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Brief Report

Does antidepressant treatment response depend on specific symptoms of depression? A multi-trial study

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ABSTRACT

Background: There is considerable heterogeneity in antidepressant treatment response across individuals. As people with depression may manifest different symptom profiles, we hypothesized that the constellation of specific depressive symptoms might explain some of the heterogeneity in antidepressant treatment response. To assess this hypothesis, we examined symptom-specific remission related to antidepressant vs placebo treatment among those with and without a treatment response.

Methods: Data were from 19 randomized controlled trials (n = 7,344). Depressive symptoms were assessed with the 17-item Hamilton Depression Rating Scale (HDRS-17). Data on treatment were dichotomized into active treatment vs placebo. Treatment response was defined as ≥50% reduction in the HDRS-17 sum score during trial follow-up. Associations of antidepressant treatment with symptom remission were assessed in logistic regression models conducted separately for each symptom, adjusting for age, sex, follow-up time, and the presence of the symptom at baseline. Treatment responders and non-responders were analyzed separately. We also assessed trajectories of symptom remission across the trial follow-up in both treatment conditions among responders and non-responders.

Results: There were no coherent differences in symptom remission between the antidepressant and placebo conditions either among responders (OR=0.75–1.28) or non-responders (OR=0.49–1.35). Likewise, there were no coherent differences between the remission trajectories either among treatment responders or non-responders.

Limitations: Treatment responders and non-responders were analyzed separately, which may have introduced bias that could affect the validity of our findings.

Conclusions: We observed no consistent evidence that treatment response to antidepressants depends on the patient's specific symptom profile.

1. Introduction

Antidepressants are widely used to treat major depressive disorder. Meta-analytic evidence suggests that antidepressants are moderately effective compared to placebo, with effect sizes for efficacy ranging between 1.37 and 2.13 (odds ratios) (Cipriani et al., 2018). However, there is substantial heterogeneity in the treatment response, indicating that some individuals benefit more than others. Up to a half of treated individuals may not have a clinically significant treatment response (Corey-Lisle et al., 2004; Gueorguieva, 2011; Thomas et al., 2013), which is commonly defined as a reduction of ≥50% in the total depression score (Bobo et al., 2016; Furukawa et al., 2007; Nierenberg and DeCecco, 2001). Part of the antidepressant treatment effect may also be explained by a placebo effect (Furukawa et al., 2016).

Despite the effectiveness of antidepressants, it is still unclear how antidepressants work, and which factors determine individual differences in treatment response. Symptom-specific analyses of antidepressants have suggested that the antidepressant treatment effect may be greater for some depressive symptoms than others (Hieronymus et al., 2016a). For example, treatment effect may be more marked for 'depressed mood' compared to the sum of all symptoms. Other studies have shown differences in risk factors and social impairment between specific

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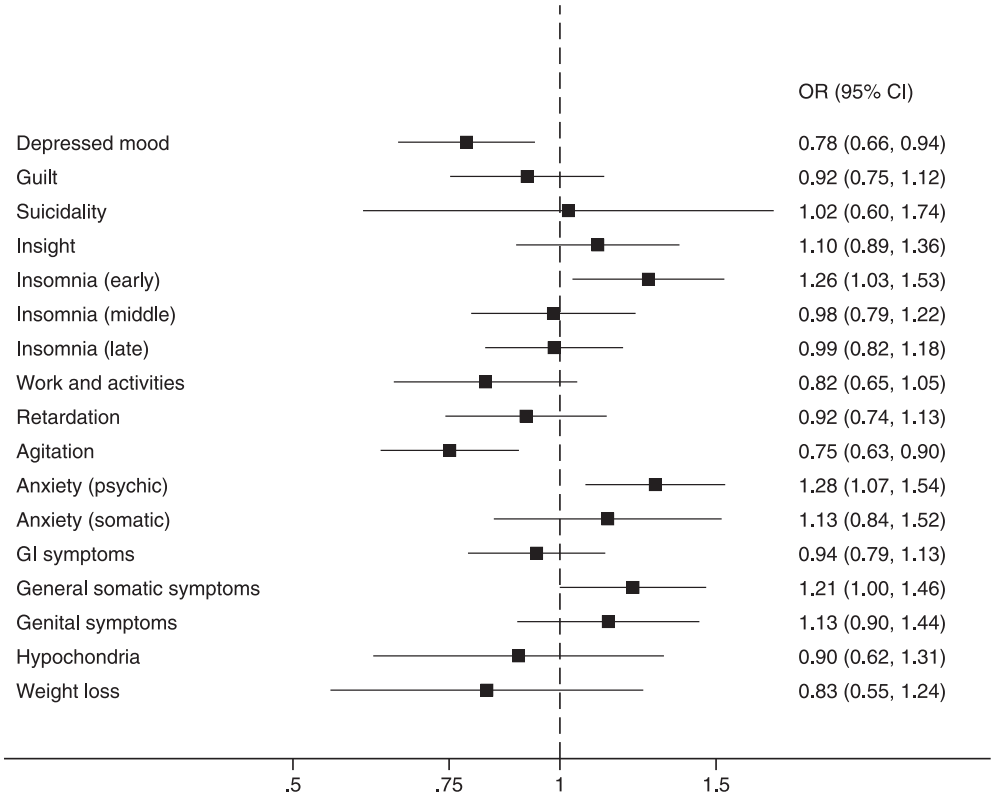

Fig. 1. Associations of antidepressant treatment (vs placebo) with presence of a symptom at follow-up among treatment responders.
Abbreviations: OR, odds ratio; CI, confidence interval n = 3304 (active treatment vs placebo n = 2604 vs 700).

symptoms of depression (Fried and Nesse, 2014; García-Velázquez et al., 2019). Together these results suggest that the constellation of specific depressive symptoms might help to explain some of the heterogeneity in antidepressant treatment response.

However, a more detailed symptom-specific analysis of treatment-response heterogeneity needs to examine the symptom trajectories associated with antidepressant treatment versus placebo among those who achieve clinically significant treatment response. These trajectories can then be compared to symptom trajectories among those who do not achieve treatment response in order to assess whether any differences between antidepressant treatment and placebo are specifically related to treatment response versus non-response. We used data from 19 randomized controlled trials to examine these symptom-specific associations related to antidepressant treatment vs placebo treatment among those with and without a treatment response.

2. Methods

Data were from 19 industry-sponsored, US Food and Drug Administration (FDA)-registered, placebo/active treatment-controlled phase 3 efficacy trials among adult patients with major depression for paroxetine (GSK/003, GSK/009, GSK/115, GSK/448, GSK/449, GSK/487, GSK/810, GSK/874, HMATa, HMATb, HMAYa, HMAYb, HMCV), duloxetine (HMAH, HMATa, HMATb, HMAYa, HMAYb, HMBHa, HMBHb, HMBV, HMCB, HMCR, HMCV), fluoxetine (GSK/115), imipramine (GSK/003) and escitalopram (HMCR) from GlaxoSmithKline (Brentford, UK) and Eli Lilly (New York, NY). We included all randomized patients with baseline assessment and at least one post-baseline assessment (n = 7344). Depressive symptoms were measured with the 17-item Hamilton depression rating scale (HDRS-17, see Fig. 1 for list of symptoms) on scales ranging 0–4 or 0–2 (greater values indicate greater severity). To assess post-treatment symptom remission, the responses to HDRS-17 items were dichotomized into 0 (symptom not present, i.e., an indication of remission) vs ≥1 (symptom present, i.e., no remission) at the last available assessment for each patient. Data on treatment were dichotomized into active antidepressant treatment vs placebo. Treatment response was defined as ≥50% decrease in the HDRS-17 sum score between baseline and the last available assessment for each patient.

Associations of antidepressant treatment with symptom remission were assessed in a series of logistic regression models where antidepressant treatment (vs placebo) was used to predict the presence of a symptom at the follow-up (i.e. each patient's last available assessment). Separate models were conducted for each HDRS-17 symptom. All models were adjusted for age, sex, follow-up time and the presence of the outcome symptom at baseline. Treatment responders (n = 3304) and non-responders (n = 4040) were analyzed separately. To illustrate the trajectories of symptom remission associated with antidepressant treatment, we plotted marginal predictions for the probability of each symptom being present at each assessment time in both treatment conditions. These predictions were obtained from sex- and age-adjusted population-averaged random-intercept logistic multilevel regression models in which the presence of a symptom was predicted by the treatment condition, time indicator (assessment week coded as a categorical variable) and an interaction term between the treatment condition and the time indicator.

As sensitivity analyses, we conducted all analyses separately among patients receiving SSRI (paroxetine, fluoxetine and escitalopram) vs placebo and among patients receiving SNRI (duloxetine) vs placebo.

3. Results

Of the 7344 patients, 4542 (62%) were women. The mean age was 45.4 years (SD=15.5). Follow-up times (between baseline and last available assessment for each patient) varied between 1 and 12 weeks, with a mean of 9 weeks (SD=2.3) among treatment responders and 8 weeks (SD=3.2) among non-responders. A total of 2604 (79%) responders and 2629 (65%) non-responders received antidepressant treatment.

In symptom-specific analyses among treatment responders, the overall pattern of results with most of the HDRS-17 symptoms suggested no coherent differences between the antidepressant and placebo conditions

at follow-up: no specific symptom cluster or domain (e.g., cognitive, affective, somatic) showed higher or lower likelihood of remission associated with antidepressant treatment, although associations with some individual symptoms were observed. Antidepressant treatment was associated with higher probability of remission in depressed mood and agitation, but lower probability of remission in early-night insomnia, psychic anxiety, and general somatic symptoms (**Fig. 1**). The trajectories of symptom remission between antidepressant vs placebo conditions were mostly overlapping (**Fig. 2**), although there were some symptom-specific differences corresponding to the results comparing follow-up vs baseline (e.g., higher probability of remission in depressed mood and agitation, but lower probability of remission in insomnia (early in the night), psychic anxiety and general somatic symptoms).

Similarly to those with treatment response, the symptom-specific pattern of results among patients with no treatment response suggested no coherent differences: antidepressant treatment was not associated with remission in any specific domain of depressive symptoms, although associations of antidepressant treatment with remission in individual symptoms were observed. Antidepressant treatment was associated with higher probability of remission in depressed mood, guilt, suicidality, difficulties in work and activities, agitation and genital symptoms, but lower probability of remission in psychic and somatic anxiety as well as hypochondria (**Supplementary Fig. 1**). Among non-responders, the differences in the trajectories between the antidepressant vs placebo conditions were somewhat more pronounced than among treatment responders. For instance, we observed higher probability of remission in depressed mood, guilt and suicidality, and lower probability of remission in anxiety and hypochondria in the antidepressant condition among those with no treatment response. However, as with responders, no systematic differences between the remission trajectories were observed among non-responders (**Supplementary Fig. 2**).

The results were similar when patients receiving SSRI and SNRI (vs placebo) were analyzed separately (**Supplementary Figs. 3–10**).

4. Discussion

In this analysis of 7344 patients from 19 randomized antidepressant trials, we did not observe systematic differences in the remission of specific depressive symptoms when comparing antidepressant vs placebo conditions among those with or without a treatment response (i.e., ≥50% decrease in total depression score). Most of the symptoms showed no differences between antidepressant and placebo groups, and the differences that were observed were not uniform: some symptoms showed higher and others lower likelihood of remission in antidepressant treatment versus placebo. Furthermore, the trajectories of symptom remission between antidepressant versus placebo conditions were mostly overlapping throughout the course of the treatment. The associations were largely similar among those with no treatment response (i.e., <50% decrease in total depression score), which further provided evidence against symptom-specific associations that would specifically describe a more successful treatment response associated with antidepressant treatment.

Recent research based on network models and symptom-specific analysis of depressive symptoms has suggested that specific symptoms of depression may be characterized by different etiology, temporal dynamics, response to treatment, and associations with social impairment (Fried and Nesse, 2015, 2014; Hieronymus et al., 2016b; Komulainen et al., 2020). We therefore hypothesized that symptom-specific associations might also help to explain individual differences in treatment response to antidepressants as compared to placebo response. That is, a successful antidepressant treatment might act specifically on certain symptoms more than others, which would differentiate the treatment response to antidepressants from the corresponding placebo effect. We observed no systematic evidence to support this hypothesis, as the treatment response and placebo response were mostly similar, and the differences that were observed were mixed.

Our result is in agreement with a recent meta-analysis that found little evidence for the presence of subpopulations that would benefit from antidepressant treatment above the average treatment effect (Volkmann et al., 2020). However, it must be emphasized that our analysis focused specifically on the symptom differences between antidepressant treatment and placebo among those with a treatment response, so the current analysis should not be interpreted as an analysis of the effectiveness of antidepressants. Rather, we were interested in the symptom-specific patterns related to successful treatment response.

Some limitations need to be acknowledged. First, at least one study has suggested that the pattern of depressive symptoms in a depressive episode may depend on the events and life circumstances that triggered the depressive episode (e.g., death of a loved one, ending a romantic relationship, personal failure, or chronic stress) (Keller et al., 2007). These life events may also influence the probability of treatment response and recovery. We did not have data on the background variables related to the onset of depression, so we could not adjust for these potential confounding factors. Second, although our data were from randomized trials, we assessed the associations of antidepressant treatment with symptom-level remission separately among those with and without treatment response. This naturally makes the study design not randomized, and the selection of only treatment responders in the analysis may have introduced bias that could have affected the validity of our findings. Third, symptom remission was assessed with dichotomous measures (symptom absent vs present) that did not capture more detailed reductions in symptom severity; while complete symptom remission is the desired outcome of antidepressant treatment, even smaller reductions in symptom severity may be relevant. Fourth, the patients were adults with major depressive disorder who had to meet the standard eligibility criteria for antidepressant trials, which may limit the generalizability of our findings to more natural clinical settings. Fifth, we conducted the analyses in the intention-to-treat population where the follow-up times between treatment initiation and assessment of symptom remission ranged from 1 to 12 weeks. It is possible that not all participants had sufficient time to experience consistent symptom-level remission, if more systematic patterns of symptom remission only occur at longer time intervals. Finally, although we additionally analyzed patients receiving SSRI and SNRI (vs placebo) separately, we did not distinguish between paroxetine, duloxetine, fluoxetine, imipramine, and escitalopram. However, different antidepressants may act differently on specific depressive symptoms.

In conclusion, we did not find evidence to suggest that the treatment response to antidepressants would be characterized by specific depressive symptoms as compared to the symptom-specific patterns of the placebo effect, or the corresponding difference among those with no treatment response. These findings suggest that a successful treatment response to antidepressants may not depend on the specific symptoms that constitute the person's major depressive disorder diagnosis.

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Declaration of Competing Interest

None.

CRediT authorship contribution statement

Kaisla Komulainen: Conceptualization, Visualization, Data curtion, Writing – original draft, Writing – review & editing. **Jaakko Airaksinen:**

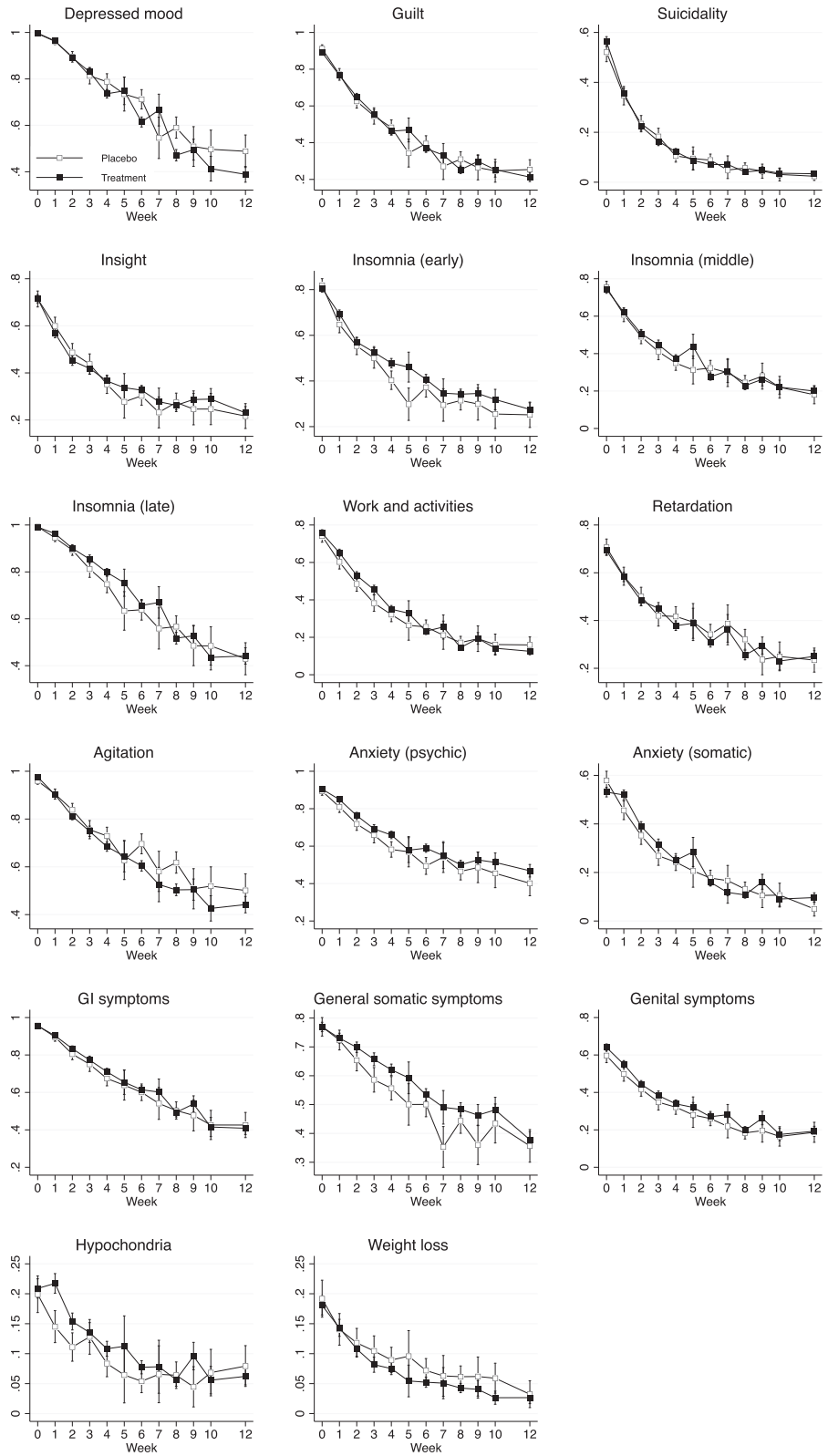

Fig. 2. Trajectories of the probability of a symptom being present at each assessment time in antidepressant vs placebo conditions among treatment responders.
Based on marginal predictions from sex- and age-adjusted population-averaged random-intercept logistic multilevel regression models.

Conceptualization, Visualization, Formal analysis, Data curtion, Writing – review & editing. **Kateryna Savelieva:** Conceptualization, Visualization, Data curtion, Writing – review & editing. **Kia Gluschkoff:** Conceptualization, Visualization, Data curtion, Writing – review & editing. **Regina García Velázquez:** Conceptualization, Visualization, Data curtion, Writing – review & editing. **Markus Jokela:** Conceptualization, Visualization, Formal analysis, Data curtion, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2021.100153.

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