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Polygenic Risk Score Analysis of Antidepressant Treatment Outcomes: A CAN-BIND-1 Study Report

Analyse des résultats du traitement antidépresseur à l'aide des scores de risque polygéniques : Rapport sur l'étude CAN-BIND-1

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Abstract

Objective: The genetic architecture of antidepressant response is poorly understood. This study investigated whether polygenic risk scores (PRSs) for major psychiatric disorders and a personality trait (neuroticism) are associated with antidepressant treatment outcomes.

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Methods: We analysed 148 participants with major depressive disorder (MDD) from the Canadian Biomarker Integration Network for Depression-1 (CAN-BIND-1) cohort. Participants initially received escitalopram (ESC) monotherapy for 8 weeks. Nonresponders at week 8 received augmentation with aripiprazole (ARI), while responders continued ESC until week 16. Primary outcomes were remission status and symptom improvement measured at weeks 8 and 16. At week 16, post-hoc stratified analyses were performed by treatment arm (ESC-only vs. ESC + ARI). Eleven PRSs derived from genome-wide association studies of psychiatric disorders (e.g., MDD and post-traumatic stress syndrome (PTSD)) and neuroticism, were analysed for associations with these outcomes using logistic and linear regression models.

Results: At week 8, a higher PRS for PTSD was nominally associated with a lower probability of remission (odds ratio (OR) = 0.08 [0.014–0.42], empirical *p*-value = 0.017) and reduced symptom improvement (beta (standard error) = −29.15 (9.76), empirical *p*-value = 0.019). Similarly, a higher PRS for MDD was nominally associated with decreased remission probability (OR = 0.38 [0.18–0.78], empirical *p*-value = 0.044). However, none of the results survived multiple testing corrections. At week 16, the stratified analysis for the ESC-only group revealed that a higher PRS for MDD was associated with increased remission probability (empirical *p*-value = 0.034) and greater symptom improvement (empirical *p*-value = 0.02). In contrast, higher PRSs for schizophrenia (empirical *p*-value = 0.013) and attention-deficit hyperactivity disorder (empirical *p*-value = 0.032) were associated with lower symptom improvement. No significant associations were observed in the ESC + ARI group.

Conclusions: These findings suggest that PRSs may influence treatment outcomes, particularly in ESC monotherapy. Replication in larger studies is needed to validate these observations.

Keywords
polygenic risk scores, major depressive disorder, antidepressant, treatment outcomes

Résumé

Objectif: L'architecture génétique de la réponse aux antidépresseurs est mal comprise. Cette étude visait à établir si les scores de risque polygéniques (SRP) pour les troubles psychiatriques majeurs et un trait de personnalité (neuroticisme) sont associés aux résultats des traitements antidépresseurs.

Méthodologie: Nous avons analysé 148 participants ayant un trouble dépressif majeur (TDM) de la cohorte du Réseau canadien d'intégration des biomarqueurs pour la dépression. Les participants ont reçu initialement l'escitalopram (ESC) en monothérapie pendant huit semaines. Les non-répondeurs à la semaine 8 ont reçu en plus l'aripiprazole (ARI) et les répondeurs ont continué l'escitalopram jusqu'à la semaine 16. Les principaux paramètres de réponse étaient l'état de rémission et l'amélioration des symptômes mesurée aux semaines 8 et 16. À la semaine 16, des analyses stratifiées post-hoc ont été effectuées par groupe de traitement (ESC seul *vs* ESC + ARI). Onze SRP identifiés dans les études d'association pangénomique pour les troubles psychiatriques (p. ex. TDM, trouble de stress post-traumatique [TSPT]) et neuroticisme ont été analysés à l'aide de modèles de régression logistique et linéaire à la recherche d'associations avec ces paramètres.

Résultats: À la semaine 8, un plus haut SRP pour le TSPT a été nominalement associé à une plus faible probabilité de rémission (RR = 0,08 [0,014–0,42], *p* empirique = 0,017) et à une plus faible amélioration des symptômes (ET bêta) = −29,15 (9,76), *p* empirique = 0,019). De même, un SRP plus élevé pour le TDM a été nominalement associé à une probabilité moindre de rémission (RR = 0,38 [0,18–0,78], *p* empirique = 0,044). Toutefois, aucun résultat n'a survécu aux corrections pour comparaisons multiples. À la semaine 16, l'analyse stratifiée portant sur le groupe ESC seul a révélé qu'un SRP plus élevé pour le TDM était associé à une plus forte probabilité de rémission (*p* empirique = 0,034) et à une plus nettte amélioration des symptômes (*p* empirique = 0,02). Par contre, des SRP plus élevés pour la schizophrénie (*p* empirique = 0,013) et le TDAH (*p* empirique = 0,032) étaient associés à une amélioration moins marquée des symptômes. Aucune association significative n'a été observée dans le groupe ESC+ARI.

Conclusions: Ces observations suggèrent que les SRP peuvent influer sur les paramètres de réponse au traitement, notamment de la monothérapie par l'escitalopram, mais elles doivent êre répliquées dans des études plus larges pour être validées.

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide,[1] affecting over 250 million people and contributing significantly to the global mental health burden.[2,3] Second-generation antidepressants (ADs), specifically selective serotonin reuptake inhibitors (SSRIs), are first-line interventions for MDD.[4] Despite the widespread use of ADs and their greater efficacy compared to placebo,[5] only about one-third of MDD patients achieve complete remission

following their initial prescription.[6,7] Another one-third requires treatment change or augmentation, while the remaining one-third experience treatment failure (i.e., they do not respond to at least 2 different AD medications).[6,7] This variability in treatment outcomes emphasizes the need to identify clinical and biological predictors of AD response.

Response to ADs has a genetic basis,[8] with 42% (standard error (SE) = 18%; 95% confidence interval [CI], 7% to 77%) of the variance may be explained by common single nucleotide polymorphisms (SNPs).[9] Notably, accumulating evidence from genome-wide association studies (GWASs) suggests that AD response is a complex polygenic trait influenced by many genetic variants or SNPs.[9–13] Each of these variants has a small but cumulative effect on treatment response to AD.[9–13] The aggregation of those SNPs through polygenic risk scoring (PRS) has emerged as a promising approach to predict AD treatment outcomes in patients with MDD.[14]

PRS is a method that calculates an individual's genetic risk for a trait by using genome-wide SNPs, which are weighted according to their effect sizes from GWAS data and corresponding summary statistics.[15] Recent studies using PRS have found genetic links between common psychiatric and non-psychiatric disorders and AD treatment outcomes.[16] These studies indicate that higher genetic loading for MDD,[17,18] neuroticism,[17] schizophrenia,[14,18] coronary artery disease,[19] or obesity[19] are associated with less favourable AD treatment response. In addition, a higher PRS of attention-deficit hyperactivity disorder (ADHD) was associated with treatment-resistant depression.[20] Therefore, using PRSs could be valuable in identifying MDD patients at risk for poor treatment response or the development of treatment-resistant depression. A recent systematic review, which summarized current evidence of the genetic overlap between AD treatment response and PRSs for 30 traits in patients with MDD, has concluded that the majority of these studies were underpowered and assessed heterogeneous populations.[16] As a result, additional studies using standardized outcome measures are needed to expand the MDD patient cohort and to facilitate meta-analyses, which could identify more robust genetic associations.

In this exploratory study, we assessed the genetic associations between AD treatment outcomes and both psychiatric disorders and non-psychiatric traits in MDD patients from the well-characterized Canadian Biomarker Integration Network For Depression (CAN-BIND-1) cohort.[21] The CAN-BIND-1 cohort included 211 adults treated with escitalopram (ESC) and/or aripiprazole (ARI; an antipsychotic used for augmentation therapy) for 16 weeks. We constructed PRSs for clinical disorders (MDD,[11] bipolar disorder,[22] schizophrenia,[23] ADHD,[24] primary anxiety disorders,[25] post-traumatic stress disorder (PTSD),[26] and substance-use disorders (SUDs)[27]), a personality trait (neuroticism[28]), and treatment outcomes (antidepressant non-remission and percentage improvement).[14] We then examined the association of these individual scores with our 2 phenotypes of antidepressant response: (a) remission, a binary outcome (remitter vs. non-remitter) and (b) symptom improvement, a continuous outcome measured as a percentage change in rating scale scores.

Given the complexity of the antidepressant response, which may involve multiple biological pathways and shared genetic influences across psychiatric and nonpsychiatric traits (see Supplemental Figure 1), we further investigated the joint predictive capacity of combining these individual PRSs.[29] This approach, known as the multiple polygenic risk score (mPRS) methodology, has been shown to capture more genetic variance than individual scores.[30,31]

Methods

Target Dataset

The PRS analysis was conducted on the dataset collected from the CAN-BIND-1 cohort. CAN-BIND-1 was a multicenter discovery study designed to identify predictors of treatment response in MDD participants (ClinicalTrials.gov identifier: NCT01655706). The CAN-BIND-1 sample consisted of 211 (18–61 years old) participants diagnosed with MDD in a current major depressive episode of ≥3 months according to the Diagnostic and Statistical Manual for Mental Disorders IV[32] using the Mini International Neuropsychiatric Interview.[33] In addition, all participants were free of psychotropic medications for at least 5 half-lives prior to the start of the study and had a Montgomery–Asberg Depression Rating Scale (MADRS) score ≥24 at the time of screening.[34] A detailed description of the CAN-BIND-1 protocol, study design, inclusion, and exclusion criteria are available elsewhere.[21,35]

CAN-BIND-1 consisted of a 2-phase study protocol following screening and baseline visits. During Phase I (weeks 0 to 8), all participants received open-label ESC monotherapy (10–20 mg/day, flexible dosage). Depressive symptoms were assessed using the MADRS every 2 weeks. At the end of Phase I or week 8, participants were classified as responders if they achieved a 50% or greater reduction in their MADRS from baseline, or non-responders if the reduction in their MADRS from baseline was <50%. During Phase II (weeks 8–16), responders continued with ESC monotherapy until the end of the study period, whereas non-responders were given augmentation therapy with ARI (2–10 mg/day, flexible dosage). Treatment remission was defined as a MADRS score of ≤10, assessed at the end of Phase I (week 8) and Phase II (week 16) visits (see Supplemental Figure 2).

Blood samples for genetic analysis were collected in week 4. Genomic DNA was extracted from venous blood samples using a modified version of the FlexiGene DNA kit (Qiagen, Hilden, Germany) and sent for genotyping to the Pharmacogenetics Research Clinic (Centre for Addiction and

Mental Health, Toronto, Canada). Genotyping was performed on 190 participants using the Illumina Omni 2.5 BeadChip genome-wide microarray according to the manufacturer's protocol. Imputation was also conducted, see Supplemental Material for detailed methodology. Quality control on the genome-wide array data was performed using PLINK 2.00[36] (https://www.cog-genomics.org/plink2). Variants with missing rate ≥5%, minor allele frequency <1%, and Hardy-Weinberg equilibrium test with p-value $<5\times10^{-6}$ were excluded.[37,38] Furthermore, we excluded participants with genotyping rate <99% ($n=4$), sex discrepancies between self-reported sex and genetic sex ($n=3$), abnormal heterozygosity ($n=4$), and related participants (identity by descent >0.185, $n=4$).[37,38] Our final sample included 175 participants who passed genetic data quality control and included 1,575,137 SNPs.

Polygenic Risk Scores (PRSs)

Discovery Cohorts for PRS Derivation. PRSs were constructed on the target dataset using summary statistics from well-powered GWASs. These studies were selected based on their large sample sizes (i.e., mega- and meta-analyses) and the availability of publicly accessible summary statistics from the Psychiatric Genomic Consortium (https://pgc.unc.edu/for-researchers/download-results/).[39] Risk scores were constructed for outcomes across 9 large genome-wide studies, including MDD (with and without the data from 23andMe),[11] bipolar disorder,[22] schizophrenia,[23] ADHD,[24] primary anxiety disorders,[25] PTSD,[26] neuroticism,[28] SUD,[27] and antidepressant non-remission and percentage improvement,[14] see Supplemental Table 1.

Single PRS Calculation and Association With Outcome of Interest. PRSs were constructed using the clumping and thresholding method with the PRSice-2 software (version 2.3.5)[15] across 10 p-value thresholds, ranging from $P_T=0.0001$ to $P_T=1$. Only SNPs with a GWAS association p-value below the specified thresholds were included in the PRS calculation; all other SNPs were excluded. The constructed scores were then evaluated with our following primary outcome measures at the end of Phase I (week 8) and Phase II (week 16) using logistic and linear regressions:

1. *Remission status*: A dichotomous measure, where participants were classified as remitters if their MADRS score was ≤10, and non-remitters otherwise.
2. *Symptom improvement*: Defined as the percentage change in MADRS score from baseline.

In Phase II (week 16), all participants were initially analysed together with the treatment arm (ESC-only or ESC + ARI) included as a covariate. We then conducted a post-hoc stratified analysis by treatment arm (ESC-only vs. ESC + ARI) to further explore potential differences in genetic associations. All regression models were adjusted for covariates including age, sex, baseline MADRS, and the first 3 principal components to account for population stratification. We also conducted 10,000 permutations testing to obtain empirical p-values, accounting for potential inflation and overfitting. The "meff" function from the R package "poolr"[38] was used to calculate the number of independent tests in our target dataset.[40] To correct for multiple testing, we employed Nyholt's method, which adjusts for the nonindependence of the variables in the analysis.[41] As a result, the effective number of independent tests was estimated to be 38, resulting in a corrected p-value threshold of <0.0013 (=0.05/38) for statistical significance. When describing results from this study, nominal significance refers to empirical p-values < 0.05 that did not reach the multiple testing correction threshold.

Post-hoc PRS Score Stratification. To explore whether participants with higher polygenic risk exhibited distinct clinical or demographical profiles, we divided participants into high and low PRS groups based on the median split of individual PRSs. Participants with PRS values above the median were categorized as the high PRS group, while those below the median were categorized as the low PRS group. Differences in clinical and demographic variables between the high and low PRS groups were assessed using chi-square tests for categorical variables and t-tests for continuous variables. See Supplemental Tables 10–13 for detailed results.

Multiple PRSs and Model Evaluation. We explored the collective predictive capability by combining individual polygenic scores using an mPRS methodology.[30] Predictive models were constructed using elastic net regression, with detailed information regarding model building, hyperparameter tuning, and performance evaluation provided in the Supplemental material. Briefly, 2 types of models were developed for each outcome (remission and symptom improvement) at weeks 8 and 16: (1) a clinical model including age, sex, ethnicity, baseline MADRS, and treatment arm, and (2) a full model incorporating all covariates in the clinical model with the addition of PRSs.

Results

CAN-BIND-1 Target Dataset Characteristics

Genome-wide data were available for 190 participants. We excluded 15 participants who failed quality control checks, as described in the "Target Dataset" section, and 27 participants who dropped out prior to week 8, resulting in a lack of MADRS scores for both Phases I and II. Therefore, the final sample size for Phase I included 148 participants from the CAN-BIND-1 target dataset, of whom 70 (47%) continued ESC monotherapy, and 78 (53%) received adjunctive ARI (ESC + ARI) in Phase II. By the end of Phase II (week 16), 12 additional participants dropped out, resulting in a sample size of 136 for Phase II analyses. Demographic and clinical characteristics of the target dataset for both Phases I and II are

Table 1. Demographic and Clinical Characteristics of the CAN-BIND-1 Target Dataset Stratified by Treatment Arm.

Variables	Overall ($N = 148$) *N* (%)	Phase II Treatment Arm		
		ESC ($N = 70$) *N* (%)	ESC + ARI ($N = 78$) *N* (%)	*P*-value[a]
Sex				0.659
Female	86 (58.1%)	42 (60.0%)	44 (56.4%)	
Ethnicity				0.868
Non-White	39 (26.4%)	18 (25.7%)	21 (26.9%)	
White	109 (73.6%)	52 (74.3%)	57 (73.1%)	
[b]Ancestry				0.629
Admixed	7 (4.7%)	3 (4.3%)	4 (5.1%)	
African	3 (2.0%)	3 (4.3%)	0 (0%)	
American	7 (4.7%)	3 (4.3%)	4 (5.1%)	
East Asian	17 (11.5%)	7 (10.0%)	10 (13.0%)	
European	109 (73.6%)	52 (74.3%)	57 (73.1%)	
South Asian	5 (3.4%)	2 (2.9%)	3 (3.8%)	
Remission status at week 8				**<0.001**
Remitter	47 (31.8%)	47 (67%)	0 (0%)	
Non-remitter	101 (68.2%)	23 (33%)	78 (100%)	
Remission status at week 16				**<0.001**
Remitter	82 (55.4%)	50 (71.4%)	32 (41.0%)	
Non-remitter	54 (36.5%)	14 (20.0%)	40 (51.3%)	
ESC dosage at week 2				>0.999
10 mg	147 (99.3%)	70 (100%)	77 (98.7%)	
20 mg	1 (0.7%)	0 (0%)	1 (1.3%)	
ESC dosage at week 16				0.207
10 mg	14 (9.5%)	9 (12.9%)	5 (6.4%)	
15 mg	1 (0.7%)	1 (1.4%)	0 (0%)	
20 mg	119 (80.4%)	54 (77.1%)	65 (83.3%)	
ARI dosage at week 10				>0.999
2 mg	67 (45.3%)	0 (0%)	67 (85.9%)	
5 mg	2 (1.4%)	0 (0%)	2 (2.6%)	
ARI dosage at week 16				0.600
2 mg	14 (9.5%)	0 (0%)	14 (17.9%)	
5 mg	25 (16.9%)	1 (1.4%)	24 (30.8%)	
10 mg	26 (17.6%)	0 (0%)	26 (33.3%)	
	Mean (SD)	Mean (SD)	Mean (SD)	*P*-value[a]
Age	36.28 (13.11)	35.13 (12.77)	37.32 (13.40)	0.310
Baseline MADRS score	30.21 (5.56)	29.07 (5.46)	31.23 (5.48)	**0.010**
%Δ in MADRS score from Baseline at week 8	46.26 (31.36)	72.93 (15.82)	22.32 (20.63)	**<0.001**
%Δ in MADRS score from baseline at week 16	66.69 (26.50)	77.35 (21.68)	57.21 (26.93)	**<0.001**

Note. Mean (with standard deviation) and frequency are displayed for continuous and categorical variables, respectively.
ESC = escitalopram; ARI = aripiprazole; MADRS = Montgomery–Åsberg depression rating scale; SD = standard deviation. Statistically significant differences between treatment arms are indicated in bold.
[a]Kruskal–Wallis rank sum test for continuous variables; Pearson's chi-squared test or Fisher's exact test for categorical variables.
[b]Categories for ancestry are adapted from the International Genome Sample Resource 1000 Genomes Project (http://www.internationalgenome.org/category/population/).

summarized in Table 1 and Supplemental Tables 2 and 3. Overall, the 148 participants had a mean age of 36.3 (standard deviation (SD) = 13.1) years, of which 58.1% were female ($n =$ 86 out of 148) and 73.6% were considered of European ancestry ($n = 109$ out of 148), with no significant differences between the 2 treatment arms. The overall remission rates at the end of Phases I and II were 31.8% ($n = 47$ out of 148) and 55.4% ($n = 82$ out of 148), respectively. At week 16, the proportion of remitters in the ESC group was significantly higher than in the ESC + ARI group (71.4% vs. 41.0%, p-value < 0.001).

Association of PRSs With Outcomes of Interest in the Target Dataset

Phase I (Week 8) Results for all Participants ($n = 148$). The associations of PRSs with remission status and symptom improvement at week 8 are shown in Figures 1 and 2 and Tables 2 and 3 (see also Supplemental Figures 3 to 6 showing the associations across all GWAS p-value thresholds). At week 8, the PRS for PTSD, MDD, and anxiety were nominally associated with ESC remission and/or

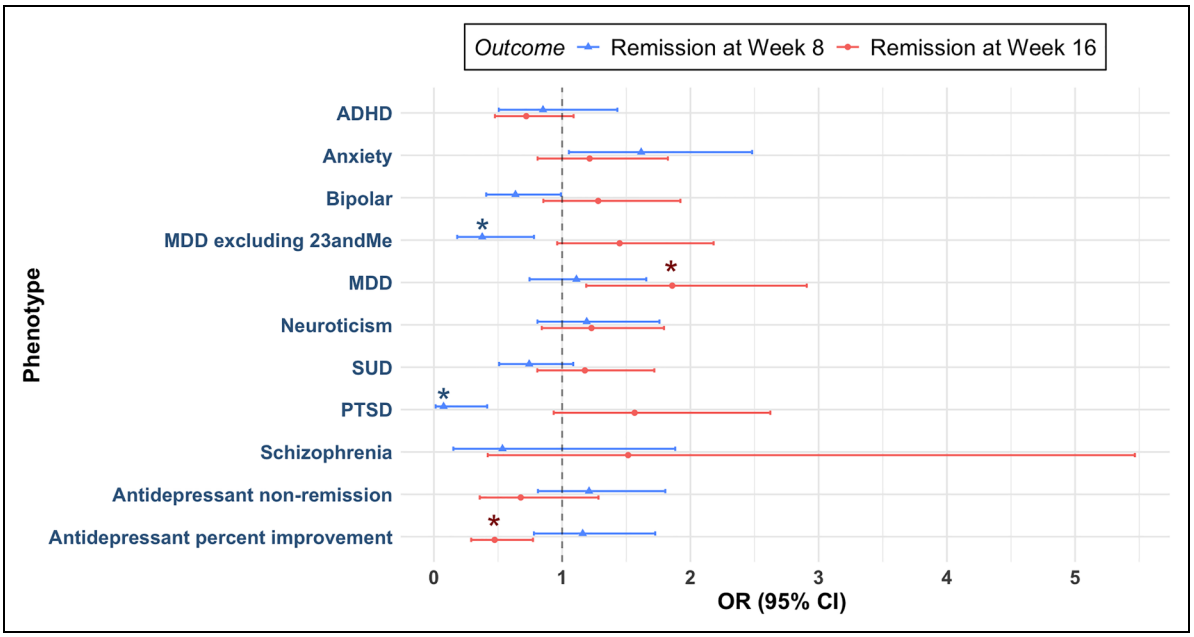

Figure 1. Association of PRSs for various phenotypes with remission status (remitter vs. non-remitter) at week 8 ($n = 148$) and week 16 ($n = 136$). A logistic regression was used with covariates age, sex, baseline MADRS scores and the first 3 principal components to account for population heterogeneity. At week 16, the treatment arm was also added as a covariate (as there were individuals who were given escitalopram only and individuals who were given escitalopram + aripiprazole). MDD refers to MDD with 23andMe data. *Empirical p-value < 0.05 before multiple testing correction. All empirical values became nonsignificant after multiple testing corrections at a threshold of p-value < 0.0013.

Note. ADHD = attention-deficit hyperactivity disorder; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SUD = substance-use disorders; PRS = polygenic risk score.

symptom improvement. A 1 SD increase in polygenic risk for PTSD was associated with decreased probability of remission (OR = 0.08 [0.014–0.42], p-value = 0.003, empirical p-value = 0.017) and lower symptom improvement (Beta (SE) = −29.15 (9.76), p-value = 0.003, empirical p-value = 0.019). Similarly, the PRS for MDD (excluding 23andMe) was associated with a decreased probability of remission (OR = 0.38 [0.18–0.78], p-value = 0.009, empirical p-value = 0.044). In contrast, a 1 SD increase in polygenic risk for primary anxiety disorders was associated with better symptom improvement (Beta (SE) = 7.76 (2.75), p-value = 0.006, empirical p-value = 0.029). Nonetheless, none of the PRS associations above survived the multiple testing correction threshold of p-value < 0.0013.

Phase II (Week 16) Results for all Participants (n = 136). The associations of PRSs with remission status and symptom improvement at week 16 are shown in Figures 1 and 2 and Tables 2 and 3 (see also Supplemental Figures 3–6 showing the associations across all GWAS p-value thresholds). Specifically, the PRS for MDD (with 23andMe) was nominally associated with increased probability of remission (OR = 1.86 [1.19–2.91], p-value = 0.007, empirical p-value = 0.025) and better symptom improvement (Beta (SE) = 5.56 (2.24), p-value = 0.014, empirical p-value = 0.04). In contrast, the PRS for antidepressant percentage improvement was nominally associated with decreased probability of remission (OR = 0.47 [0.291–0.773], p-value = 0.003, empirical p-value = 0.015). The PRS for ADHD was nominally associated with lower symptom improvement (Beta (SE) = −7.34 (2.87), p-value = 0.012, empirical p-value = 0.049). None of the PRS associations above survived the multiple testing correction threshold of p-value < 0.0013.

Phase II Post-hoc Stratified Analyses by Treatment Arm (ESC vs. ESC + ARI). The associations of PRSs with remission status and symptom improvement stratified by treatment arm at week 16 are present in Supplemental Tables 4 and 5. For the ESC-only group ($n = 64$), the PRS for MDD (with 23andMe) was associated with an increased probability of remission (OR = 3.69 [1.40–9.73], p-value = 0.008, empirical p-value = 0.034) and better symptom improvement (Beta (SE) = 7.65 (2.68), p-value = 0.006, empirical p-value = 0.02). Furthermore, the PRSs for schizophrenia (Beta (SE) = −23.69 (7.78), p-value = 0.003, empirical p-value = 0.013), ADHD (Beta (SE) = −9.52 (3.4), p-value = 0.007, empirical p-value = 0.032) and antidepressant percentage improvement (Beta (SE) = −10.21 (2.59), p-value = 0.0002, empirical p-value = 0.002) were associated with lower

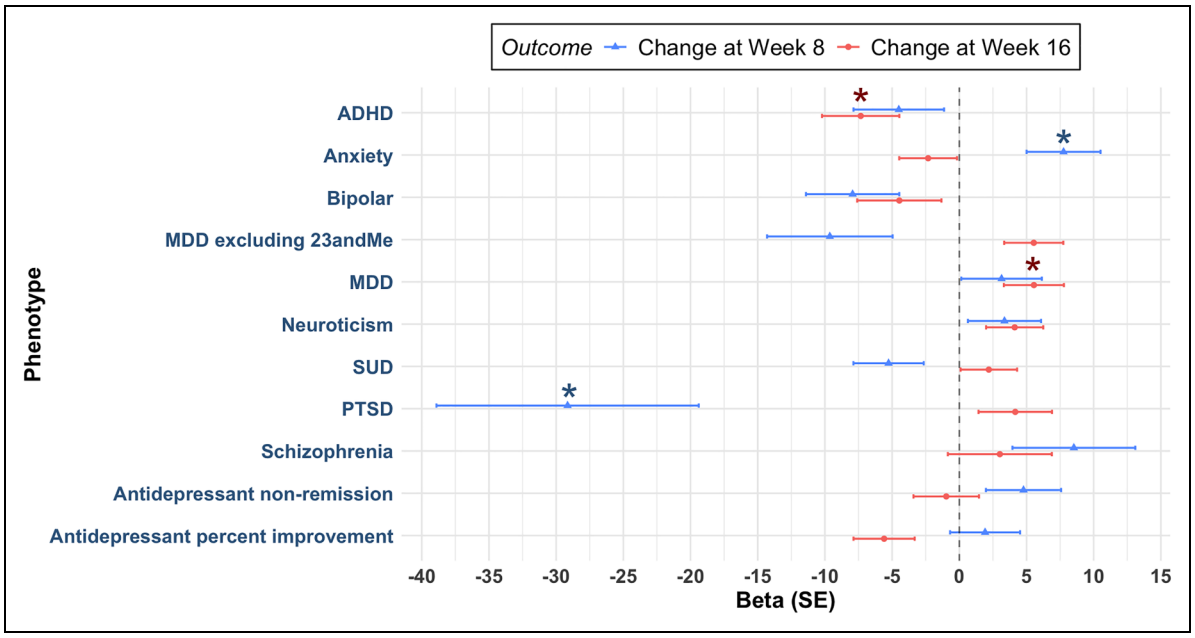

Figure 2. Association of PRSs for various phenotypes with symptom improvement (i.e., % change in MADRS; also referred to as a *change* in the figure) at week 8 ($n = 148$) and week 16 ($n = 136$). A linear regression was used with covariates age, sex, baseline MADRS scores, and the first 3 principal components to account for population heterogeneity. At week 16, the treatment arm was also added as a covariate (as there were individuals who were given escitalopram only and individuals who were given escitalopram + aripiprazole). MDD refers to MDD with 23andMe data. *Empirical p-value < 0.05 before multiple testing correction. All empirical values became nonsignificant after multiple testing corrections at a threshold of p-value < 0.0013.
Note. ADHD = attention-deficit hyperactivity disorder; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SUD = substance-use disorders; PRS = polygenic risk score.

symptom improvements. For the ESC + ARI group ($n = 72$), there were no significant associations present.

Post-hoc PRS Score Stratification. Demographic and clinical characteristics were compared between high and low PRS groups for MDD, PTSD, Anxiety, and ADHD (see Supplemental Tables 10 to 13). No significant differences were observed in age, sex, baseline MADRS scores, or treatment arm across PRS groups (p-value > 0.05). However, a significant difference in ethnicity distribution was observed for all PRS types (p-value < 0.001), with a higher proportion of White individuals in the low PRS group. Furthermore, high PRS groups for PTSD and ADHD had lower rates of family history of psychiatric illness and reported fewer previous MDD episodes (p-value < 0.05).

Predicting Treatment Outcomes Using the mPRS Model. We evaluated the predictive capacity of the 11 risk scores when added to a clinical-only model for both remission status and symptom improvement at weeks 8 and 16. For symptom improvement at week 16, the mPRS model achieved similar significant predictive performance to the clinical-only model (root mean square error = 22.08, $R^2 = 0.13$, mean above error = 19.43, Pearson's $\rho = 0.36$ [0.04, 0.61], p-value = 0.028), see Supplemental Tables 6 to 9.

Discussion and Conclusion

In this exploratory study, we investigated the association between PRSs for major psychiatric disorders and the personality trait neuroticism with ESC and ARI treatment outcomes in patients with MDD from the CAN-BIND-1 clinical trial. We have identified nominal associations of PRSs for PTSD, MDD, anxiety, ADHD, and schizophrenia with remission and symptom improvement.

PTSD is a common, prevalent, and debilitating mental psychiatric disorder that affects individuals following traumatic events. In our study, a higher polygenic risk for PTSD was nominally associated with a lower probability of remission and reduced symptom improvement to ESC monotherapy at week 8. Studies exploring the genetic overlap between PTSD and other psychiatric disorders have reported a moderate shared genetic liability with MDD, with common genetic influences explaining up to 58% of the genetic variation in PTSD.[42–44] Furthermore, one GWAS reported a strong positive genetic correlation between PTSD and more severe depressive symptoms ($r_g = 0.8$), as well as between PTSD and MDD ($r_g = 0.62$).[26] This shared genetic liability between both disorders may contribute to a more complex clinical presentation of MDD, affecting both the underlying biology of the depression and variability in treatment response.[14] Interestingly, this nominal association did not

Table 2. Association of Polygenic Risk Scores with Remission Status (Remitter vs. Non-remitter) at Weeks 8 ($n = 148$) and 16 ($n = 136$) for all Participants.

Phenotype	Threshold	PRSR^2	PRS R^2 (adj.)	Full R^2	NullR^2	Coef.	SE	*P*-value	No. of SNPs	Empirical *P*-value	OR	[95% confidence interval]
Remission at Week 8												
Schizophrenia	1.0000	0.008	0.010	0.210	0.200	−0.626	0.642	0.330	128,087	0.675	0.535	[0.152–1.882]
PTSD	0.0500	0.081	0.100	0.300	0.200	−2.581	0.869	0.003	17,950	**0.017***	0.076	[0.014–0.415]
MDD with 23andMe	0.0010	0.002	0.003	0.202	0.200	0.105	0.204	0.604	669	0.926	1.111	[0.746–1.656]
SUD	1.0000	0.020	0.025	0.225	0.200	−0.300	0.193	0.126	87,549	0.400	0.743	[0.508–1.081]
Neuroticism	0.0001	0.007	0.008	0.208	0.200	0.175	0.199	0.377	103	0.887	1.192	[0.807–1.759]
MDD excluding 23andMe	0.0500	0.061	0.076	0.276	0.200	−0.976	0.371	0.009	20,793	**0.044***	0.377	[0.182–0.780]
Bipolar	0.0010	0.035	0.043	0.243	0.200	−0.453	0.226	0.045	2502	0.148	0.636	[0.408–0.991]
Anxiety[a]	0.0500	0.042	0.052	0.252	0.200	0.480	0.219	0.028	17,760	0.130	1.616	[1.053–2.481]
Antidepressant percentage improvement	0.0001	0.005	0.006	0.205	0.200	0.149	0.203	0.463	81	0.941	1.160	[0.780–1.726]
Antidepressant non-remission	0.0010	0.007	0.009	0.209	0.200	0.190	0.204	0.350	482	0.841	1.210	[0.811–1.804]
ADHD	0.3000	0.003	0.004	0.204	0.200	−0.161	0.265	0.542	62,272	0.954	0.851	[0.506–1.430]
Remission at Week 16												
Schizophrenia	1.0000	0.003	0.004	0.270	0.266	0.415	0.655	0.526	128,087	0.900	1.515	[0.420–5.467]
PTSD	0.0001	0.025	0.029	0.295	0.266	0.448	0.263	0.089	95	0.352	1.565	[0.934–2.623]
MDD with 23andMe	0.0001	0.065	0.077	0.343	0.266	0.620	0.228	0.007	206	**0.025***	1.858	[1.188–2.907]
SUD	0.0001	0.006	0.007	0.272	0.266	0.163	0.193	0.400	316	0.848	1.177	[0.806–1.719]
Neuroticism	0.0010	0.010	0.011	0.277	0.266	0.206	0.193	0.286	693	0.776	1.229	[0.842–1.794]
MDD excluding 23andMe	0.0001	0.027	0.032	0.297	0.266	0.370	0.209	0.076	254	0.286	1.448	[0.962–2.181]
Bipolar	0.0001	0.012	0.014	0.280	0.266	0.248	0.207	0.232	859	0.545	1.281	[0.854–1.922]
Anxiety[a]	0.0100	0.007	0.009	0.275	0.266	0.194	0.208	0.349	4668	0.849	1.215	[0.808–1.825]
Antidepressant percentage improvement	0.0001	0.083	0.099	0.364	0.266	−0.747	0.249	0.003	81	**0.015***	0.474	[0.291–0.773]
Antidepressant non-remission	0.0500	0.012	0.015	0.236	0.221	−0.390	0.326	0.232	15,998	0.676	0.677	[0.357–1.283]
ADHD	0.0010	0.020	0.024	0.290	0.266	−0.328	0.211	0.120	1819	0.363	0.720	[0.476–1.089]

[a]Primary anxiety disorders. Logistic regression was used for analysis. Covariates included age, sex, the first 3 principal component analysis, baseline MADRS and treatment arm (for week 16 only). Empirical *p*-value: correction for overfitting. *Empirical (EMP.) *p*-value < 0.05 before multiple testing corrections. All empirical values became nonsignificant after multiple testing corrections at a threshold of *p*-value < 0.0013. ADHD = attention-deficit hyperactivity disorder; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SUD = substance-use disorders; MADRS = Montgomery–Åsberg depression rating scale.

Table 3. Association of Polygenic Risk Scores With Symptom Improvement (Percent Change in MADRS From Baseline) at Weeks 8 ($n = 148$) and 16 ($n = 136$) for all Participants.

Phenotype	Threshold	PRS R^2	Full R^2	Coef.	SE	*P*-value	No. of SNPs	Empirical *p*-value[b]
Change at Week 8								
Schizophrenia	0.0100	0.023	0.063	8.526	4.573	0.064	12,107	0.182
PTSD	0.0500	0.0575	0.093	−29.149	9.758	0.003	17,950	**0.019***
MDD with 23andMe	0.0100	0.008	0.047	3.143	2.993	0.295	2556	0.606
SUD	1.000	0.027	0.066	−5.264	2.616	0.046	87,549	0.163
Neuroticism	0.0001	0.010	0.050	3.360	2.723	0.219	103	0.668
MDD excluding 23andMe	0.0500	0.028	0.068	−9.635	4.671	0.040	20,793	0.172
Bipolar	0.0100	0.035	0.074	−7.940	3.471	0.024	9024	0.079
Anxiety[a]	0.0500	0.052	0.091	7.758	2.754	0.006	17,760	**0.029***
Antidepressant percentage improvement	0.01	0.004	0.043	1.917	2.603	0.463	4133	0.941
Antidepressant non-remission	0.0010	0.007	0.059	4.777	2.800	0.090	482	0.332
ADHD	0.3000	0.012	0.052	−4.504	3.368	0.183	62,272	0.502
Change at Week 16								
Schizophrenia	0.0100	0.004	0.190	3.015	3.871	0.437	12,107	0.824
PTSD	0.0001	0.015	0.200	4.162	2.733	0.130	95	0.470
MDD with 23andMe	0.0001	0.038	0.224	5.555	2.235	0.014	206	**0.042***
SUD	0.001	0.007	0.192	2.194	2.104	0.299	1100	0.729
Neuroticism	0.0010	0.023	0.209	4.119	2.128	0.055	693	0.226
MDD excluding 23andMe	0.0001	0.038	0.225	5.387	2.202	0.013	254	0.060
Bipolar	0.0500	0.013	0.198	−4.463	3.135	0.157	23,754	0.394
Anxiety[a]	0.0010	0.007	0.193	−2.321	2.150	0.282	616	0.753
Antidepressant percentage improvement	0.0001	0.037	0.223	−5.597	2.274	0.015	81	0.068
Antidepressant non-remission	0.0001	0.001	0.187	−0.972	2.439	0.691	58	0.997
ADHD	0.0100	0.400	0.226	−7.337	2.873	0.012	7381	**0.049***

[a]Primary anxiety disorders. Null R^2 at week 8 is 0.0395 and at week 16 is 0.186. Linear regression was used for analysis. Covariates included age, sex, baseline MADRS, the first 3 principal component analyses and the treatment arm (for week 16 only).

[b]Empirical *p*-value: adjusted *p*-value after 10,000 permutation tests to correct for overfitting.

*Empirical *p*-value < 0.05 before multiple testing correction. All empirical values became nonsignificant after multiple testing corrections at a threshold of *p*-value < 0.0013. ADHD = attention-deficit hyperactivity disorder; MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SUD = substance-use disorders; MADRS = Montgomery–Åsberg depression rating scale; SE = standard error.

persist at week 16, suggesting a potential time-dependent effect of genetic predisposition to PTSD on early antidepressant outcomes.

Furthermore, our results showed a nominal association between higher PRS for MDD and decreased probability of remission at week 8. This is in line with previous findings from various studies showing that higher polygenic loading for MDD is associated with less favourable treatment outcomes.[16] For example, a meta-analysis combining 3 cohorts and including 760 patients reported that a higher PRS for MDD was associated with poorer response to SSRIs, as reflected by the smaller reduction in depression scores after 4 and 8 weeks of antidepressant treatment.[17] Additionally, studies using antidepressant prescription data from population cohorts and the UK Biobank have shown a positive association between PRS for MDD and prescription of more than 2 ADs, indicative of treatment resistance.[45,46] Higher PRS for MDD may affect treatment response by influencing symptom severity, with individuals having a higher genetic risk for MDD potentially presenting more severe depressive symptoms.[46,47] Interestingly, at week 16, post-hoc stratified analyses revealed an opposite effect: in the ESC-only group, a higher PRS for MDD was significantly associated with an increased probability of remission and greater symptom improvement. These contrasting results suggest that genetic predisposition to depression may influence treatment outcomes differently based on treatment strategy and duration. Specifically, individuals with higher genetic risk may initially present with more severe symptoms and require a longer duration of consistent treatment to achieve meaningful improvement.

Another interesting finding was that a higher PRS for primary anxiety disorders was nominally associated with better symptom improvement (empirical p-value = 0.029) at week 8. Such genetic correlations between PRS for anxiety and SSRI response have not been extensively studied. Notably, a GWAS by Li et al.[48] reported no significant association between PRS for primary anxiety disorders and esketamine response or symptom improvement in 527 patients with treatment-resistant depression. Differences in the patient population and the antidepressant used may explain the discrepancy in results. Since anxiety and depression are highly comorbid[49] and both show a strong positive genetic correlation ($r_g = 0.78$),[50,51] genetic liability to anxiety may influence treatment response through shared biological pathways. These pathways mainly involve the serotonin (5-HT) neurotransmitter system targeted by SSRIs, and the hypothalamic–pituitary–adrenal

axis regulated by stress-induced corticotropin-releasing factor (CRF).[52] Stress-induced CRF release positively enhances the 5-HT receptor sensitivity, modulating anxiety-related behaviours.[52] Therefore, it could be postulated that individuals with a higher PRS for anxiety, due to their heightened sensitivity to these mechanisms, may respond better to antidepressant medications, as demonstrated in our study.

Our post-hoc stratified analysis by treatment arm at week 16 revealed significant associations in the ESC-only group but not in the augmented group, suggesting a differential genetic influence based on treatment type. In the ESC-only group, the PRSs for schizophrenia and ADHD were significantly associated with lower symptom improvements. Schizophrenia is known to share genetic factors with MDD, and prior studies reported a suggestive association between PRS for schizophrenia and poor antidepressant treatment response.[14,16] Similarly for ADHD, a higher polygenic risk for the disorder has been associated with being prescribed multiple ADs.[45] In the recent systematic review by Meerman et al.,[16] it was suggested that ADHD could potentially be a useful predictive factor for poor response to ADs and thus warrants further investigations. We also observed that a high PRS for antidepressant percentage improvement (based on Pain et al.[14] GWAS) was negatively associated with remission and symptom improvement at week 16. This could reflect that the Pain et al. GWAS captured genetic variants linked to short-term symptom relief. Additionally, the small sample size of the Pain et al. GWAS may have limited its ability to fully capture the genetic architecture of antidepressant response, contributing to variability in the observed effects.[14] As for the PRSs for bipolar disorder, neuroticism, and SUDs, no significant associations were found, consistent with prior studies.[18,45,46,53]

The strength of our study is using a well-defined target sample of adults with MDD from the CAN-BIND-1 clinical trial to explore PRS associations with response to ADs. While we observed nominal associations of PRSs for PTSD, MDD, anxiety, schizophrenia, and ADHD with antidepressant treatment outcomes, these findings should be interpreted with caution given these several limitations. First, due to our relatively small sample size ($n = 148$), we were unable to validate these findings through cross-validation or using an independent sample.[15] However, we did use empirical p-values to mitigate potential overfitting. Second, we recognize that the GWAS base data used to generate PRS may have limitations in terms of phenotype characterization and population diversity. Since most of the GWAS data were derived from European populations, the generalizability of our findings to other ancestries may be limited. Finally, we acknowledge that MDD is a highly heterogeneous disorder, and additional clinical characteristics could influence genetic and biological mechanisms. Future studies incorporating additional clinical risk factors and non-genetic biomarkers of treatment response could help define more homogeneous subtypes of depression, potentially enhancing the predictive utility of PRS.

In conclusion, further research using the PRS approach may identify individuals genetically predisposed to limited antidepressant response. Once validated, PRSs could serve as a tool to inform pharmacotherapy decisions for individuals with MDD.

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Data Availability

Select CAN-BIND-1 data can be accessed through the Home | Brain-CODE Portal (braincode.ca).

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Institutional Review Board Statement

CAN-BIND-1 was conducted ethically in accordance with the World Medical Association Declaration of Helsinki of 1975, as revised in 1983. Written informed consent was obtained from all participants, and all study procedures were approved by the ethical review board at each of the participating sites.

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Supplemental Material

Supplemental material for this article is available online.

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