



The impact of age on antidepressant response: A mega-analysis of individuals with major depressive disorder

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ABSTRACT

Introduction: Understanding how age affects antidepressant response in patients with major depressive disorder has been complicated by small and heterogeneous studies. Yet, understanding how age—across the lifespan—contributes to variation in response could inform treatment selection across the lifespan. This study sought to identify how age impacts antidepressant response using participant-level data from large, NIH-sponsored trials in individuals with MDD aged 12–74 years.

Materials and methods: Participant-level data were abstracted from three NIH-sponsored trials of pharmacotherapy (Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study, Treatment of Adolescent Depression Study (TADS), and the Combining Medications to Enhance Depression Outcomes Study (COMED)) in patients with MDD. Bayesian Hierarchical Models (BHMs) of individual treatment trajectories were developed using Hamiltonian Monte Carlo No U-Turn Sampling. The individual trajectory of improvement in depressive symptoms (Clinical Global Impression-Severity [CGI-S] and CGI-S equivalent from COMED) was modeled across studies and across individuals with logarithmic trend “random effects” coefficients BHMs. Age and sex (and their interaction) were examined categorically across patients.

Results: Study participants ($N = 907$) were 29.7 ± 17 years of age, 66.3% women, and had a mean baseline CGI-S score of 4.6 ± 0.9 . Patients ≤ 21 years and those > 55 years had slower and less response to pharmacotherapy compared to those aged 21–35. Additionally, women improved more than men, and this effect did not differ across ages.

Discussion: The patient's age should be considered in predicting antidepressant response, particularly in older and younger individuals who may benefit from other interventions to enhance treatment response.

1. Introduction

Major depressive disorder (MDD) frequently begins in adolescence (Beesdo et al., 2010; Kessler et al., 2003), inflicts significant morbidity and mortality across the lifespan (Pratt et al., 2016), and frequently persists into late adulthood. Globally, between 1990 and 2007, the number of years lived with disability attributed to depressive disorders increased by more than a third and depressive disorders became the third most common cause of years lived with disability worldwide

(James et al., 2017). Across the lifespan, selective serotonin reuptake inhibitors (SSRIs) are frequently the first-line pharmacotherapy, although the role of serotonin-norepinephrine and dopamine-norepinephrine reuptake inhibitors increases with age. However, the impact of age on antidepressant treatment in patients with MDD across the lifespan has not been explored, despite evidence that—relative to placebo—SSRIs may be less effective in children and adolescents (Cipriani et al., 2016; Hetrick et al., 2021) and older adults with depression (Hsu et al., 2022).

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For adults with MDD, response rates approach 50% with antidepressant monotherapy, and there are limited data to suggest whether any one antidepressant has greater efficacy relative to others (Cipriani et al., 2018). Treatment response varies considerably across studies and among patients. Given this heterogeneity of response, there has been considerable effort to predict which individuals will have faster or slower and less robust treatment responses. Efforts to understand these differences have focused on clinical characteristics, pharmacogenetics, neuroimaging, and molecular probes. The potential utility of these predictors is based on the premise that if slower or less improvement is likely, clinicians could intensify treatment, augment the current therapy, or change to alternative treatments and, in doing so, decrease morbidity.

Across the age span, treatment response relates to a surfeit of clinical and genetic factors (e.g., inflammatory burden, comorbidity). Clinical features such as employment (Mills et al., 2022), college education (Mills et al., 2022), less severe and less chronic depression (Nemeroff, 2020), the absence of mixed features, and a lack of adversity predicted better treatment response in adults. In children and adolescents with depression, those patients who are younger, less chronically depressed, and those with higher functioning, less hopelessness, less suicidal ideation, and limited melancholic features and comorbidity are more likely to respond to acute treatment (Curry et al., 2006). Additionally, less inflammation has also been associated with a greater response to SSRIs in several studies of adults with MDD (Jha et al., 2017). Comorbidity attenuates response, particularly the combination of MDD and an anxiety disorder (Howland et al., 2009). The relationship between age and antidepressant response is complex. It may vary as a function of other factors, including comorbidity, which is often greater in older patients, inflammation (Felger et al., 2020) (also higher, on average, in older patients); and chronicity of illness (often greater in older patients).

The effect of age on antidepressant response in patients with depression has generally been studied in single-study samples (Grigoriadis et al., 2003; Mulder et al., 2003). Prior meta-analytic studies of antidepressants often fail to adjust for age (Furukawa et al., 2019). When age is included, particularly in large trials, it is generally examined as a linear covariate. This approach assumes that the effect of increasing age on response is constant (i.e., a linear and monotonic relationship between age and response). Understanding variation across patients and across these studies is best accomplished with Bayesian hierarchical models (BHM) that allow the integration of multi-level information (e.g., individual, treatment, comorbidity) to estimate the change in symptoms or probability of improvement at each level of a hierarchy, with sub-models within the hierarchy combined with the observed data to account for uncertainty (McGlothlin and Vele, 2018). These BHM allow observed variability to be separated so that random differences vs. true differences in treatment outcomes can be identified (McGlothlin and Vele, 2018). For example, applying a BHM to studies of MDD across studies involving different antidepressants allows us to examine the influence of age and different pharmacotherapy on response while controlling for the influence of other factors to ultimately determine treatment effects “in relation to the totality of information available in all the studies” (McGlothlin and Vele, 2018).

With these considerations in mind, we evaluated response in antidepressant-treated adolescents and adults across three large multi-site trials of individuals with MDD: Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study, Treatment of Adolescent Depression Study (TADS) and the Combining Medications to Enhance Depression Outcomes Study (COMED). In this mega-analysis of 1068 individuals across the lifespan, we hypothesized that treatment response would be attenuated in younger and older participants compared to middle-aged individuals and that sex would interact with age to dampen antidepressant response at extreme ages. This hypothesis was informed by the prevailing evidence suggesting that older and possibly younger individuals do not respond as well to treatment as adults in the 30s–50s range (Hsu et al., 2022), and the low likelihood that age has a monotonic

relationship with treatment effect (an implicit assumption of linear and logarithmic model specifications).

2. Materials and Methods

2.1. Source of data

The study team accessed the complete, de-identified, original TORDIA, TADS, and COMED data sets from the NIMH (Brent et al., 2008; March, 2004; Rush et al., 2011). The analyses focused on the acute phase of each trial in which symptom severity (based on Clinical Global Impression-Severity [CGI-S]) was determined at baseline, week 4, week 8, and week 12. CGI-S was selected as the primary outcome as it was the consistent measure across all time points in most studies. Clinical and demographic data were extracted as previously described (Suresh et al., 2020a).

2.2. Study details

COMED, the Combining Medications to Enhance Depression Outcomes (www.co-med.org) study randomized adults with chronic or recurrent MDD (1:1:1 ratio) to 3 antidepressant treatments — escitalopram + placebo, venlafaxine + mirtazapine, or escitalopram + bupropion—for 12 weeks (Rush et al., 2011). Research participants ($N = 569$, $N = 551$ after missing values were eliminated) were recruited from six primary and nine psychiatric care sites. The inclusion criteria were broad, and the exclusion criteria were minimal. Briefly, research participants had to be in the index episode for ≥ 2 months and had a score ≥ 16 on the 17-Item Hamilton Rating Scale for Depression (HRSD-17) (24). A list of exclusion criteria is available at www.co-med.org. The protocol and all consent and study procedures were approved by the institutional review boards at the National Coordinating Center (University of Texas Southwestern Medical Center) and all clinical sites. Treatment visits—for the acute phase—were at baseline and weeks 1, 2, 4, 6, 8, 10, and 12, and the medication dose was adjusted in response to the 16-item Quick Inventory of Depressive Symptomatology—Clinician-rated (QIDS) based on the COMED Operations Manual (available at www.co-med.org).

TADS was a prospective, randomized trial involving adolescents (aged 12–17) with MDD ($N = 439$, $N = 188$ after missing values and individuals receiving CBT eliminated) who were randomized to (1) fluoxetine monotherapy (10–40 mg/d), (2) CBT monotherapy, (3) CBT + fluoxetine (10–40 mg/d), or (4) placebo. Following 12 weeks of treatment, individuals who received fluoxetine + CBT were significantly more improved (effect size 0.98) compared to those who received fluoxetine (effect size = 0.68) and those who received CBT monotherapy (effect size 0.03) (March et al., 2006).

TORDIA was a prospective, randomized controlled trial of outpatients ($N = 334$, $N = 168$ after missing values and those receiving CBT eliminated) aged 12–18 years with MDD. Adolescents who failed at least eight weeks of SSRI trial were randomized, using a 2×2 balanced factorial design, to a switch to a different SSRI (paroxetine, citalopram, or fluoxetine, 20–40 mg daily) or venlafaxine ER (150–225 mg) or to switch to a different SSRI plus CBT or a switch to venlafaxine plus CBT. Additional study details and results have been described elsewhere (Brent et al., 2008, 2009; Kennard et al., 2009). Medication switches combined with CBT yielded higher response rates compared to a medication switch alone (without the addition of CBT).

2.3. Response modeling

In COMED, symptom severity was assessed with the Quick Inventory of Depressive Symptomatology (QIDS). In contrast, TADS and TORDIA used the Children's Depression Rating Scale-Revised (CDRS-R), as these measures are among gold standard measurements of depression severity for these age groups. In addition, the TADS and TORDIA studies used the

CGI-S to assess global severity of depression. Therefore, the COMED QIDS scores were rescaled and categorized into a CGI-S equivalent scale to model improvement across all three studies. The COMED QIDS scores were categorized into seven groups to match the seven CGI-S scores as follows,

$$CGI-S = \begin{cases} 7, & QIDS \geq 24 \\ 6, & 20 \leq QIDS < 24 \\ 5, & 16 \leq QIDS < 20 \\ 4, & 12 \leq QIDS < 16 \\ 3, & 8 \leq QIDS < 12 \\ 2, & 4 \leq QIDS < 8 \\ 1, & QIDS < 4 \end{cases}$$

The partition cut-offs were selected by a comparison across the three studies of score histograms for CGI-S from TADS and TORDIA and QIDS from COMED. An alternative based on scaling QIDS (CGI-S equiv. = $7 \times \frac{QIDS}{30} + 1$, so that $1 \leq CGI-S \text{ equivalent} \leq 7$) was also considered and provided very similar results.

The individual trajectory of improvement in depressive symptoms (CGI-S and CGI-S equivalent from QIDS) was modeled across studies and individuals with logarithmic trend “random effects” coefficients BHM. The logarithmic trend models, specifically the individual trends BHM, have several advantages over the standard mixed model with repeated measures (MMRM) (Suresh et al., 2020; Walker and Shostak, 2010). The BHM logarithmic trend approach explicitly models an individual’s correlation in symptoms over time rather than attempting to adjust for estimator bias. Models were estimated using the Hamiltonian Monte Carlo No U-Turn Sampler in the package Turing.jl, in Julia (version 1.7) (Bezanson et al., 2014; Ge et al., 2018). Bayesian posterior p-values ≤ 0.05 were considered statistically significant for all analyses.

To capture nonlinearity in the hypothesized relationship between an individual’s age and improvement from treatment, research participant’s age was categorized into the following groups: $age_{21} \leq 21$, $21 < age_{2235} \leq 35$, $35 < age_{3655} \leq 55$, $age_{55} > 55$. These age categorizations a) provided a distributional level in a BHM, and b) defined a set of indicator variables for inclusion as explanatory variables in all other models estimated. Variations in the age categorizations (partition cut-off points) were explored in model estimation to determine the robustness of the results to reasonable variations in age group definitions. The oldest age group was finalized at either $age > 55$ or $age > 64$. The former oldest age group (> 55) was found to be superior because higher age cut-offs had too few observations, leading to imprecise estimates (large standard errors). The youngest age group was finalized as $age \leq 21$ to ensure that individuals from all three studies appeared in the group. Of note, in a sensitivity analysis examining the improvement trajectories for research participants < 18 and 18 – 21 years of age, there was no statistically significant difference in response trajectory ($p = 0.59$).

To allow for unobserved heterogeneity across age groups, a BHM with separate “random effects” logarithmic improvement trajectory coefficients for each age group was specified. For age group $s = 1, \dots, 4$, explanatory variable $k = 1, \dots, K$, individual i , $t = 1, 2, \dots, T$ time periods: $y_{it} \sim N(\mu_{it}, \sigma)$, $\mu_{it} = \delta_s \log t_i + X_{it}\beta$, $\beta = [\beta_1, \beta_2, \dots, \beta_K]$, $\beta_k \sim N(0, 1)$, $\delta_s \sim N(\delta, 1)$, $\delta \sim \text{Truncated}(N(-1, 1), -3, 0)$, $\sigma \sim U[0.001, 5]$. Then, to allow for unobserved heterogeneity across individuals, a BHM was specified with a separate trajectory coefficient for each individual, i.e., for $i = 1, 2, \dots, N$, $\delta_i \sim N(\delta, 1)$, $\mu_{it} = \delta_i \log(t_i) + X_{it}\beta$, $y_{it} \sim N(\mu_{it}, \sigma)$. Prior parameter values (as indicated in the above specifications) were selected to ensure that the prior distributions were relatively uninformative, and alternative prior specifications were explored to ensure results were robust to reasonable variations in the priors.

To examine the sensitivity of the age effects results to variations in the model specification and to allow for improvement prediction conditional on individual’s age, a model including higher order polynomials in age-log trend interaction terms was specified. A fifth-order polynomial in age was found to sufficiently capture the nonlinearity in age effect on improvement through examination of model selection criteria

AIC and BIC, the statistical significance of polynomial trend coefficients, etc. Predictions were generated from the above model at 12 weeks ($t = 4$) for males and females, assuming white and nonwhite in COMED and TADS. Separate predictions were generated for males and females in TORDIA to allow for the treatment-resistant nature of the TORDIA individuals’ symptoms.

3. Results

3.1. Demographic and clinical characteristics

Characteristics of the research participants across all three trials are shown in Table 1. Briefly, research participants were aged 29.7 ± 17 years and 66.3% were women ($n = 737$). Twenty-four percent were non-white ($n = 262$), and anxiety disorders were more prevalent in COMED (75%, $n = 426$) compared to TORDIA and TADS (46 and 54%, respectively). Symptom severity at baseline, as reflected by the CGI-S score was similar across studies, and the average baseline CGI-S score in the combined sample was 4.6 ± 0.9 . Additional characteristics are shown in Table 1. After combining data sets for research participants receiving antidepressant monotherapy and eliminating missing observations, observations from 907 individuals remained for analysis.

3.2. Age on antidepressant response

Antidepressant response was greatest in participants aged 22–35 years ($\beta = -0.668 \pm 0.060$, $p < 0.001$) and least in individuals younger than 21 years of age ($p < 0.001$) (Fig. 1B and C). This effect was not influenced by the presence of an anxiety disorder ($p = 0.493$, Supp. Table 1), but treatment response was reduced in minoritized research participants ($\beta = 0.244 \pm 0.045$, $p < 0.001$, Supp. Table 1).

3.3. Biological sex on antidepressant response

Antidepressant response was significantly greater in females compared to males at all ages ($\beta = -0.284 \pm 0.039$, $p < 0.001$) (Fig. 1D), although, at baseline, CGI-S scores were 4.66 ± 0.9 in women and 4.43 ± 0.8 in men ($p = 0.850$). In a model examining the interaction of age and sex, this effect was largest in individuals 36–54 ($\beta = -0.339 \pm 0.095$, $p = 0.0003$) and in those older than 55 ($\beta = -0.311 \pm 0.125$, $p =$

Table 1
Clinical and Demographic Characteristics of participants.

	COMED (n = 551)	TORDIA (n = 168)	TADS (n = 188)	Combined (n = 907)
Age	43.3 ± 12.82	15.9 ± 1.57	14.6 ± 1.54	29.67 ± 16.75
Sex (female)	389 (68.4%)	231 (70.0%)	117 (55.2%)	737 (66.3%)
Nonwhite	187 (32.9%)	38 (11.5%)	37 (17.5%)	262 (23.6%)
CGI-S, baseline ^a	4.49 ± 1.09	4.53 ± 0.66	4.72 ± 0.84	4.55 ± 0.94
QIDS-R	10.30 ± 5.81			
Comorbid anxiety disorder	426 (74.9%)	153 (46.4%)	102 (54.3%)	682 (65.4%)
Pharmacotherapy				
SSRI only	189 (33.2%)	85 (50.6%)	212 (100%)	486 (51.2%)
Venlafaxine	196 (34.4%)	83 (49.4%)	NA	279 (29.4%)
bupropion + escitalopram	184 (32.3%)	NA	NA	184 (19.4%)

^a CGI-S, Clinical Global Impression-Severity; QIDS-R, Quick Inventory of Depressive Symptoms – Revised. Note: The CGI-S score for COMED was constructed from QIDS-R.

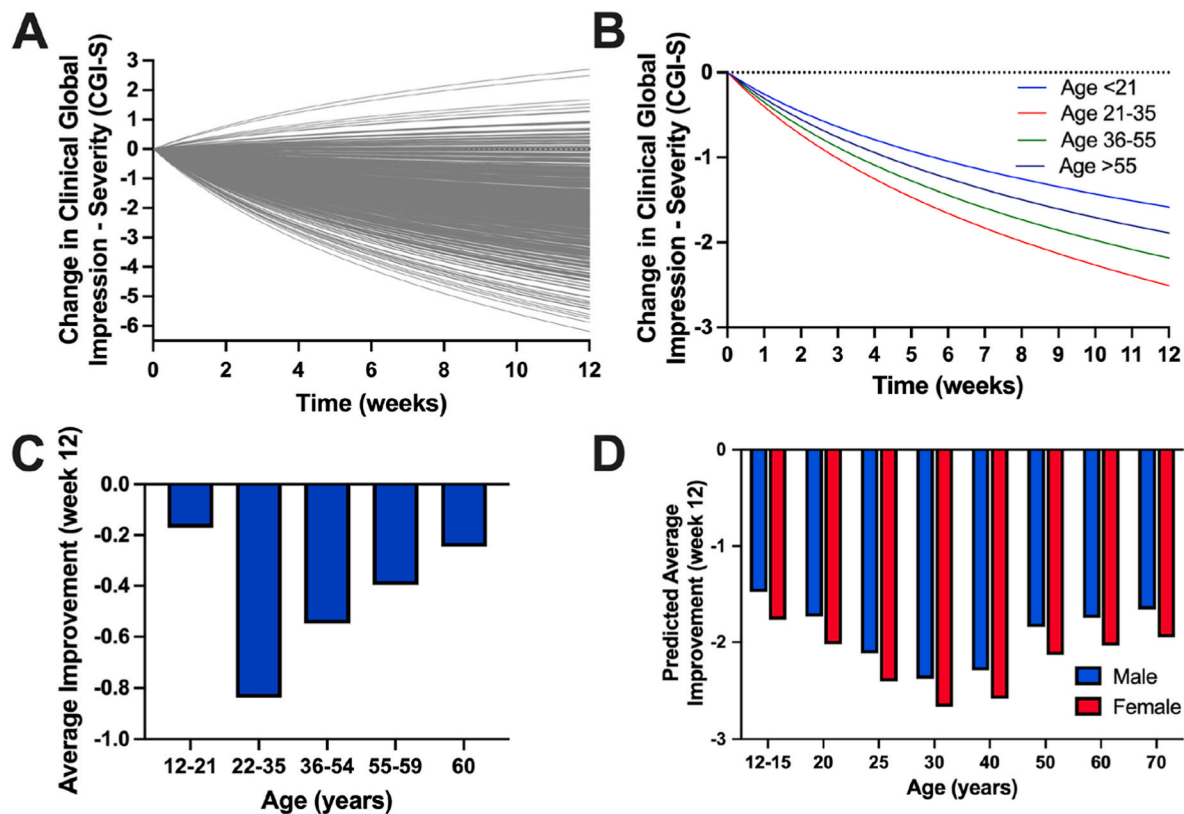


Fig. 1. Response at 12 weeks and Trajectory of Response in Antidepressant-Treated Research Participants. Response, based on CGI-S varied considerably across all participants (A). The trajectory of response was significantly less in older and younger individuals (B and C) and, across the age span, was less in males compared to females (D).

0.013).

3.4. Assessment of heterogeneity

There was substantial variability in individual response trajectories among individuals based on the response estimates (Fig. 1A). Despite this variability, the mean trend coefficient estimates for improvement in depressive symptoms were similar in the models with individual trends ($\beta_{trends\ mean} = -1.11 \pm 0.049$, $p < 0.001$), and those that assume a homogeneous trend ($\beta_{trend} = -1.11 \pm 0.050$, $p < 0.001$, Supp. Table 1). The results were robust across several different model specifications.

4. Discussion

This is the first study to examine how antidepressant treatment response varies across the lifespan and informs precision medicine approaches in youth and adults with MDD. That response varies by age and follows a quadratic pattern (less improvement in younger and older individuals) has important implications for clinicians and researchers. These results suggest that in younger and older individuals, strategies to improve treatment may be important to improve antidepressant response. In individuals aged 21–35, monotherapy or combinatorial antidepressant treatment may be a sufficient early-stage approach. This study highlights the tremendous variation in response even when controlling for multiple factors known to influence response. The spaghetti plot in Fig. 1A reminds us that response heterogeneity is substantial even in well-controlled, federally-sponsored clinical trials in which treatment is provided and dosing is carefully controlled. Understanding age-related differences in treatment response could help clinicians to set realistic treatment expectations, while understanding which individuals in an age group have less response could help clinicians to tailor treatments.

Grigoriadis and colleagues examined differences in antidepressant treatment response in younger and older women. Although tolerability was similar, depression in younger women appears more responsive to serotonergic medications (Grigoriadis et al., 2003). The present study had greater heterogeneity, a broader age range, a larger sample, and used contemporary computational approaches. In our analyses of response across age groups, men did not respond as well as women. This difference in response—in each age group—may relate to endocrine factors and potential psychological factors. However, it is noteworthy that baseline severity does not differ between men and women. While clinicians often see and acknowledge this heterogeneity, we rarely systematically use this information to tailor treatment.

The reasons for the age-related differences in response may relate to multiple factors across the lifespan. For example, in younger research participants, the attenuated response may have been related to the influence of family and school-related factors, with the neurobiology of early-onset MDD distinct from MDD that emerges in adulthood. By contrast, the reduced response seen in older adults may relate to greater systemic inflammation, molecular senescence, more chronicity, or unique psychosocial stressors. Antidepressants may exert therapeutic effects through changes in neuroplasticity (Duman et al., 2016; Klöbl et al., 2022; Patrício et al., 2015). Although speculative, early adulthood may be an optimal age for the induction of neuroplastic effects of antidepressants (Song et al., 2021; Winkel et al., 2021).

The natural course of depressive disorders may also vary across the lifespan which could contribute to differences in response. In both adolescents and adults, different subtypes have been described and may be characterized based on clinical features (e.g., atypical, melancholic, mixed, anxious distress), emergence pattern (early-onset, seasonal) or based on the course/chronicity (e.g., recurrent, single episode) (Giles et al., 1987; Rush et al., 1995, 2022). Within this heterogeneous disorder, some individuals experience relative differences in somatic or

cognitive symptoms (Carragher et al., 2009). Specifically, within adolescent (Blom et al., 2013; Lamers et al., 2012) or adult (Giles et al., 1987; Rush et al., 1995) cohorts of individuals with depression, the relative prevalence of these ‘subtypes’ varies. Thus, whether differential representation of these subtypes across the lifespan—and in particular within our age groups—contributes to the age-related effects is unclear.

Several treatment-related factors may influence differences in response at the extreme age groups that may have clinical implications. Specifically, in older adults, particularly those older than 65, CYP2C19 activity decreases and is associated with age-related increases in citalopram/escitalopram (Jukić et al., 2018) and potentially sertraline exposure (e.g., concentration over time). Additionally, total water tends to decrease in older adults. This decreases the volume of distribution for water-soluble drugs, while total body fat will result in a larger volume of distribution for lipid-soluble drugs. These factors, in addition to age-related differences in clearance—whether related to changes in cytochrome activity or other factors—produce significant pharmacokinetic variation. Additionally, pharmacodynamic factors may be relevant in older and younger patients and have been hypothesized to underlie some specific side effects in younger individuals (e.g., activation, extrapyramidal symptoms) and older individuals (e.g., anticholinergic symptoms). These factors could contribute to differences in tolerability that confound or adversely affect treatment response. Moreover, considering these factors clinically raises the possibility that dosing or monitoring approaches should consider the patient’s age.

These findings have implications for clinical trials. Many antidepressant trials in adults include a large age range (e.g., 18–65). In these trials, age-related effects may obscure our ability to detect differences in response. To address this, trials could consider (1) including age in response models; (2) examining response in different age groups. Also, age may be a proxy for other factors that influence response in clinical trials, such as inflammation (Nemeroff, 2020), overall health, and employment-related factors; therefore, measuring these variables could decrease the effect of unobserved heterogeneity.

Finally, while this is the first examination of age and sex on antidepressant treatment response to use BHMs, several important limitations warrant additional discussion. First, to compare COMED with TORDIA and TADS, clinical global impression severity scores were generated from the QIDS-SR, the primary outcome measure. This was necessary as the COMED dataset did not contain CGI-S scores. While this approach has been used in prior studies (Zhang et al., 2022), it may have increased the heterogeneity of the results. Second, while we examined response across classes of antidepressants and while dosing of these medications followed established protocols to minimize ‘under-dosing’, variation in pharmacokinetic genes that produces differences in exposure (i.e., blood levels) was not assessed and could contribute to response variation. Including multiple trials, medication classes, and pharmacodynamic approaches across studies may limit the specificity of the overall finding and application to pharmacological approaches across the lifespan. Third, our results assume that improvement is logarithmic, and we allowed this assumption based on response in prior studies of children, adolescents, and adults with depressive disorders, and this approach increases the precision of improvement estimates. Fourth, some participants in the younger group (<21 years of age) came from the TORDIA study and thus may have been more treatment resistant. However, in a sensitivity analysis examining the improvement trajectories for individuals <18 and 18–21 years of age, there was no statistically significant difference in response trajectory ($p = 0.59$). Fifth, given that this is a secondary analysis of previously published studies from publicly-available datasets, we were not blind to treatment allocation.

5. Conclusion

The present findings suggest that individuals in the early and later stages of the life cycle have slower and less responsiveness to antidepressant medications compared to young adults aged 21–35. Treatment

planning for younger and older participants with depression may need to include specific strategies to boost ‘antidepressant response.’ However, whether improving response in these age groups would be best accomplished by early psychotherapy, adjunctive treatments, or other interventions remains to be determined. Regarding gender, women appear to improve more than men across the lifespan, suggesting earlier consideration of multimodal approaches for depressed men.

Author statement

Jeffrey R. Strawn: Conceptualization, Methodology, Visualization, Writing – Original draft preparation. Jeffrey A. Mills: Conceptualization, Methodology, Data curation, Analysis, Visualization, Writing – Original draft preparation. Vikram Suresh: Analysis, Visualization, Writing – revision. Taryn Mayes and Madhukar Trivedi: Conceptualization, Conduct of Study, Writing- Reviewing and Editing. Melanie T. Gentry: Conceptualization, Writing- Reviewing and Editing. Paul E. Croarkin: Conceptualization, Methodology, Writing – Reviewing and Editing.

Declaration of competing 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.2023.01.043>.

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