Current guidelines of describing specific ethnic groups are followed (e.g., capitalizing and using adjectival forms instead of nouns): 'White' and 'Black' are used instead of 'Caucasian' and 'African-American'.

Methods

Selection of studies

We included all studies (n = 10) submitted to the Dutch Medicines Evaluation Board during an 11-year period (1991–2004) as part of market authorization applications in Europe for the indication acute manic episode of BD. All studies were short-term double-blind randomized, placebo-controlled trials involving patients diagnosed with an acute manic episode of BD (DSM IV criteria). Pharmaceutical companies provided data to enable an IPD meta-analysis. All studies were approved by the ethic committees of their respective research-centers, and all participants gave informed consent. Availability of data on ethnicity was a prerequisite for inclusion. In the database, the following predefined ethnic groups were available: Caucasian, Black, Asian, Oriental, Hispanic, Native American, and Other. The original studies were identified for the purpose of collecting manuscripts and corresponding authors were contacted in case of unclarities or missing information (e.g., on the definition of ethnic subgroups). In addition, the ethnic subgroups were examined and redefined according to the current JAMA Network guidelines as: American Indian or Alaska Native, Asian, 'Black', Native Hawaiian or Other Pacific Islander, 'White' and 'Some Other Race' (Flanagin et al. 2021). In the original studies, the term 'race' was used, or may have been used interchangeably with 'ethnicity'.

We further restricted the analyses to subjects that were given a potential effective dose of the medication, as indicated in the Summary of Product Characteristics (SmPC). Patients receiving dosages under the minimal effective dose or over the maximum doses as stated in the SmPC) were excluded. Risk of bias was assessed using the Risk of Bias tool (Stewart et al. 2015). The guideline for the preferred reporting items for systematic reviews and meta-analyses (PRISMA) was followed except for items pertaining specifically to systematic reviews (Flanagin et al. 2021). We pre-specified our methods and analysis plan in the PROSPERO database for systematic reviews (ID: CRD42024543671). There were no deviations from the analysis-plan state in the PROSPERO protocol.

Instruments

Severity of manic episode

The severity of the acute manic episode of BD 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 items are scored on a 0–8 scale. The total score thus 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 thus ranges from 0 (no symptoms) to 52 (severe symptoms) (Endicott and Spitzer 1978).

Outcome

We used two efficacy outcomes: the standardised difference in mean change score on the (Y)MRS from baseline to follow-up and the difference in percentage of responders. Patients were considered a responder if their score on the YMRS or MRS decreased by 50% or more from baseline to follow-up (Endicott and Spitzer 1978). Since two different rating scales were used in the studies, we decided to use mean percent improvement as primary outcome measure. The endpoint was defined as 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, we imputed 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 percent responders between active treatment and placebo at endpoint (LOCF) were considered as the main outcome measures.

To examine possible confounding effects, baseline severity, age, and gender were used as covariates in the various statistical models. To provide an impression of the possible influence of the publication date of the individual studies on the results, the studies were ranked in chronological order.

Statistical analysis

We used a one-stage, random effects IPD meta-analysis. Traditional methods for meta-analysis synthesis use aggregate study level data that are generally obtained from publications. Meta-analysis synthesis of individual patient data uses the crude data from individual patients from each study. To explore participant-level variations and to control for potential confounders and between-study heterogeneity, IPD meta-analysis was chosen over pooled linear regression analysis or study aggregate meta-analysis Because of existing heterogeneity between studies (e.g., different patient populations, different types of medications, and different companies), random effect rather than fixed effect models were used. The one-stage approach was chosen over the two-stage for primary analysis, as it can analyse predictors at the subject-level, has more power to detect treatment-covariate interactions and leads to less bias when few studies or studies with small sample sizes are included.

In case of missing data for some subjects in one or more studies, the last observation will be carried forward (LOCF). This approach was chosen to maintain consistency across different studies that provided incomplete data, ensuring comparability in the pooled estimates. Also, this approach was chosen in all original efficacy trials, making our resulst better interpretable in context. However, we acknowledge that LOCF can introduce bias—particularly if dropout is related to lack of effect or adverse events—and may therefore overestimate or underestimate the true treatment effect. In addition, imputing missing (Y)MRS items using LOCF may reduce variance inappropriately or produce misleading effect sizes if attrition is non-random. Despite these limitations, LOCF was deemed appropriate based on our short-term data set constraints and the need to harmonize data handling across multiple trials. Forest plots for each primary outcome will be visualized as it provides an overview in which combined estimates, inconsistency across studies and the precision of individual studies can be examined.

Between-study heterogeneity was in part be mitigated by the study-specific fixed intercept and random treatment effect, and was further be corrected by adjusting for confounders such as baseline severity,

age, and gender in order to determine the effect of a treatment*ethnicity interactionterm in addition to an ethnicity variable.

As a sensitivity analysis for the one-stage IPD, a two stage approach was used. The two-stage IPD analysed studies that included at least 5 patients from each ethnicity group in each study arm in order to ensure adequately powered analysis. In the two stage analysis ethnicity was defined as a dichotomous variable, alternating two ethnicity subgroups so every effect between them can be compared.

For the first step, we calculated the total scores on the respective questionnaires at baseline and week three. We also calculated response rate, defined as at least 50% reduction of (Y)MRS score between baseline and week three. Subsequently, for each study, multivariate linear regression analyses were performed with mean percentual (Y)MRS change from baseline as the dependent variable and treatment condition, ethnicity, and treatment condition*ethnicity as the independent variables.

Similarly, for each study, a multivariate logistic regression analysis was performed with response as dependent variable. Thus, in both analyses (symptom change from and response as the dependent variable), for each study, the interaction of ethnicity*treatment condition (active medication vs placebo) was added to the main effects (ethnicity and treatment condition) as an independent variable for a modifier effect of ethnicity on treatment effect. Subsequently, to examine the effect of baseline severity, age, and gender these variables were cumulatively added as independent variables to the main effects and the interaction of ethnicity by treatment. For these analyses, the Statistical Package for the Social Sciences (SPSS) version 26 was used.

As the second step, a random effect meta-analysis was performed with the regression-coefficients and odds ratios (ORs) for the treatment condition*ethnicity interactions in the different studies. In these analyses, the 95% confidence interval (CI) indicates the scope of uncertainty in the effect estimate of the treatment condition*ethnicity interactions considering heterogeneity between studies. For these analyses, the Comprehensive Meta-Analysis (CMA) version 2 software was used.

Finally, the treatment effect in the different ethnic subgroups (White, Black and Asian) was examined separately. A conventional IPD meta-analysis for each ethnic group was performed, yielding ethnicity-specific pooled mean differences in outcomes (symptom change and response) between participants receiving active medication and participants receiving placebo.

Results

Study selection and baseline characteristics

The original database consisted of 10 studies with a total of 2199 patients. Of these, 1281 (58.3%) were White patients, 175 (8.0%) were Black patients 269 (12.2%) were Asian, 41 (1.8%), were Oriental, 45 (1.8%) were Hispanic, and 384 (17.5) were described as having " Other" ethnicity. All patients could be included in the one-stage IPD. Six of these studies, with a total of 874 patients, had enough participants per study arm ($n > 5$) to perform adequately powered comparisons between White and Black patients: 700 White patients (80.1%) and 174 Black patients (19.9%). Four of the studies had enough participants per study arm to perform adequately powered comparisons between Asian and white patients: 662 (72.5) white patients and 251 (27.5%) asian patients. Two studies had enough participants per study arm to compare Black and Asian patients: 79 (51.6%) black and 74 Asian (48.4%). Nkone of the studies had enough patients included of ethnicities other than White, Black, or Asian to perform adequately powered analyses. The 'Other' group had patients with mixed ethnicities, rendering them unsuitable to be subdivided into the existing groups.

Based on the Cochrane Risk of Bias Tool, all studies were determined as low risk (Table S1).

Table 1 presents demographic and clinical baseline characteristics per ethnic group. There were no relevant baseline differences between ethnic groups. There was no relevant difference in dropout rate between ethnic groups.

For a list of demographic characteristics per study, please see appendix 1.

Moderating effect of ethnicity on treatment effect

Figure 1 presents the result of the one-stage IPD meta-analysis. It shows that the effect modifying properties on the YMRS change from baseline between placebo and active modification, is almost identical for being White, Black or Asian. This is represented by a β that is respectively 0.898 (95% CI − 0.289 to 2.068), 0.890 (95% CI − 0.279 to 2.057) and 0.889 (− 0.276 to 2.989). There was nog statistically significant difference between these groups.

Figure 2 presents the results of the two-stage IPD meta-analysis of the interaction term ethnicity*treatment (with ethnicity defined as a dichotomous variable White or Black). There is no significant overall treatment condition*ethnicity effect, indicating that ethnicity does not moderate the effect of drug treatment in these studies on acute mania between White and Black patients. This is represented by an over-all pooled beta of − 0.063

Table 1 Baseline characteristics

	White		Black		Asian	
	Active compound	**Placebo**	**Active compound**	**Placebo**	**Active compound**	**Placebo**
N (%)	1281 (60.4)		175 (8.0)		269 (12.7)	
N (%)	763 (59.6)	518 (40.4)	102 (58.3)	73 (41.7)	159 (59.1)	110 (40.9)
N using mood stabiliser	118		15		71	
Age in years, mean (SD)	41.9 (12.769)	40.54 (12.20)	38.79 (11.00)	39.9 (9.470)	33.50 (10.708)	34.5 (11.63)
Gender f %	415 (54.4)	257 (49.6)	40 (39.2)	32 (43.8)	23 (74.2)	11 (78.2)
MRS						
N (%)	171		32		63	
N (%)	68	103	15	17	23	40
MRS score at baseline, mean (SD)	27.35 (6.8)	26.31 (6.52)	29.5 (8.749)	32.8 (7.248)	28.43 (4.143)	28.1 (4.971)
YMRS						
N (%)	795		143			
N (%)	695	415	87	56	136	70
YMRS score at baseline, mean (SD)	30.08 (5.936)	29.88 (6.603)	28.8 (5.535)	28.64 (6.019)	33.07 (7.483)	33.01 (6.736)
Dropout rate N (%)	289 (38.0)	253 (0.49)	40 (39.8)	35 (0.48)	67 (0.36)	56 (0.51)

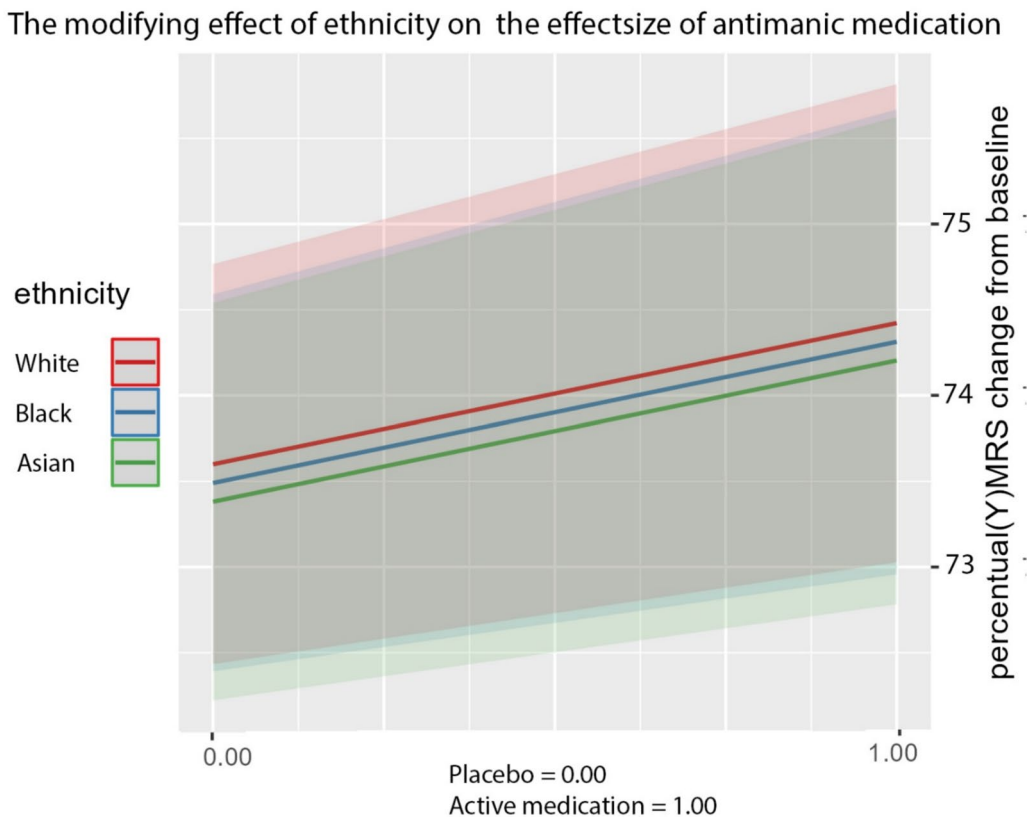
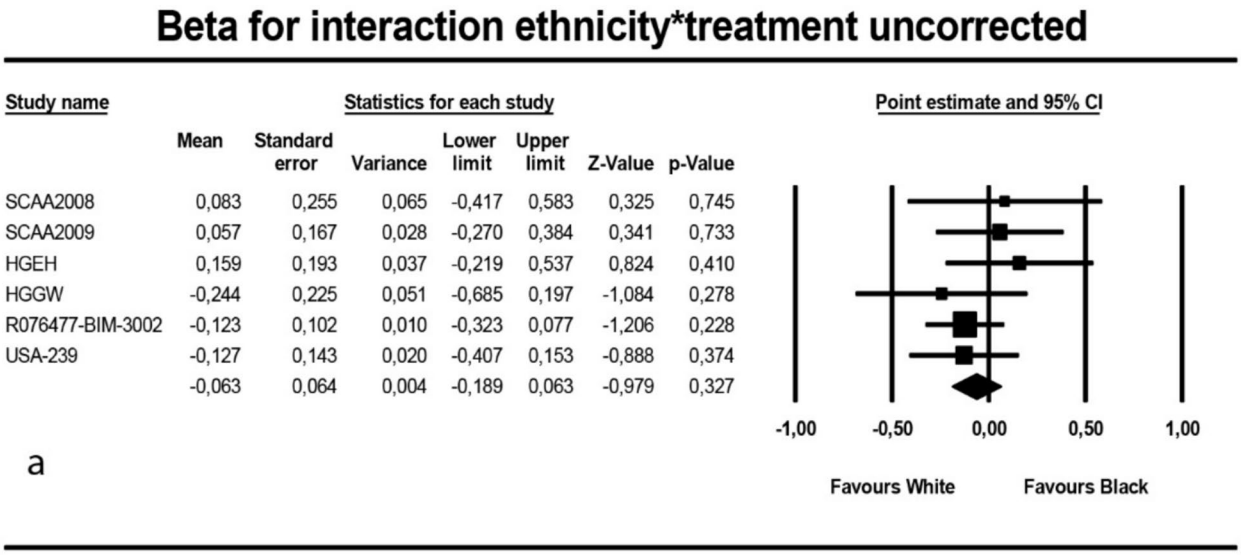


Fig. 1 The modifying effect of ethnicity on the effectsize of antimanic medication

(95% CI of − 1,189 to 0,063) for mean percentual (Y)MRS change as the dependent variable (Fig. 2a) and a pooled beta of − 0,406 (95%CI of − 1,198 to 0,387) for response



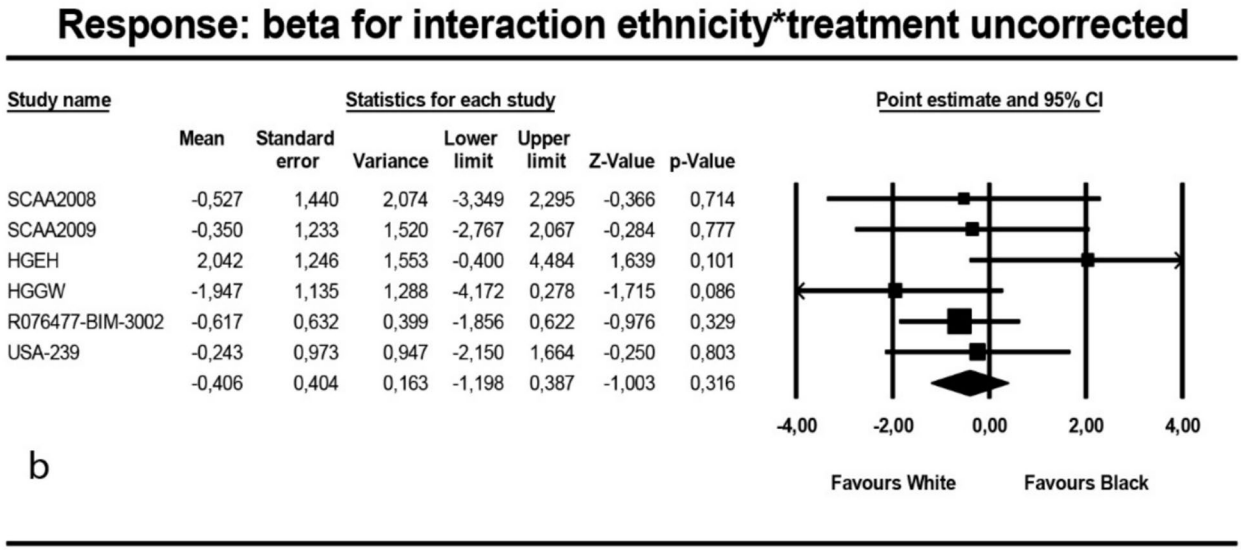
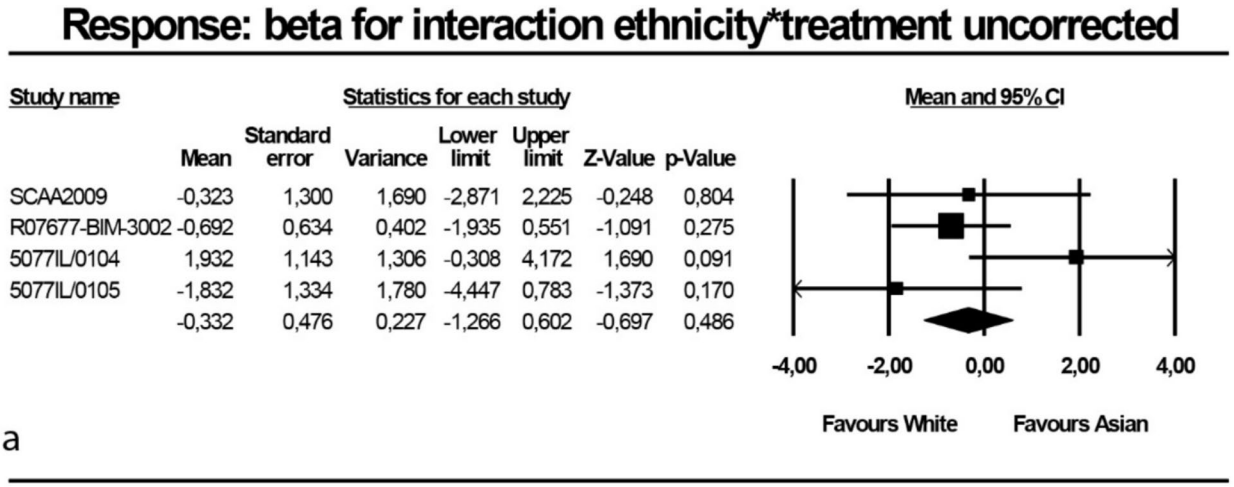


Fig. 2 The modifying effect of White vs. Black ethnicity on the effectsize of antimanic medication

as the dependent variable (Fig. 2b), the latter translating to a to an OR of 0.663 (95% CI of 0.302 to 1.473). Adding confounders to the model did not substantially change results (Figure S1).

Figure 3 presents the results of the two-stage IPD meta-analysis of the interaction term ethnicity*treatment (with ethnicity defined as a dichotomous variable White or Asian). There is no significant overall treatment condition*ethnicity effect, indicating that ethnicity does not moderate the effect of drug treatment in these studies on acute mania between White and Asian patients. This is represented by an over-all pooled beta of − 0.332 (95% CI of − 1,266 to 0,602) for mean percentual (Y)MRS change as the dependent variable (Fig. 3a) and a pooled beta of − 0,111 (95%CI of − 0,355 to 0,134) for response as the dependent variable (Fig. 3b), the latter translating to a to an OR of 0.895 (95% CI of 0.701 to 0.875). Adding confounders to the model did not substantially change results (Figure S2).

Figure 4 presents the results of the two-stage IPD meta-analysis of the interaction term



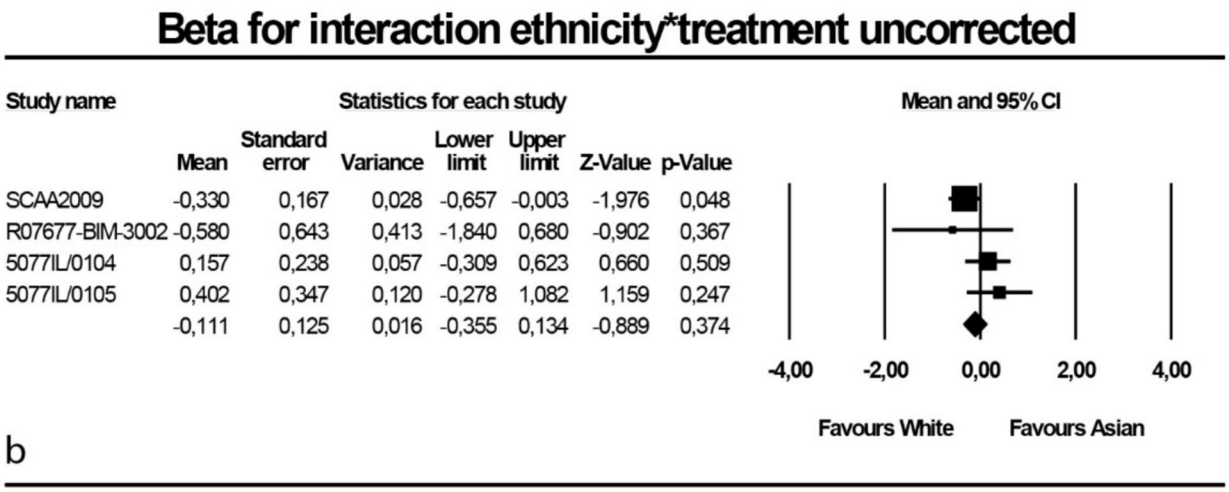
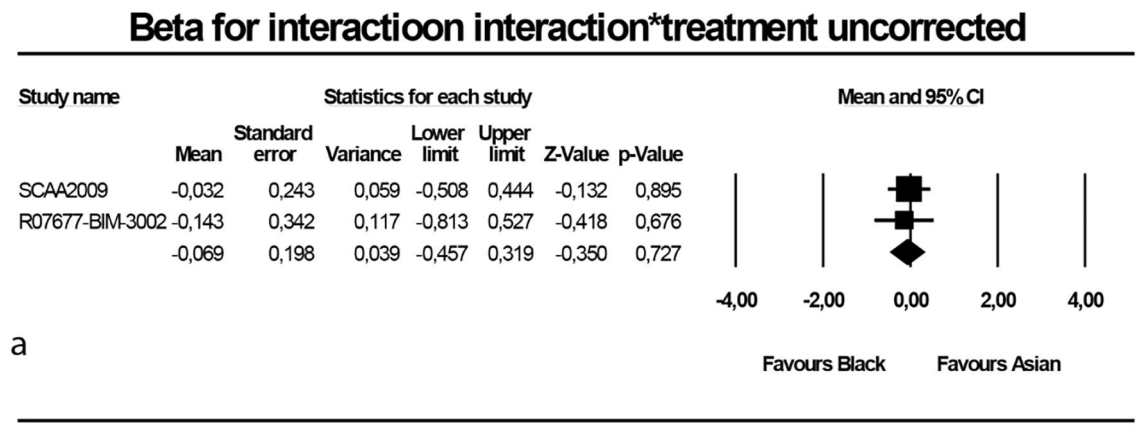


Fig. 3 The modifying effect of White vs. Asian ethnicity on the effectsize of antimanic medication

ethnicity*treatment (with ethnicity defined as a dichotomous variable Black or Asian). There is no significant overall treatment condition*ethnicity effect, indicating that ethnicity does not moderate the effect of drug treatment in these studies on acute mania between White and Asian patients. This is represented by an over-all pooled beta of − 0.069 (95% CI of − 0,457 to 0,319) for mean percentual (Y)MRS change as the dependent variable (Fig. 4a) and a pooled beta of − 0,001 (95%CI of − 2,335 to 2,334) for response as the dependent variable (Fig. 4b), the latter translating to a to an OR of 0.999 (95% CI of 0.097 to 10.319). Adding confounders to the model did not substantially change results (Figure S3).

Conventional meta-analysis of treatment effect separately for the two ethnicity-groups

Figure 5 shows the over-all pooled effect sizes of (Y)MRS change and response separately for Black and White patients. The effect sizes show a statistically significant beneficial effect of active treatment compared to placebo in both White and Black patients. In White patients, there is a statistically significant pooled standardized mean difference of 0.340 (95% CI of 0.184 to 0.496) in (Y)MRS change (Fig. 5a) and a statistically significant



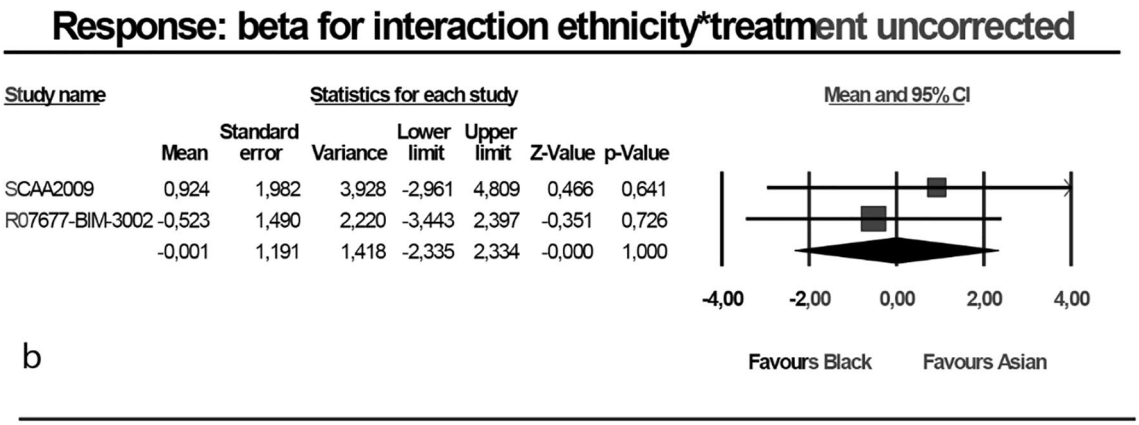


Fig. 4 The modifying effect of Asian vs. Black ethnicity on the effectsize of antimanic medication

pooled odds ratio of 2.122 (95% CI of 1.537 to 2.930) for response (Fig. 5b). In Black patients, there is a statistically significant pooled standardized mean difference of 0.158 (95% CI of 0.042 to 0.661) in (Y)MRS change (Fig. 5c) and a pooled odds ratio of 1.428 (95% CI of 0.698–2.922) for response, which was not significant (Fig. 5d). In Asian patients, there is a statistically significant pooled standardised mean difference of 0.240 (95% CI 0.110 to 0.894) in (Y)MRS change (figure Asian patients (Fig. 5e) and a pooled odds ratio of 2.122 (95% CI of 1.537 to 2.930).

Discussion

In this individual patient data (IPD) meta-analysis we did not find a significant moderating effect of ethnicity (White patients vs. Black patients vs. Asian patients) in the effect of antipsychotics or mood stabilisers in the treatment of an acute manic episode of bipolar disorder. This finding was independent of baseline severity, age, and gender. Thus, medication was equally effective in these three ethnic groups.

Our selection of studies resulted in the inclusion of more White patients than Black or Asian patients (60.1% White patients compared to 8.0% Black patients an 12.0% Asian patients) (Table 1 indicating that these ethnicities were adequately represented when compared to the ethnic distribution of the United States population(Bureau 2020).

Our main analysis showed that the effect of being of White, Black, or Asian ethnicity is clinically irrelevant, as none of these variables were significant in moderating the effect of YMRS symptom change when comparing the placebo-group to the active medicationgroup. To illustrate our findings: the Beta coefficient for the interaction term of treatment and ethnicity came out at 0.063, indicating that the improvement in (Y)MRS trends towards only 6.3 percentage points less in black patients compared to white patients which is also a not significant finding.

In a comparable study performing IPD meta-analysis on 22 short term randomised controlled registration trials for atypical antipsychotics in schizophrenia we found

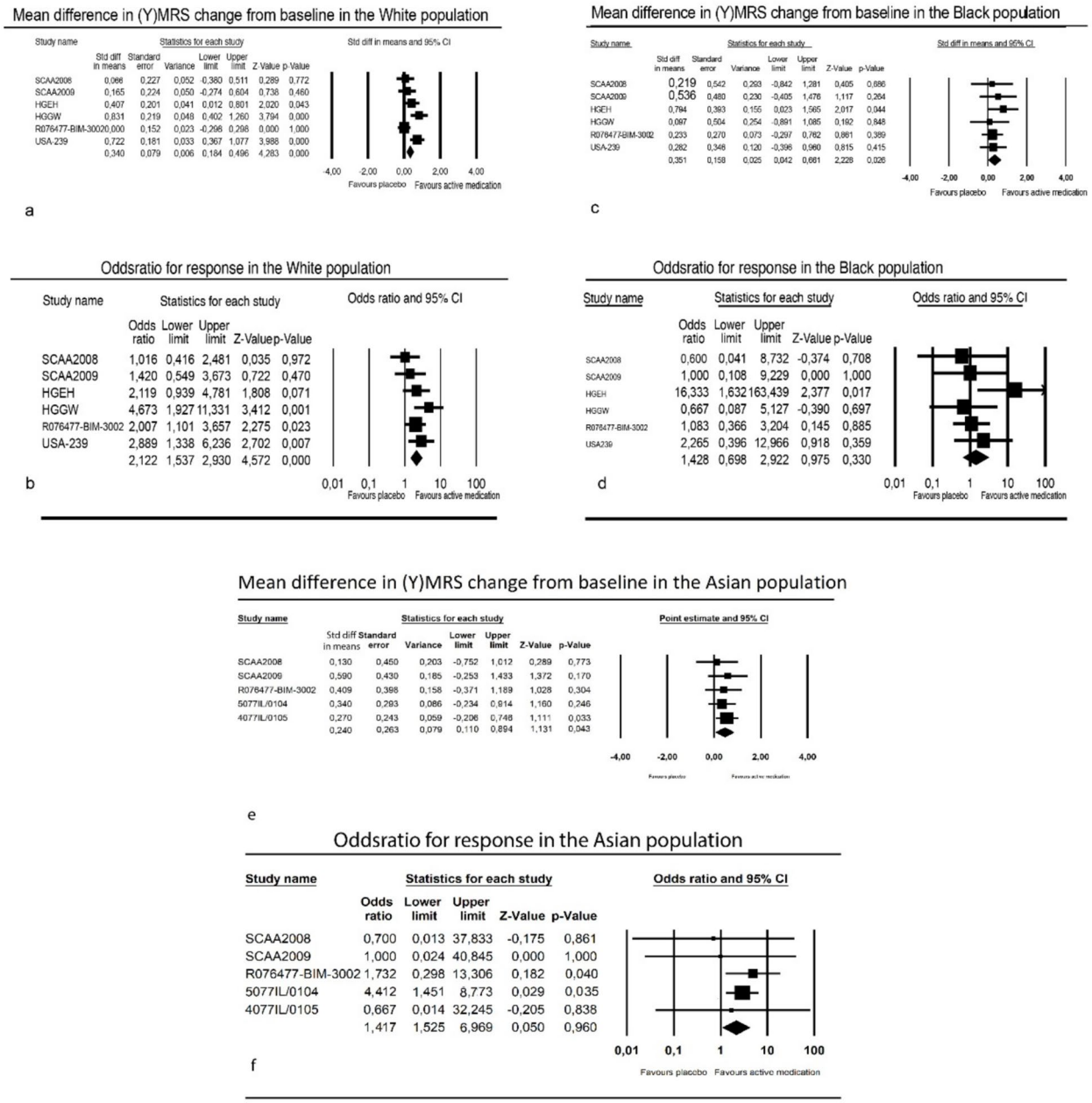


Fig. 5 Effectsize of antimanic medication in White, Black, and Asian ethnicities

very similar results: drug treatment was equally effective in Black (N = 1328) and White (N-2552) patients with schizophrenia. (Storosum et al. 2022b). It is of note that although Black patients were not adequately included in the registration trials for schizophrenia compared to the ethnic distribution of schizophrenia in the US population, the total absolute number of Black patients in these trials was higher than in this current study.

This leads us to a possible explanation for not finding a difference in efficacy of medication treatment in acute mania between Black and White patients in this study. Although we pooled individual patient data from ten different registration trials, creating the largest dataset investigating effect size differences between ethnicities to date, it could still be underpowered to find these differences, with only 175 Black participants allowing for false negative results.

Also, ethnicity may be associated with many factors that could increase or decrease efficacy of medication (Stronks et al. 2013). We were not able to control for

underlying or associated factors that may have influenced treatment efficacy. There are some indications that there is a difference in side effects between different ethnic groups (Degenhardt et al. 2011; Tamayo et al. 2007) and that genetic ancestry may influence the pharmacodynamic profile (Wiers et al. 2018; Chaudhry et al. 2008). A review of 51 studies describing side effects of antipsychotic medication in patients with schizophrenia found evidence of ethnic differences in the risk of adverse events (Arnold et al. 2013). In addition, genetic profiles vary widely within ethnic groups and there is no proof of an underlying explanation for possible differences in the prevalence of side effects.

The main strength of our study is the inclusion of individual patient data from a relatively large group of patients with acute mania from double-blind randomised placebo-controlled trials. This increases the reliability and generalisability of our findings, by quantifying the effect modification while accounting for heterogeneity between studies. Our study is, however, not without limitations. Only a few of the studies analysed in the main analysis could be included in the sensitivity analysis due to an insufficient number of participants per study arm ($n > 5$). This may limit the generalisability of our findings. Second, because the enrolment of included studies was between 1991 and 2004, the newest medications were not examined. However, medications included in the current study are still the most prescribed drugs in current clinical practice (Hálfdánarson et al. 2017). In addition, due to agreements with pharmaceutical companies, we were not able to examine the effect of ethnicity for specific (types of) medications. This may be an important limitation as antipsychotics were found to be significantly more effective in the treatment of acute mania than mood stabilisers, with haloperidol, risperidone, and olanzapine ranked as the most potent (Cipriani et al. 2011). The fact that we could not examine the drugs individually may mask possible ethnic differences for specific medications. Finally, it should be noted that meta-analysis even with data from randomized controlled trials should be viewed as a naturalistic experiment with a serious risk of confounding. Fortunately, we were able to control for several potential confounders, but residual confounding cannot be excluded. For example, patients with a rapid cycling course or with mixed episodes are associated with a more severe course and could be associated with ethnicity and treatment outcome (Valenti et al. 2015; Vieta et al. 2013). These data were not available in our dataset.

Due to a lack of complete information on the inclusion date of patients, we were not able to examine the inclusion date as a confounder to the model. However, the forest plots were sorted on publication date of the studies (with ascending date ranging from 1990 to 2004). When viewing these forest plots, there does not seem to be an influence of publication date on the moderating effect of ethnicity.

In conclusion, our findings show that in medication is equally effective in White and in Black patients with acute mania.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40345-025-00371-0.

Additional file 1.

Additional file 2.

Author contributions

B.W.C. Storosum: Conceptualization, Methodology, Formal analysis, Investigation, Writing—Original Draft, Visualization,, S.E. Cohen: Methodology, Formal analysis, Validation, Cedrine Steinz: Formal analysis, Validation, Dr. T. Mattila: Methodology, Supervision, Writing—Review & Editing, Data Curation, Prof. dr. K.C.B. Roes: Methodology, Prof. Dr. C.C. Welten: Methodology, Writing—Review & Editing, Data Curation, Prof. Dr. W. van den Brink: Writing—Review & Editing, Supervision, Prof. Dr. L. de Haan: Writing—Review & Editing, Supervision, Conceptualisation, Prof. Dr. D.A.J.P. Denys: Writing—Review & Editing, Supervision, Conceptualisation J.B. Zantvoord:Writing—Review & Editing, Supervision, Conceptualisation, Project administration, Methodology.

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Availability of data and materials

Restrictions apply to the public availability of these data, especially regarding the specific compounds that were investigated. 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 active treatments.

Declarations

Ethics approval and consent to participate

Internal Review Boards of the various pharmaceutical companies have approved of the randomised controlled trials that were included in this study. All participants of these trials gave informed consent to participate.

Competing interests

The authors declare no competing interests.

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