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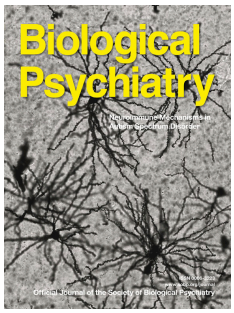

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Evening chronotypes with depression report poorer outcomes of SSRIs: A survey-based study of self-ratings

Running title: Chronotype and antidepressant outcomes

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ABSTRACT

Background: Preliminary evidence suggests evening chronotype relates to poorer efficacy of selective-serotonin reuptake inhibitors (SSRIs). 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% female; 18-90 years; 68% with ≥1 other lifetime diagnosis), a survey assessed experiences with 10 antidepressants and the reduced Morningness-Evening Questionnaire; a chronotype polygenic score (PGS) was calculated. Age- and sex-adjusted regression models (Bonferroni-corrected) estimated associations among antidepressants 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-PGS explained 4% of the variance in self-rated chronotype (r=0.21). Higher self-rated eveningness was associated with poorer efficacy of escitalopram (OR=1.04; 95% CI 1.02-1.06; p=0.000035), fluoxetine (OR=1.03; 95% CI 1.01-1.05; p=0.001), sertraline (OR=1.02; 95% CI 1.01-1.04; p=0.0008), and desvenlafaxine (OR=1.03; 95% CI 1.01-1.05; p=0.004), and a profile of increased side effects (80% of those recorded; ORs=0.93-0.98), with 'difficulty getting to sleep' most likely. Self-rated chronotype was not related to duration of improvement or discontinuation due to side effects. The chronotype-PGS 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 phenotypic chronotype relative to its genetic proxy was driving relationships with antidepressant outcomes.

Conclusions: The idea that variation in circadian factors influences antidepressant responses was supported and encourages exploration of circadian mechanisms of depressive disorders and antidepressant treatments.

INTRODUCTION

The search for better treatments of depression is a global priority (1). A network meta-analysis comparing the effects of 21 antidepressants from >522 double-blind trials in adults with depression, reported 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 clear that antidepressants are not equally effective for all individuals. Another review of individual participant data (IPD) from 232 double-blind trials of antidepressant monotherapy reported 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 influencing variation in antidepressant outcomes, which may lead to better pre-treatment stratification.

The circadian system has been proposed to contribute to individual differences in treatment outcomes (6, 7). Studies have linked depression to *chronotype*—the biobehavioural preference the daily timing of sleep and activity, among other behaviours and physiology—including evening types people being over-represented among people with depression, and eveningness being associated with a worse clinical profile (e.g., suicidality) (8-11) . At least four studies have examined whether chronotype is associated with response to antidepressant medication. In an open-label study of agomelatine in outpatients with depression in a major depressive episode, morning chronotype was associated with greater reductions in depressive symptoms compared to evening chronotype (12). Second, in an online survey of antidepressant response, evening chronotype was associated with lower self-rated efficacy of SSRIs and more depressive symptoms and suicidality during SSRI treatment (13). Third, in a secondary analysis of an RCT of antidepressant medication plus cognitive behavioural therapy for insomnia (CBT-I) in people with depression and insomnia, eveningness was associated with less improvement in depressive symptoms, both for patients receiving CBT-I or a control therapy as adjunct to medication (14). Finally, in a general population-based trial (including cases with depression), digital CBT-I was superior to psychoeducation for insomnia and fatigue, but not depressive symptoms, among evening types (15).

This literature has three key gaps. First, a limited subset of antidepressants have been explored: SSRIs broadly (13), agomelatine (12), and two SSRIs (sertraline and escitalopram) and one 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, while none have examined genetic liability to chronotype, which might have unique associations. A genome-wide association study (GWAS) of chronotype identified 351 independent genome-wide significant loci, and a chronotype polygenic score 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 hypothesised 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 suggesting this association (13, 14), there are five conceptual and theoretical reasons for this hypothesis. 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 remain 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 that 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 depression disorder underpinned by circadian disturbance (6). Fourth, while serotonergic and noradrenergic systems are implicated in sleep-wake behaviours (e.g., alternation between sleep/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 slower to antidepressants compared to other symptoms (e.g., psychomotor symptoms); for evening types that 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).

The goal of this study was to examine in the *Australian Genetics of Depression Study* (31) relationships among chronotype and self-rated outcomes of common antidepressants (efficacy, duration of improvement, side effects, and discontinuation due to side effects). We examine

both self-rated chronotype and a genetic index of chronotype. We hypothesise greater self-rated eveningness will be associated with lower efficacy of SSRIs and SNRIs, and specifically, for sertraline, escitalopram, and desvenlafaxine. Based on clinical experience, we hypothesise that for SSRIs and SNRIs, greater self-rated eveningness will be associated with a shorter total duration of improvement in symptoms, more side effects (e.g., sleep disturbance, agitation), and discontinuation due to side effects. Our genetic analyses are exploratory.

METHODS AND METHODS

Participants and Study Design

Study participants were members of the *Australian Genetics of Depression Study* (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: (i) 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 (ii) a media publicity campaign looking for adults who have experienced clinical depression (www.geneticsofdepression.org.au). A much larger proportion of participants were recruited via public appeal (~85%) compared to the prescription history invitation. Greater 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 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., behavioural preference for morningness-eveningness) (36). For illustrative purposes (Figure 1), the following ranges index chronotype categories: Definite evening (rMEQ=4-7); Moderately evening (8-11); Intermediate (neither type) (12-17); Moderately morning (18-21); and Definitely morning (22-25). We calculated a total score (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. Samples were merged with the 1000 Genomes project samples (37) and principal components were calculated

using a set of unlinked single-nucleotide polymorphisms (SNPs). Pre-imputation quality control (QC) was done using PLINK 1.9 (38, 39). QC involved removing SNPs with a minor allele frequency <0.005, or a significant departure from Hardy-Weinberg equilibrium ($p<1x10^{-6}$), 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 SD from Ancestry Principal Components PC1/PC2 centroid) were excluded Summary statistics from a recent GWAS of chronotype were used to identify SNPs associated with chronotype, using UK Biobank data from Jones et al. (16) (N=449734); 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 $5x10^{-8}$ (16). SBayesR (42), a Bayesian method, was used to generate allele weights for the polygenic score (PGS) which were calculated for each individual using the PLINK (38) score function.

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

The survey asked about experiences with 10 common antidepressants: sertraline, escitalopram, venlafaxine, amitriptyline, mirtazapine, desvenlafaxine, citalopram, fluoxetine, duloxetine, and paroxetine.

1. *Efficacy* was assessed with the question, "How well does/did each antidepressant work for you?" Four responses were analysed on the ordinal scale: *Not at all well* (0); *Moderately well* (1); *Very well* (2); and *Don't know* (no participants in the analytic sample endorsed this response).

2. *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 analysed on the ordinal scale: *I didn't have any improvement in symptoms* (0); *Less than a month* (1); *1 to 2 months* (2); *3 to 6 months* (3); *7 to 12 months* (4); *More than 12 months* (5); and *Don't know* (which was excluded).

3. *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; diarrhoea; 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; no side effects. Responses were analysed as a binary variable: *No* (0); *Yes* (1).

4. *Discontinuation* of antidepressants was assessed with the question, "Did you have to stop taking any antidepressant because of side effects?" Responses were analysed as a binary variable: *No* (0); *Yes* (1).

Statistical Analysis

Analyses were conducted in RStudio using R (version 4.2.2) (43). 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 were included age and sex as covariates. Coefficients for the rMEQ reflect a one-point increase, while coefficients for the Chronotype-PGS reflect a one standard deviation increase. The threshold for statistical significance was determined using a Bonferroni correction for multiple testing, adjusting for the number of comparisons performed within each of the outcomes. The corrected significance thresholds for the four outcomes were: (a) efficacy: $p<0.0025$ (10 antidepressant medications x 2 chronotype variables); (b) duration of symptom improvement: $p<0.0025$ (same as efficacy); (c) discontinuation due to side effects: $p<0.0025$ (same as efficacy); and (d) $p<0.001$ (25 side effects x 2 chronotype variables). We reported regression results from fitting rMEQ and PGS jointly and correct for multiple testing based on the number of phenotypes tested. For completeness, we also report regression analyses when fitting rMEQ and PGS separately. The coefficient of PGS when fitted together with rMEQ is equivalent to a regression on the rMEQ residuals from a regression of rMEQ on PGS, which represents the deviation of the self-reported chronotype from its "biologically" predicted value. Hence, 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% female; mean [SD] age 42.8 years [15.3]), self-report and genetic data (that passed quality control) were available for 15,108 participants. Of this analytic sample, 75% were female and the mean [SD] age was 43.6 years [15.3] (range=18-90). 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 a lifetime major depressive episode (MDE). Self-reported lifetime diagnoses are reported in Table S1. Most participants (67.7%) self-reported at least one other lifetime diagnosis (other than depression), of which the three most common were anxiety disorder (54.0%), PTSD (13.3%), and social anxiety disorder (10.6%). The mean [SD] score on the rMEQ was 14.6 [4.2] (range=4-25; median=15), indicating that the sample were, on average, "intermediate" chronotypes. After normalising to the sample, the mean of the chronotype-PGS was 0 (SD=1; range = -3.81-4.23).

TABLE 1 HERE

Association among rMEQ and chronotype-PGS

The distributions of the rMEQ and chronotype-PGS are shown in Figure 1. The Pearson's product-moment correlation between rMEQ and chronotype-PGS was 0.21 ($p<0.001$), i.e., the chronotype-PGS explains 4% of the self-reported chronotype (rMEQ).

FIGURE 1 HERE

Antidepressant efficacy

Figure 2 summarises 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). There were Bonferroni-significant ($p<0.005$) associations between higher phenotypic morningness (rMEQ) and greater self-rated efficacy of escitalopram (OR=1.04; 95% CI 1.02-1.06; $p=3.5^{-6}$), fluoxetine (OR=1.03; 95% CI 1.01-1.05; p=0.001), sertraline, (OR=1.02; 95%

CI 1.01-1.04; p=0.0008), and desvenlafaxine (OR=1.03; 95% CI 1.01-1.05; p=0.004). By contrast, the chronotype-PGS was not associated with self-rated efficacy any antidepressant (p's=0.059-0.94).

FIGURE 2 HERE

Duration of symptom improvement and treatment discontinuation due to side effects

Under Bonferroni correction ($p<0.005$) there were no significant associations between the rMEQ or chronotype-PGS and duration of symptom improvement (Table S32-S61; Figure S1) or treatment discontinuation for any antidepressant (p's=0.005-0.989) (Table S62-S91; Figure S2). Between 16-22% of respondents endorsed "Don't know" to the duration of symptom improvement item (and were excluded). There were minor differences between "Don't know" responders compared to the other responses: (i) age (older for amitriptyline, desvenlafaxine, and escitalopram; younger for sertraline); (ii) sex (more females for venlafaxine); (iii) chronotype-PGS (higher for mirtazapine). There were no differences for the rMEQ.

Side effects and chronotype

As presented in Figure 3 there were Bonferroni-significant associations ($p<0.002$) between higher phenotypic morningness (rMEQ) and 20 of 25 side effects, with the exceptions of weight loss, vomiting, rash, 'no side effect', and 'other side effect' (Table S92-S162). The three strongest significant associations were for difficulty getting to sleep (OR=0.93; 95% CI 0.92-0.95; $p=0.7\times10^{-28}$), diarrhoea (OR=0.94; 95% CI 0.92-0.96; $p=0.3\times10^{-10}$), and blurred vision (OR=0.95; 95% CI 0.93-0.97; $p=0.2\times10^{-7}$). The chronotype-PGS was associated with suicidal thoughts (OR=1.09; 95% CI 1.03-1.16; p=0.002) and attempted suicide (OR=1.15; 95% CI 1.05-1.25; p=0.002). Notably, these associations were stronger in the model where chronotype-PGS was fitted jointly with rMEQ than when fitted alone.

FIGURE 3 HERE

Sensitivity analyses

We conducted three sensitivity analyses. First, given that a subset of our sample (12%) did not meet DSM-5 criteria for an MDE, we tested the effect of restricting the sample to the 88% who

318 did meet criteria. Second, given that extreme chronotypes are more likely in youth (i.e., more
319 extreme eveningness) and older people (i.e., more extreme morningness) (44), we tested the
320 effect of restricting the sample to the middle-aged (40-59-years). In both sensitivity analyses,
321 most associations were slightly attenuated (but of largely similar magnitude), and several were
322 robust at Bonferroni-corrected levels, particularly for higher phenotypic eveningness and lower
323 efficacy of escitalopram, and for higher phenotypic eveningness and more side effects. Third,
324 we examined whether side effects influence self-reported efficacy. We summed the individual
325 side effects for each used this 'side effect count' as a covariate in a sensitivity analysis of the
326 efficacy models. As shown in Figure 4 and Figures S1-S5, most associations between the
327 phenotypic chronotype and efficacy were attenuated when accounting for side effect count, and
328 while most remained significant at $p<0.05$, only the association between higher eveningness
329 and lower efficacy of escitalopram was significant under Bonferroni correction ($p<0.005$). This
330 pattern of attenuation suggests that increased side effects are a mediator of the link between
331 chronotype and perceived efficacy of antidepressant medication.
332
333 FIGURE 4 HERE

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 endorsing higher eveningness reported poorer efficacy of sertraline, citalopram, escitalopram, fluoxetine, and desvenlafaxine (under Bonferroni-correction), while there was weaker suggestion of a similar pattern for venlafaxine. These results are consistent with a study reporting that evening chronotype was associated with poorer self-reported response to SSRIs broadly (13). Our findings suggest a clearer link for four SSRIs (escitalopram, citalopram, fluoxetine, sertraline) and one SNRI (desvenlafaxine). Against 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 contrasted the others. We can only speculate on the reasons for this, but one possibility is a cohort effect, whereby paroxetine is prescribed less in younger cohorts and its use may be more relevant to an older group with different characteristics. While not our focus here, we note differences by age and sex in the efficacy and duration of improvement of certain medications (Tables S2-S31, S32-S61).

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 three strongest were for difficulty getting to sleep, diarrhoea, and blurred vision. This concurs with a study showing that evening types undergoing treatment with SSRIs reported more suicidality (13); here, eveningness was associated with 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 effect). 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 note differences by age and sex regarding side effects (Tables S92-S162), and while weight gain was a common side effect and potentially a reason for discontinuation, the distribution of BMI

was almost identical across antidepressants (Table S163), and chronotype was unrelated to discontinuation. Because we collapsed side effects across antidepressants, we cannot directly compare our results to studies of individual medications (45, 46). While these results should be interpreted cautiously given the multiple testing, the difference in direction of effect and the fact that the coefficients for the rMEQ and chronotype-PGS became larger and more significant in joint models (compared to when fitted separately) is consistent with a hypothesis of dysregulated 24-hour patterns of sleep-wake, rest-activity, feeding, and other functions relative 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 time 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 might 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) *might* be more effective for these cases (47); more studies are needed to test this (48). Second, citalopram has been shown to acutely delay melatonin onset and increase sensitivity to light (49). People taking citalopram (and possibly escitalopram) might have circadian disruption caused by a sensitisation of the phase-shifting effect of light at night (50-52). 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 might create a hard-to-treat depression (53, 54). Meta-analyses have reported that many antidepressants are associated with increased insomnia or somnolescence relative to placebo (55, 56) and an IPD meta-analysis reported that antidepressants did not have different effects on improving sleep symptoms compared to CBT (29). Finally, sleep and sleep-wake disturbances are associated with negative outcomes in some studies: increased episode severity and relapse (57), treatment-resistance (58), and non-remission with psychotherapy and/or pharmacotherapy (53, 54). Speculatively, such outcomes may be more common among evening types who are more vulnerable to sleep-wake disturbance.

The difference between phenotypic and genetic chronotypes and antidepressant outcomes were somewhat unexpected. Given that chronotype changes across the lifespan (59), it is likely that the self-rated and genetic measures are picking up different bio-behavioural signals. The rMEQ estimates the current chronotype, 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. Self-rated chronotype may therefore be more relevant to recent outcomes compared to genetic liability (a more distal marker).

The study has important limitations. First, information about antidepressant outcomes was self-reported and subject to recall biases (e.g., misremembering aspects of lifetime antidepressant use). Relatedly, information about dose was not collected. Second, the MEQ has been criticised as not being a valid estimate of chronotype (60); other more biologically-valid measures may better predict outcomes. We used a restricted version of the MEQ, and the variation in scores is truncated compared to the full version. Third, the chronotype-PGS was derived from a GWAS of a single item of diurnal preference and does not provide a robust mapping of endogenous timing. We encourage 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 in other mood-disorder samples show that self- and objectively-measured chronotype are frequently misaligned, complicating interpretations of findings (61). Fifth, while other lifetime diagnoses were common (particularly GAD at 54%, which is reasonably similar, given our data are self-ratings, to an estimate from the WHO World Mental Health Surveys of 45.7% of ≥1 lifetime anxiety disorders in people with lifetime depression) (Table S1) (62), 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 AGDS has a female:male ratio of 3:1, which may have implications for study generalisability as the prevalence ratio is typically 2:1 (63). Some explanations for this sex ratio are that females are more likely to score high on agreeableness, moral obligation, and prosociality (64), and are more likely to participate in clinical research based on altruistic considerations (65). Seventh, we used Bonferroni correction to adjust for multiple comparisons. While this is a conservative approach, we varied the correction thresholds across the antidepressant outcomes as one counter-measure (as 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 lower prevalence antidepressants (e.g.,

amitriptyline). However, we note that samples were large (N>1,000) for each medication, and many associations were non-significant at $p<0.05$. Finally, we acknowledge shortcomings of the antidepressants surveyed. All medications included engage serotonergic receptors and a 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 (47, 66)); we hypothesise evening types would experience *better* outcomes for such medications.

Altogether, in adults with depression (and high overall rates of lifetime diagnoses such as GAD), eveningness is an indicator of a less favourable response to antidepressants, and in particular, SSRIs, supporting the proposal that the circadian system is involved in differential treatment responses in depression. As associations were small, chronotype is unlikely to guide treatment choice by itself; it may have a place in multivariate models predicting individualised treatment response (67). We encourage investigation of more dynamic circadian markers which may better identify an SSRI non-response subtype.

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FIGURE LEGENDS

Figure 1. Distributions and associations among the rMEQ and chronotype-PGS. Dashed lines in the histograms and density plots represent the mean value for each group.

> **Legend**: (A) The rMEQ is approximately normally distributed, with some slight skew toward greater eveningness (i.e., lower rMEQ scores); (B) The chronotype-PGS was normalised to the sample (range = -3.81-4.23); (C) While largely overlapping, the rMEQ distribution differed slightly between males and females (males reporting more morningness and females more eveningness; mean difference = 0.36 $p<0.001$); (D) Chronotype categories from the rMEQ (used only for illustrative purposes) followed the expected profile of association with the chronotype-PGS; and (E) Scores on the rMEQ and the chronotype-PGS had a small correlation (Pearson's product-moment correlation = 0.21; $p<0.001$).

Figure 2. Phenotypic and genetic chronotypes and self-reported efficacy of 10 common antidepressants.

> **Legend:** On the y axis are 10 outcome (y) variables from separate regression models, in which age, sex, rMEQ, and Chronotype-PGS were fitted (x variables). The coefficients for the rMEQ and Chronotype-PGS are visualised separately for ease of interpretation.

Figure 3. Phenotypic and genetic chronotypes and self-reported side effects of 10 common antidepressants (N=15,108).

> **Legend:** On the y axis are 25 outcome (y) variables from separate regression models in which age, sex, rMEQ, and chronotype-PGS were fitted (x variables). The coefficients for the rMEQ and chronotype-PGS are visualised separately for ease of interpretation.

Figure 4. Sensitivity analyses for phenotypic chronotype (rMEQ) and self-rated efficacy.

> **Legend:** 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.

Table 1. Characteristics of participants in the analytic sample (N=15,108).

Age, years	**N (%) or M (SD)**
Mean (SD)	43.6 (15.3)
Range	18-90
Sex	
Female	11,284 (74.8%)
Male	3,810 (25.2%)
Information not provided	14 (<0.1%)
Marital status	
Married or de facto relationship	8,122 (53.9%)
Separated or divorced	2,270 (15.1%)
Widowed	255 (1.7%)
Never married	4,429 (29.4%)
Information not provided	32 (<0.1%)
Education	
Postgraduate	4,174 (27.7%)
Degree	5,283 (35.1%)
Certificate or diploma	3,554 (23.6%)
Senior high school	1,192 (7.9%)
Junior high school or less	859 (5.7%)
No formal education	7 (<0.1%)
Information not provided	39 (<0.1%)