Biological Psychiatry

Archival Report

Evening Chronotypes With Depression Report Poorer Outcomes of Selective Serotonin Reuptake Inhibitors: A Survey-Based Study of Self-Ratings

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ABSTRACT

BACKGROUND: Preliminary evidence suggests that evening chronotype is related to poorer efficacy of selective serotonin reuptake inhibitors. It is unknown whether this is specific to particular medications, self-rated chronotype, or efficacy.

METHODS: In the Australian Genetics of Depression Study (n = 15,108; 75% women; 18–90 years; 68% with ≥1 other lifetime diagnosis), a survey recorded experiences with 10 antidepressants, and the reduced Morningness-Eveningness Questionnaire was used to estimate chronotype. A chronotype polygenic score was calculated. Age- and sex-adjusted regression models (Bonferroni-corrected) estimated associations among antidepressant variables (how well the antidepressant worked [efficacy], duration of symptom improvement, side effects, discontinuation due to side effects) and self-rated and genetic chronotypes.

RESULTS: The chronotype polygenic score explained 4% of the variance in self-rated chronotype (r = 0.21). Higher self-rated eveningness was associated with poorer efficacy of escitalopram (odds ratio [OR] = 1.04; 95% CI, 1.02 to 1.06; p = .000035), citalopram (OR = 1.03; 95% CI, 1.01 to 1.05; p = .004), fluoxetine (OR = 1.03; 95% CI, 1.01 to 1.05; p = .001), sertraline (OR = 1.02; 95% CI, 1.01 to 1.04; p = .0008), and desvenlafaxine (OR = 1.03; 95% CI, 1.01 to 1.05; p = .004), and a profile of increased side effects (80% of those recorded; ORs = 0.93–0.98), with difficulty getting to sleep the most common. Self-rated chronotype was unrelated to duration of improvement or discontinuation. The chronotype polygenic score was only associated with suicidal thoughts and attempted suicide (self-reported). While our measures are imperfect, and not of circadian phase under controlled conditions, the model coefficients suggest that dysregulation of the phenotypic chronotype relative to its genetic proxy drove relationships with antidepressant outcomes.

CONCLUSIONS: The idea that variation in circadian factors influences response to antidepressants was supported and encourages exploration of circadian mechanisms of depressive disorders and antidepressant treatments.

https://doi.org/10.1016/j.biopsych.2023.12.023

The search for better treatments for depression is a global priority (1). A network meta-analysis that compared the effects of 21 antidepressants from more than 522 double-blind trials in adults with depression found that all antidepressants had higher efficacy and acceptability than placebo, albeit with modest effects (2). While this strongly supports the use of antidepressants, it is also clear that antidepressants are not equally effective for all individuals. Another review of individual participant data from 232 double-blind trials of antidepressant monotherapy found that only 15% of patients achieved a substantial antidepressant effect (above the effects of placebo) (3). This and other articles (4,5) highlight the need to identify factors that influence variation in antidepressant outcomes, which may lead to better pretreatment stratification.

It has been proposed that the circadian system contributes to individual differences in treatment outcomes (6,7). Studies have linked depression to chronotype—the biobehavioral preference for the daily timing of sleep and activity, among other behaviors and physiology—including showing evening-type people being overrepresented among people with depression and eveningness being associated with a worse clinical profile (e.g., suicidality) (8–11). At least 4 studies have examined whether chronotype is associated with response to antidepressant medication. In an open-label study of agomelatine in outpatients who were experiencing a major depressive episode, a morning chronotype was associated with greater reductions in depressive symptoms than an evening chronotype (12). Second, in an online survey of antidepressant response, having an evening chronotype was associated with

ISSN: 0006-3223

lower self-rated efficacy of selective serotonin reuptake inhibitors (SSRIs) and more depressive symptoms and suicidality during SSRI treatment (13). Third, in a secondary analysis of a randomized controlled trial of antidepressant medication plus cognitive behavioral therapy (CBT) for insomnia in people with depression and insomnia, eveningness was associated with less improvement in depressive symptoms, both for patients who received CBT for insomnia and for participants who received a control therapy as an adjunct to medication (14). Finally, in a general population-based trial (including cases with depression), digital CBT for insomnia was superior to psychoeducation for insomnia and fatigue, but not depressive symptoms, among evening types (15).

This literature has 3 key gaps. First, only a limited subset of antidepressants has been explored: SSRIs broadly (13), agomelatine (12), and 2 specific SSRIs (sertraline and escitalopram) and 1 specific serotonin–norepinephrine reuptake inhibitor (SNRI) (desvenlafaxine) (14). Second, little is known about chronotype and other outcomes, including side effects and discontinuation of treatment due to side effects. Third, studies have focused on self-reported chronotype, but none have examined genetic liability to chronotype, which may have unique associations with outcomes. A genome-wide association study of chronotype identified 351 independent genome-wide significant loci, and a chronotype polygenic score (PGS) has been associated with circadian and sleep-wake phenotypes, with little evidence of associations with sleep phenotypes (16).

We have proposed that eveningness is a feature of a circadian pathway to depressive disorders and that sleep-wake and circadian dysregulation (common among evening types) may be a causal mechanism underlying some mood disorders (17,18). In our circadian depression model, we hypothesized that people with depression who have circadian features (e.g., higher eveningness) will experience lower efficacy of SSRIs and SNRIs (6). In addition to studies that suggest this association (13,14), there are 5 conceptual and theoretical reasons for this hypothesis. First, while the suprachiasmatic nucleus of the circadian system is densely innervated by serotonergic neurons (19) and its activity modulated by serotonin (20,21), simply elevating serotonin pharmacologically does not appear to directly affect the phase of circadian rhythms in humans (21), as suggested by some cell/animal models (22). Second, while studies have reported that some SSRIs and SNRIs affect melatonin levels (23), cortisol rhythm (24), and to some extent melatonin rhythms (25), these findings come from small samples and are yet to be replicated in controlled studies. If dysregulated circadian rhythms do underlie some forms of depression, and if eveningness does influence this dysregulation, it is not clear whether SSRIs can alter circadian phase at a sufficient magnitude to be therapeutic. Third, evening types are more likely to have characteristics that create a more difficult-to-treat depression (e.g., chronic sleep loss), and they may be more likely to have a depressive disorder underpinned by circadian disturbance (6). Fourth, while serotonergic and noradrenergic systems have been implicated in sleep-wake behaviors (e.g., alternation between sleep and wake) (26–28), an individual patient data meta-analysis suggests that many antidepressants do not differ from CBT in improving some sleep symptoms (29). Finally, sleep disturbance may respond more slowly to antidepressants than other symptoms (e.g., psychomotor symptoms); for evening types who are more likely to have sleep disturbance as a characteristic feature, it is conceivable that the core of their depression may take longer to respond to medication (30).

Accordingly, the goal of this study was to examine relationships among chronotype and self-rated outcomes of common antidepressants (efficacy, duration of improvement, side effects, and discontinuation due to side effects) in the AGDS (Australian Genetics of Depression Study) (31). We examined both self-rated chronotype and a genetic index of chronotype. We hypothesized that greater self-rated eveningness would be associated with lower efficacy of SSRIs and SNRIs, specifically sertraline, escitalopram, and desvenlafaxine. Based on clinical experience, we hypothesized that for SSRIs and SNRIs, greater self-rated eveningness would be associated with a shorter total duration of improvement in symptoms, more side effects (e.g., sleep disturbance, agitation), and more discontinuation due to side effects. Our genetic analyses were exploratory.

METHODS AND MATERIALS

Participants and Study Design

Study participants were members of the AGDS, a volunteer cohort study of the role of genetic variation in the etiology, course, and treatment of depression in adults with experience of treatment for depression. Participants were recruited via two means: 1) invitations sent from the Australian government Department of Human Services to individuals based on prescription medication records in the previous 4.5 years (obtained through the nationwide Medicare Benefits Scheme or the Pharmaceutical Benefits Scheme), and 2) a media publicity campaign looking for adults who have experienced clinical depression (http://www.geneticsofdepression.org.au). A much larger proportion of participants were recruited via public appeal (~85%) than by the prescription history invitation. Additional details about recruitment strategy and sampling are provided in a cohort profile (31). Most participants contributed a saliva sample using a mail-out kit from which DNA was extracted and processed at QIMR Berghofer Medical Research Institute. Participants completed an online survey with a core module on depression symptomatology and response to medication and a module on sleep. Data were collected between September 2016 and September 2018. Previous studies have examined genetic and metabolic factors related to antidepressant efficacy and side effects in AGDS (32–34), but this is the first study to investigate chronotype. The study was approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee in Brisbane, Australia. Written informed consent was obtained from all participants.

Phenotypic Chronotype

A reduced version (35) of the Morningness-Eveningness Questionnaire (rMEQ) was used to estimate self-rated chronotype (i.e., behavioral preference for morningness-eveningness) (36). For illustrative purposes (Figure 1), the following ranges index chronotype categories: definitely evening (rMEQ = 4–7), moderately evening (rMEQ = 8–11),

intermediate (neither type) (rMEQ = 12–17), moderately morning (rMEQ = 18–21), and definitely morning (rMEQ = 22–25). We calculated a total score (with higher scores indicating greater morningness) and used it in analyses of association with antidepressant medication outcomes.

Genetic Chronotype

Participants were genotyped using the Illumina Global Screening Array v2.0. Samples were merged with the 1000 Genomes Project samples (36), and principal components (PCs) were calculated using a set of unlinked single nucleotide polymorphisms (SNPs). Preimputation quality control was done using PLINK version 1.9 (38,39). Quality control involved removing SNPs with a minor allele frequency < 0.005 or a significant departure from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) before imputation using the Haplotype Reference Consortium 1.1 reference panel (40). Individuals with a SNP call rate <97.5% and ancestry outliers (41) from a European reference group (>4 SDs from ancestry PCs PC1/PC2 centroid) were excluded. Summary statistics from a recent genome-wide association study of chronotype were used to identify SNPs associated with chronotype using UK Biobank data from Jones *et al.* (16) (N = 449,734); summary statistics from 23andMe data were not available for this study. To provide a benchmark for the power of this study, 153 independent loci were significant at the genome-wide significance threshold of 5×10^{-8} (16). SBayesR (42), a Bayesian method, was used to generate allele weights for the PGS, which were calculated for each individual using the PLINK (37) score function.

Antidepressants: Efficacy, Duration of Improvement, Side Effects, and Discontinuation

The survey asked about experiences with 10 common antidepressants: sertraline, escitalopram, venlafaxine,

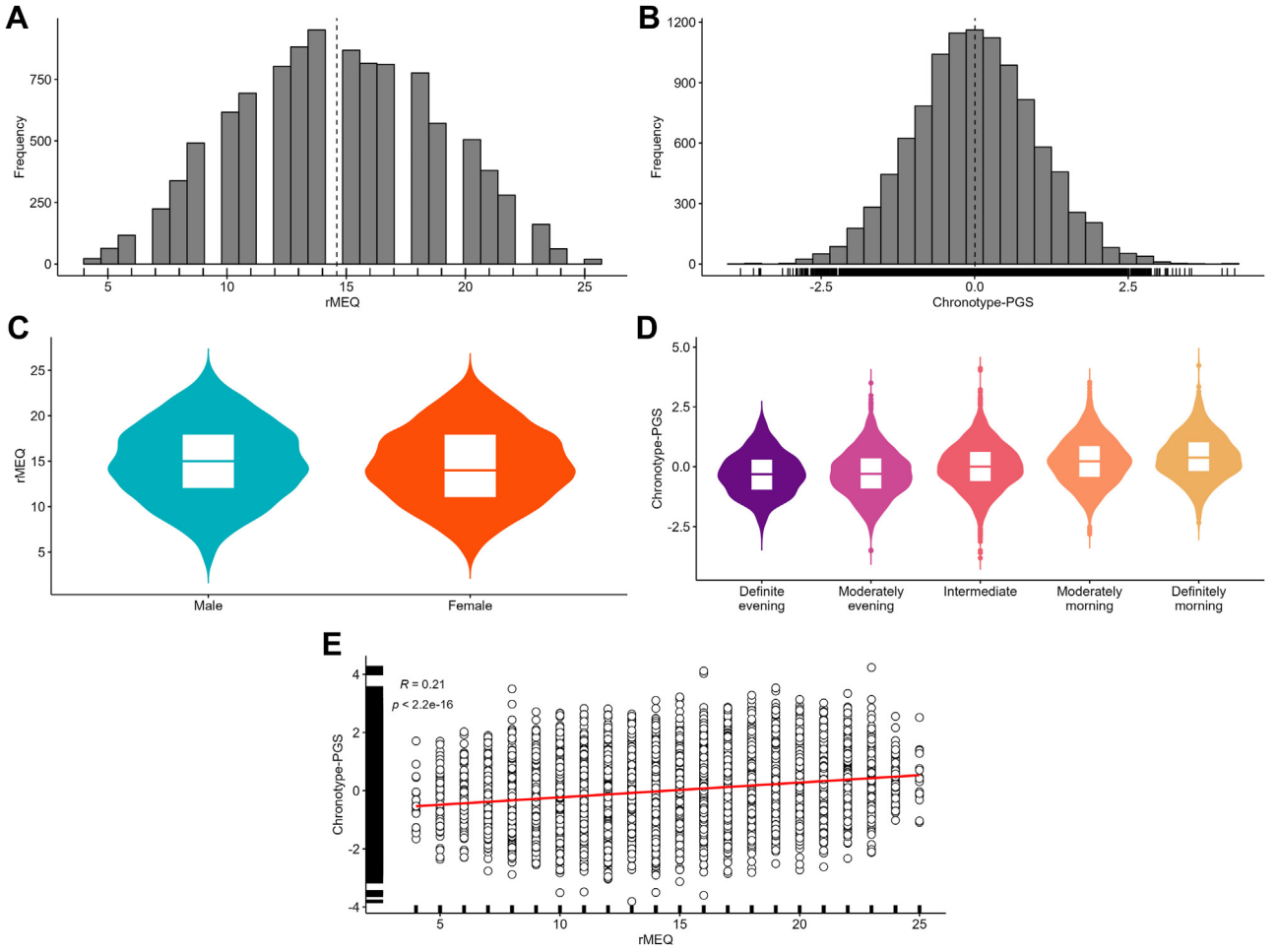

Figure 1. Distributions and associations among the reduced version of the Morningness-Eveningness Questionnaire (rMEQ) and chronotype polygenic score (PGS). Dashed lines in the histograms and density plots represent the mean value for each group. **(A)** The rMEQ is approximately normally distributed, with some slight skew toward greater eveningness (i.e., lower rMEQ scores). **(B)** The chronotype PGS was normalized to the sample (range = −3.81 to 4.23). **(C)** While largely overlapping, the rMEQ distribution differed slightly between men and women (men reported more morningness and women reported more eveningness; mean difference = 0.36, $p < .001$). **(D)** Chronotype categories from the rMEQ (used only for illustrative purposes) followed the expected profile of association with the chronotype PGS. **(E)** Scores on the rMEQ and the chronotype PGS had a small correlation (Pearson's product-moment correlation = 0.21; $p < .001$).

amitriptyline, mirtazapine, desvenlafaxine, citalopram, fluoxetine, duloxetine, and paroxetine.

Efficacy was assessed with the question "How well does/did each antidepressant work for you?" Four responses were analyzed on an ordinal scale: not at all well (scored as 0), moderately well (scored as 1), very well (scored as 2), and don't know (no participants in the analytic sample endorsed this response).

Duration of improvement in symptoms was assessed with the question "How long did the improvement in symptoms you experience after taking [antidepressant] last for?" Seven responses were analyzed on an ordinal scale: I didn't have any improvement in symptoms (scored as 0), less than a month (scored as 1), 1 to 2 months (scored as 2), 3 to 6 months (scored as 3), 7 to 12 months (scored as 4), more than 12 months (scored as 5), and don't know (excluded).

Side effects were assessed with the question "Which side effects did you experience from the following antidepressant(s)?" Participants were asked about side effects only if they indicated that they had taken the antidepressant. The following were queried: dry mouth, sweating, nausea, vomiting, diarrhea, constipation, headache, dizziness, shaking, muscle pain, drowsiness, difficulty getting to sleep, increased anxiety, agitation, fatigue or weakness, weight gain, weight loss, rash, runny nose, reduced sexual desire/function, blurred vision, suicidal thoughts, attempted suicide, other side effect, and no side effects. Responses were analyzed as a binary variable: no (scored as 0), yes (scored as 1).

Discontinuation of antidepressants was assessed with the question "Did you have to stop taking any antidepressant because of side effects?" Responses were analyzed as a binary variable: no (scored as 0), yes (scored as 1).

Statistical Analysis

Analyses were conducted in RStudio using R (version 4.2.2). Ordinal regression was used to examine associations between the efficacy and duration of symptom improvement of the 10 antidepressants (as separate outcomes) and chronotype (rMEQ and PGS). Similarly, logistic regression was used to examine associations between 25 side effects (collapsed across the 10 antidepressants) and discontinuation because of side effects and chronotype (rMEQ and PGS). These models included age and sex as covariates. Coefficients for the rMEQ reflect a 1-point increase, while coefficients for the chronotype PGS reflect a 1-SD increase. The threshold for statistical significance was determined using the Bonferroni correction for multiple testing, which adjusts for the number of comparisons performed for each of the outcomes. The corrected significance thresholds for the 4 outcomes were 1) efficacy: $p < .005$ (10 antidepressant medications), 2) duration of symptom improvement: $p < .005$ (same as efficacy), 3) discontinuation due to side effects: $p < .005$ (same as efficacy), and 4) $p < .002$ (25 side effects). We reported regression results from fitting the rMEQ and PGS jointly and corrected for multiple testing based on the number of phenotypes tested. For completeness, we have also reported regression analyses when fitting the rMEQ and PGS separately. When fitted together with the rMEQ, the coefficient of the PGS is equivalent to a regression on the rMEQ residuals from a regression of the rMEQ on the PGS, which represents the deviation of the self-reported chronotype from its biologically predicted value. Therefore, differences between the coefficients from the model fitting the variables separately and jointly could provide insight.

RESULTS

Demographic and Clinical Data

From a total cohort of 20,680 individuals (75% women; mean [SD] age = 42.8 [15.3] years), self-report and genetic data (that passed quality control) were available for 15,108 participants. Of this analytic sample, 75% were women, and the mean age was 43.6 (15.3) years [range = 18 to 90]. Basic demographics are presented in Table 1. While all participants self-reported a diagnosis of or treatment for depression, according to DSM-5 criteria, 88% had experienced a lifetime major depressive episode. Self-reported lifetime diagnoses are reported in Table S1 in Supplement 2. Most participants (67.7%) reported at least one other lifetime diagnosis (other than depression), of which the 3 most common were anxiety disorder (54.0%), posttraumatic stress disorder (13.3%), and social anxiety disorder (10.6%). The mean (SD) score on the rMEQ was 14.6 (4.2) [4 to 25; median = 15], indicating that the participants were, on average, intermediate chronotypes. After normalizing to the sample, the mean of the chronotype PGS was 0 (1) [−3.81 to 4.23]).

Association Between the rMEQ and the Chronotype PGS

The distributions of the rMEQ and the chronotype PGS are shown in Figure 1. The Pearson's correlation between rMEQ and chronotype PGS was 0.21 ($p < .001$), i.e., the chronotype PGS explained 4% of the variance in the self-reported chronotype (rMEQ).

Table 1. Characteristics of Participants in the Analytic Sample, *n* = 15,108

Characteristic	Value
Age, Years, Mean (SD) [Range]	43.6 (15.3) [18–90]
Sex, *n* (%)	
Female	11,284 (74.8%)
Male	3810 (25.2%)
Information not provided	14 (<0.1%)
Marital Status, *n* (%)	
Married or de facto relationship	8122 (53.9%)
Separated or divorced	2270 (15.1%)
Widowed	255 (1.7%)
Never married	4429 (29.4%)
Information not provided	32 (<0.1%)
Education, *n* (%)	
Postgraduate	4174 (27.7%)
Degree	5283 (35.1%)
Certificate or diploma	3554 (23.6%)
Senior high school	1192 (7.9%)
Junior high school or less	859 (5.7%)
No formal education	7 (<0.1%)
Information not provided	39 (<0.1%)

Antidepressant Efficacy

Figure 2 summarizes the associations between the phenotypic (rMEQ) and genetic (PGS) indices of chronotype and the self-rated efficacy of each of the antidepressants (Tables S2–S31 in Supplement 2). There were Bonferroni-significant ($p < .005$) associations between higher phenotypic morningness (rMEQ) and greater self-rated efficacy of escitalopram (odds ratio [OR] = 1.04; 95% CI, 1.02 to 1.06; $p = 3.5^{-6}$), citalopram (OR = 1.03; 95% CI, 1.01 to 1.05; p = .004), fluoxetine (OR = 1.03; 95% CI, 1.01 to 1.05; p = .001), sertraline (OR = 1.02; 95% CI, 1.01 to 1.04; p = .0008), and desvenlafaxine (OR = 1.03; 95% CI, 1.01 to 1.05; p = .004). By contrast, the chronotype PGS was not associated with self-rated efficacy for any antidepressant (*p*s = .059–.94).

Duration of Symptom Improvement and Treatment Discontinuation Due to Side Effects

Using Bonferroni correction ($p < .005$), there were no significant associations between the rMEQ or chronotype PGS and duration of symptom improvement (Tables S32–S61 in Supplement 2; Figure S1 in Supplement 1) or treatment discontinuation for any antidepressant (*p*s = .005–.989) (Tables S62–S91 in Supplement 2; Figure S2 in Supplement 1). Between 16% and 22% of participants responded "don't know" to the duration of

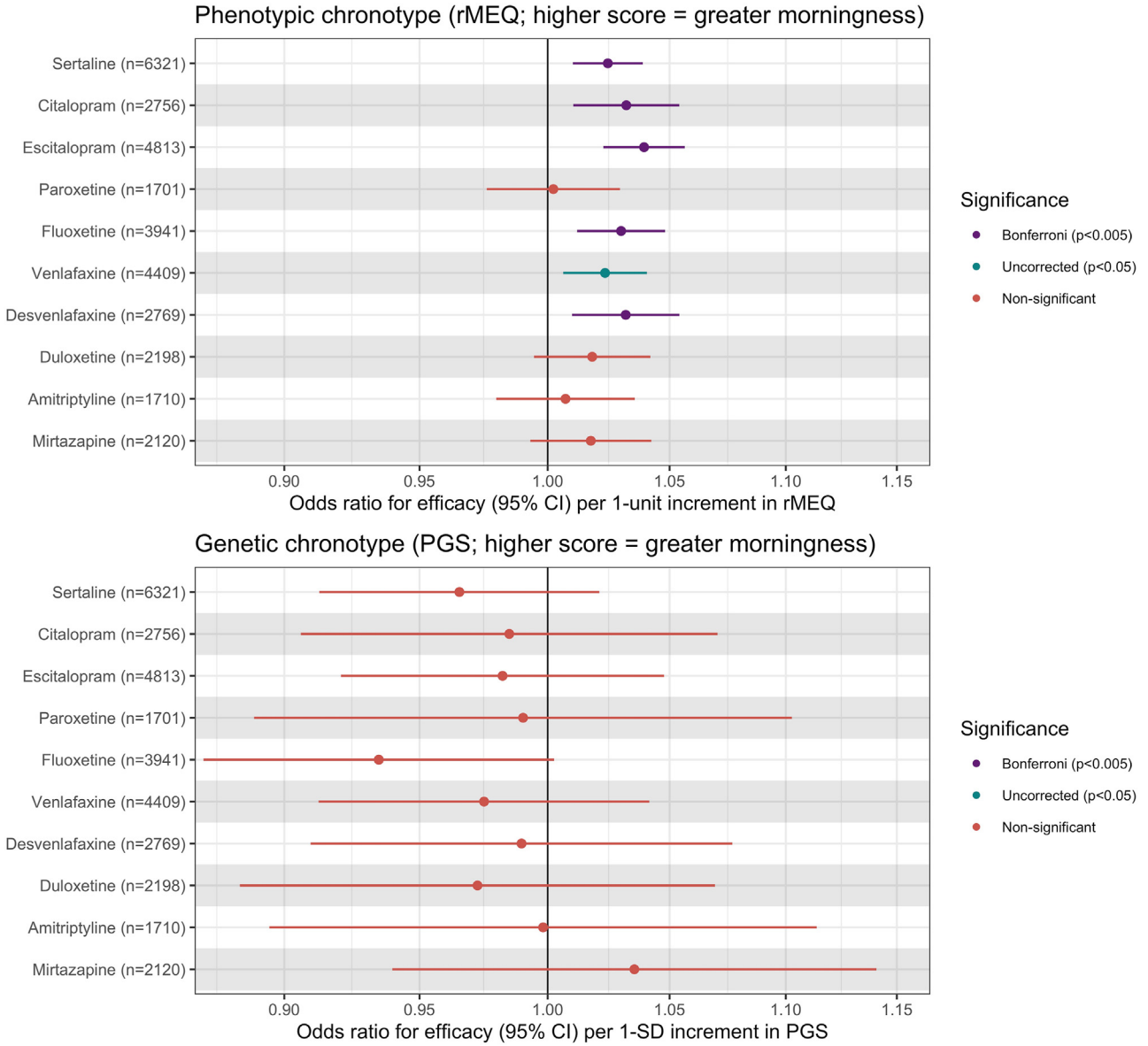

Figure 2. Phenotypic and genetic chronotypes and self-reported efficacy of 10 common antidepressants. On the y-axis are 10 outcome variables from separate regression models, in which age, sex, reduced version of the Morningness-Eveningness Questionnaire (rMEQ), and chronotype polygenic score (PGS) were fitted (x variables). The coefficients for the rMEQ and chronotype PGS are visualized separately for ease of interpretation.

symptom improvement item (the rate varies by the specific antidepressant) and were excluded. There were minor differences between "don't know" responders and the other participants: 1) age (older for amitriptyline, desvenlafaxine, and escitalopram; younger for sertraline), 2) sex (more women for venlafaxine), and 3) chronotype PGS (higher for mirtazapine). There were no differences for the rMEQ.

Side Effects and Chronotype

As shown in Figure 3, there were Bonferroni-significant associations ($p < .002$) between higher phenotypic morningness (rMEQ) and lower likelihood of 20 of 25 side effects, with the exceptions of weight loss, vomiting, rash, no side effect, and other side effect (Tables S92–S162 in Supplement 2). The 3 strongest significant associations were for difficulty getting to sleep (OR = 0.93; 95% CI, 0.92 to 0.95; $p = .7 \times 10^{-28}$), diarrhea (OR = 0.94; 95% CI, 0.92 to 0.96; $p = .3 \times 10^{-10}$), and blurred vision (OR = 0.95; 95% CI, 0.93 to 0.97; $p = .2 \times 10^{-7}$). The chronotype PGS was associated with suicidal thoughts (OR = 1.09; 95% CI, 1.03 to 1.16; $p = .002$) and attempted suicide (OR = 1.15; 95% CI, 1.05 to 1.25; $p = .002$). Notably, these associations were stronger in the model in which the chronotype PGS was fitted jointly with the rMEQ than when fitted alone.

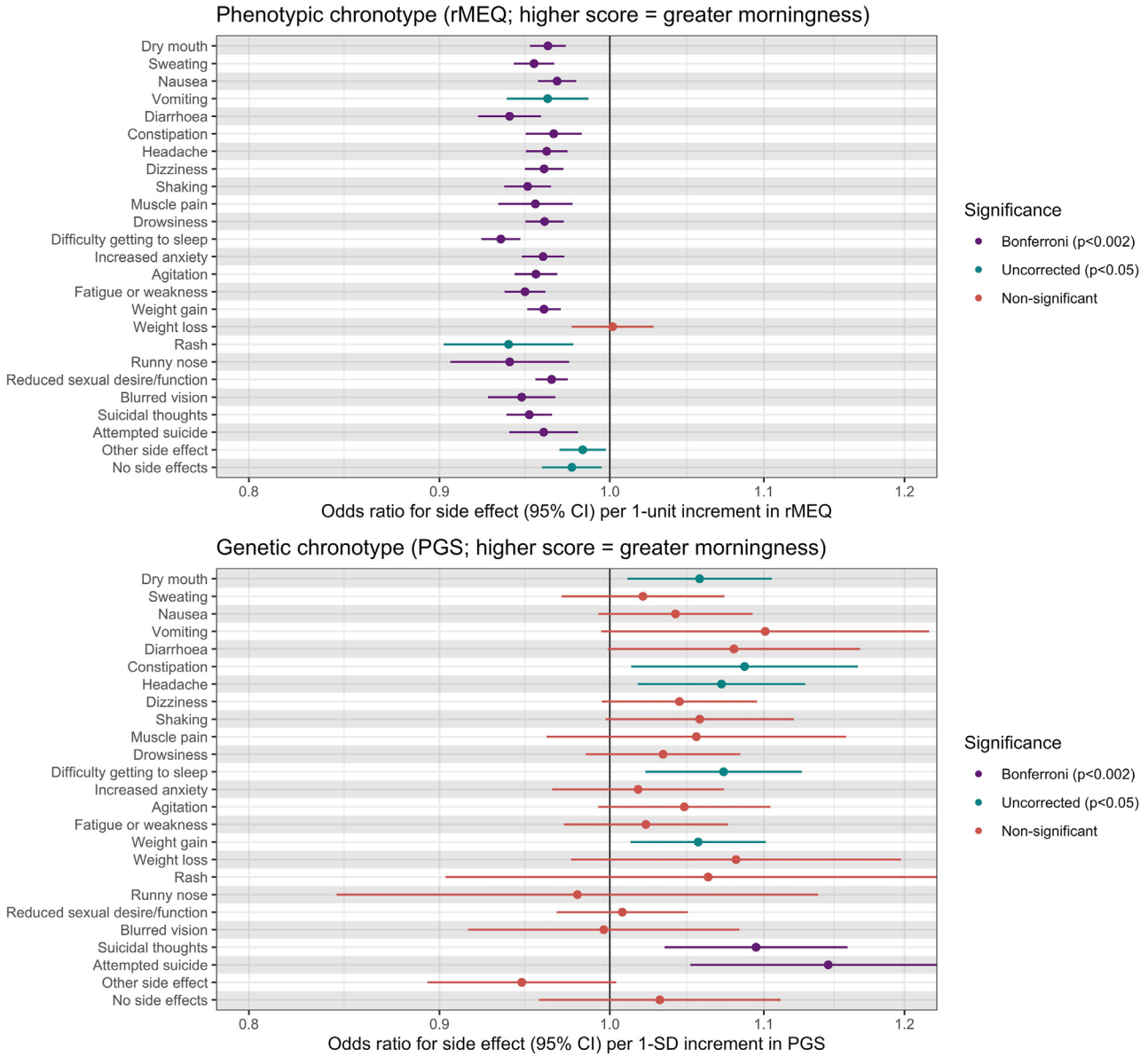

Figure 3. Phenotypic and genetic chronotypes and self-reported side effects of 10 common antidepressants (n = 15,108). On the y-axis are 25 outcome (y) variables from separate regression models in which age, sex, reduced version of the Morningness-Eveningness Questionnaire (rMEQ), and chronotype polygenic score (PGS) were fitted (x variables). The coefficients for the rMEQ and chronotype PGS are visualized separately for ease of interpretation.

Sensitivity Analyses

We conducted 3 sensitivity analyses. First, because a subset of our sample (12%) did not meet DSM-5 criteria for a major depressive episode, we tested the effect of restricting the sample to the 88% of the participants who did meet the DSM-5 criteria. Second, given that extreme chronotypes are more likely in youth (i.e., more extreme eveningness) and older people (i.e., more extreme morningness) (43), we tested the effect of restricting the sample to middle-aged participants (40–59 years). In both sensitivity analyses, most associations were slightly attenuated (but largely of similar magnitude) and several were robust at Bonferroni-corrected levels, particularly for higher phenotypic eveningness and lower efficacy of escitalopram, and for higher phenotypic eveningness and more side effects. Third, we examined whether side effects influenced self-reported efficacy. We summed the individual side effects for each medication and used this side effect count as a covariate in a sensitivity analysis of the efficacy models. As shown in Figure 4 and Figures S1–S5 in Supplement 1, most associations between the phenotypic chronotype and efficacy were attenuated when side effect count was accounted for, and while most were still significant at $p < .05$, only the association between higher eveningness and lower efficacy of escitalopram remained significant after Bonferroni correction ($p < .005$). This pattern of attenuation suggests that increased side effects are a mediator of the link between chronotype and perceived efficacy of antidepressant medication.

DISCUSSION

In a large cohort of adults with depression, we found support for our hypothesis that self-rated chronotype is associated with outcomes of SSRIs and SNRIs, such that people with greater eveningness reported lower efficacy of specific medications and a broad side-effect profile. In a genetically informative subsample, the chronotype PGS was not robustly associated with self-reported antidepressant outcomes (except for some side effects).

Participants who reported higher eveningness reported poorer efficacy of sertraline, citalopram, escitalopram, fluoxetine, and desvenlafaxine (after Bonferroni correction), and there was weaker suggestion of a similar pattern for venlafaxine. These results are consistent with a study that reported that evening chronotype was associated with poorer self-reported response to SSRIs in general (13). Our findings suggest a

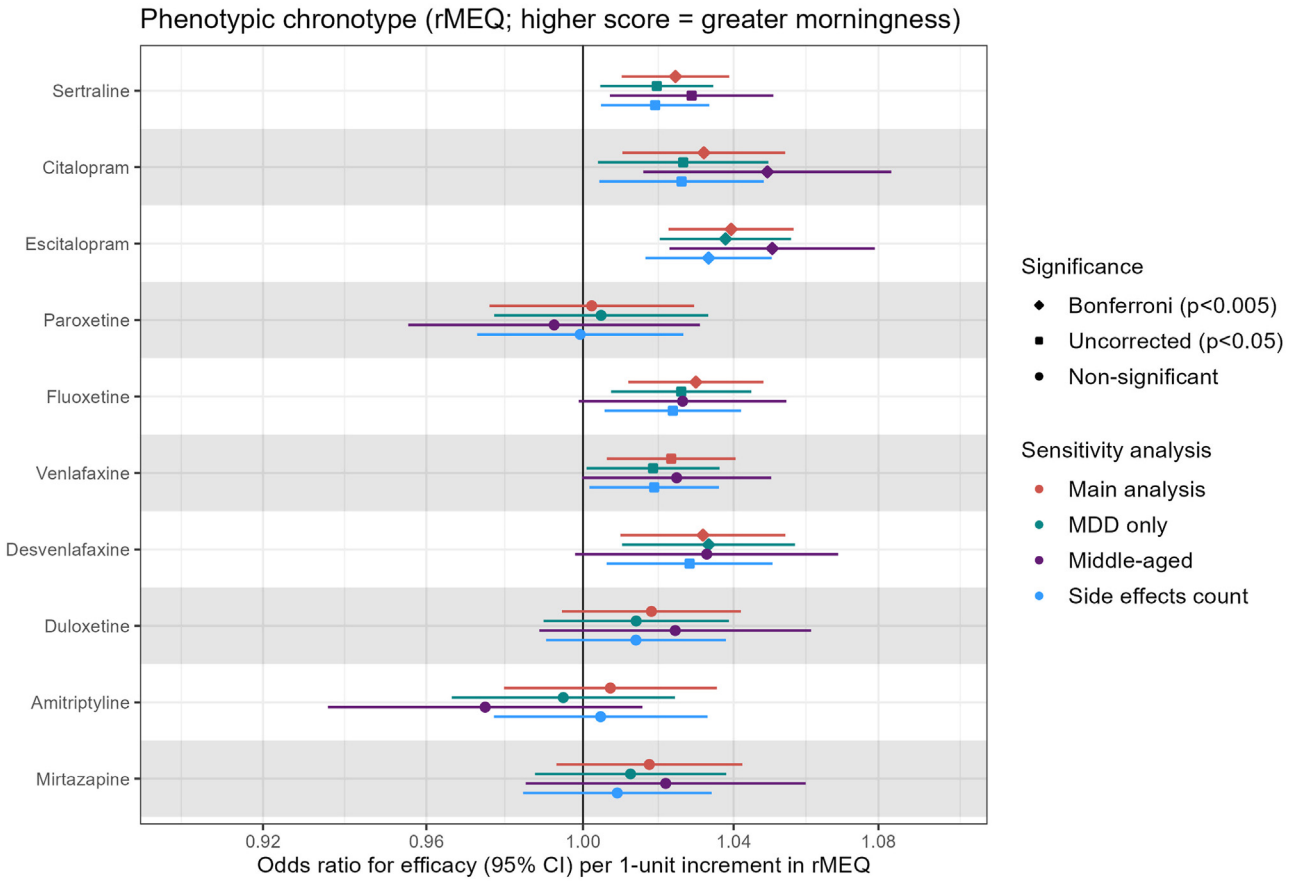

Figure 4. Sensitivity analyses for phenotypic chronotype (reduced version of the Morningness-Eveningness Questionnaire [rMEQ]) and self-rated efficacy. Three sensitivity analyses examined the effects of 1) restricting the sample to cases that met DSM-5 criteria for a major depressive episode, 2) restricting the sample to middle-aged adults, who are less likely to have extreme chronotypes, and 3) covarying for the load of self-reported side effects. MDD, major depressive disorder.

clearer link for 4 SSRIs (escitalopram, citalopram, fluoxetine, sertraline) and 1 SNRI (desvenlafaxine). Contrary to our expectations, the phenotypic measure of chronotype was not related to duration of symptom improvement, and the chronotype PGS was not associated with efficacy or duration of improvement. We note that among the SSRIs, the findings for paroxetine differed from the others. We can only speculate on the reasons for this, but one possibility is a cohort effect whereby paroxetine is prescribed less often in younger cohorts, and therefore, its use may be more relevant to an older group with different characteristics. While they were not our focus here, we also found differences by age and sex in the efficacy and duration of improvement of certain medications (Tables S2–S61 in Supplement 2).

Phenotypic eveningness was associated with an increased side-effect profile, with 80% of side effects being increased. While estimates were broadly similar (ORs = 0.93–0.98), the 3 strongest associations were for difficulty getting to sleep, diarrhea, and blurred vision. This is consistent with a study that showed that evening types who were undergoing treatment with SSRIs reported more suicidality (13); here, eveningness was associated with a higher probability of suicidal thoughts and attempted suicide (as self-reported side effects). The chronotype PGS was also associated with suicidal thoughts and attempted suicide but in the opposite direction (higher genetic morningness, higher likelihood of side effects). This has not been observed before, and we encourage caution until replication, especially given that the direction of this relationship is opposite to the phenotypic chronotype [as observed in independent studies (13)]. We also observed differences in side effects by age and sex (Tables S92–S162 in Supplement 2), and while weight gain was a common side effect and potentially a reason for discontinuation, the distribution of body mass index was almost identical across antidepressants (Table S163 in Supplement 2), and chronotype was unrelated to discontinuation. Because we collapsed side effects across antidepressants, we cannot directly compare our results to studies of individual medications (44,45). While these results should be interpreted cautiously because of the degree of multiple testing, the difference in the direction of effect and the fact that the coefficients for the rMEQ and the chronotype PGS became larger and more significant in joint models (compared to when fitted separately) are consistent with a hypothesis of dysregulated 24-hour patterns of sleep-wake, rest-activity, feeding, and other functions compared to the genetic proxy of chronotype (however broad). This should be explored with better measures of endogenous timing under controlled conditions.

What is the nature of the chronotype-SSRI link? First, given the misalignment between social and biological times among evening types, we have proposed that evening types are more likely to have a depressive disorder underpinned by circadian dysregulation (6). Speculatively, these forms of depression may respond less well to SSRIs/SNRIs because these treatments do not correct the underlying circadian dysregulation; interventions that appear to act on the circadian system (e.g., agomelatine) may be more effective for these cases (46); more studies are needed to test this hypothesis (47). Second, citalopram has been shown to acutely delay melatonin onset and increase sensitivity to light (48). People taking citalopram (and possibly escitalopram) may have circadian disruption caused by a sensitization of the phase-shifting effect of light at night (49–51). Downstream effects may include prolonged depression, sleep disturbance, fatigue, and agitation, among other side effects associated with eveningness (Figure 3). Third, evening types may experience chronic sleep loss because of the discrepancy between the later schedule of their endogenous clock and the earlier schedule of society's 9-to-5 social clock. Such chronic sleep disturbance may create a hard-to-treat depression (52,53). Meta-analyses have found that many antidepressants are associated with increased insomnia or somnolescence compared to placebo (54,55), and an individual participant data meta-analysis found that antidepressants did not have different effects on improving sleep symptoms compared to CBT (29). Finally, sleep and sleep-wake disturbances have been associated with negative outcomes in some studies, including increased episode severity and relapse (56), treatment resistance (57), and nonremission with psychotherapy and/or pharmacotherapy (52,53). Speculatively, such outcomes may be more common among evening types who are more vulnerable to sleep-wake disturbance.

The differences between phenotypic and genetic chronotypes and antidepressant outcomes were somewhat unexpected. Given that chronotype changes across the life span (58), it is likely that the self-rated and genetic measures picked up different bio-behavioral signals. The rMEQ estimates the current chronotype, which is a point estimate of the trait along a life-course trajectory. Chronotype is typically earlier in childhood, later in adolescence, and earlier again in older age (changes which self-ratings could capture). By contrast, the chronotype PGS is a single value that does not track changes in age-dependent expression. Therefore, self-rated chronotype may be more relevant to recent outcomes than genetic liability (a more distal marker).

The current study has some important limitations. First, information about antidepressant outcomes was self-reported and, therefore, subject to recall biases (e.g., misremembering aspects of lifetime antidepressant use). Relatedly, information about dose was not collected. Second, the MEQ has been criticized as not being a valid estimate of chronotype (59); other more biologically valid measures may predict outcomes better. We used a restricted version of the MEQ, and variation in scores was accordingly truncated compared to the full version. Third, the chronotype PGS was derived from a genome-wide association study of a single item of diurnal preference and does not provide a robust mapping of endogenous timing. We encourage future studies to examine how other sleep/circadian phenotypes (e.g., sleep midpoint, relative amplitude) and their genetic proxies are associated with antidepressant outcomes. Fourth, studies with other mood disorder samples have shown that self and objectively measured chronotype are frequently misaligned, thereby complicating interpretations of findings (60). Fifth, while other lifetime diagnoses were common (particularly generalized anxiety disorder at 54%, which is reasonably similar, given that our data are self-ratings, to an estimate from the World Health Organization World Mental Health Surveys of a 45.7% prevalence of ≥1 lifetime anxiety disorders in people with lifetime depression) (Table S1 in Supplement 2) (61), we did not stratify analyses by comorbid diagnosis given that our research

question was focused on people with a lifetime experience of depression. Sixth, we note that the AGDS has a female:male ratio of 3:1, which may have implications for the generalizability of the study findings because the prevalence ratio is typically 2:1 (62). Some explanations for this sex ratio are that women are more likely to score high on agreeableness, moral obligation, and prosociality (63) and are more likely to participate in clinical research based on altruistic considerations (64). Seventh, we used the Bonferroni correction to adjust for multiple comparisons. While this is a conservative approach, we varied the correction thresholds across the antidepressant outcomes as one countermeasure (because they are correlated outcomes). Eighth, exposure to specific medications differed; lack of significant associations for some medications may have been a function of lower power for the less commonly used antidepressants (e.g., amitriptyline). However, we note that samples were large ($n > 1000$) for each medication, and many associations were nonsignificant at $p < .05$. Finally, we acknowledge shortcomings of the antidepressants that we surveyed. All medications included engage serotonergic receptors, and lack of data about antidepressants with diverse mechanisms (e.g., esketamine, bupropion) limits our ability to link findings to mechanisms. A stronger test of our hypotheses would be possible if we had data about medications with circadian mechanisms (e.g., agomelatine) (46,65); we hypothesize that evening types would experience better outcomes with such medications.

Conclusions

In conclusion, in adults with depression (and high overall rates of lifetime diagnoses such as generalized anxiety disorder), eveningness is an indicator of a less favorable response to antidepressants, in particular SSRIs, which supports the proposal that the circadian system is involved in differential treatment responses in depression. Because the observed associations were small, chronotype by itself is unlikely to guide treatment choice but may have a place in multivariate models used to predict individualized treatment response (66). We encourage investigation of more dynamic circadian markers that may better identify an SSRI nonresponse subtype.

ACKNOWLEDGMENTS AND DISCLOSURES

The Australian Genetics of Depression Study was funded primarily by the National Health and Medical Research Council (NHMRC) of Australia (Grant No. 1086683 [to EMB, SEM, NRW, NGM, IBH]). This work was also supported by an NHMRC EL1 Investigator Grant (Grant No. 2008196 [to JJC]), an NHMRC EL1 Investigator Grant (Grant No. 2017176), an NHMRC EL1 Investigator Grant (Grant No. 2017176 [to BLM]), an NHMRC L1 Investigator Grant (Grant No. 1172917 [to SEM]), an NHMRC L3 Investigator Grant (Grant No. 1172990 [to NGM]), an NHMRC L3 Investigator Grant (Grant No. 1173790 [to NRW]), an NHMRC L3 Investigator Grant (Grant No. 2016346 [to IBH]), and an NHMRC Synergy Grant (Grant No. 2019260), and a philanthropic donation from families affected by mental illness (who would like to remain anonymous).

JJC and IBH were responsible for conceptualization. EMB, BLM, SEM, NRW, NGM, and IBH were responsible for methodology, investigation, and project administration. EMB, SEM, NRW, NGM, and IBH were responsible for funding acquisition. JJC and SHP were responsible for formal analysis. JJC, SHP, and KC were responsible for visualization. JJC, SHP, KC, and IBH were responsible for writing the original draft. IBH supervised the study. All authors reviewed and edited the manuscript.

We thank the participants for giving their time to contribute to this study. We thank all the people who helped in the conception, implementation, beta testing, media campaign, and data cleaning.

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Received Jul 13, 2023; revised Dec 20, 2023; accepted Dec 28, 2023.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2023.12.023.

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