ABCB1 Gene Variants and Antidepressant Treatment Outcomes: A Systematic Review and Meta-Analysis Including Results from the CAN-BIND-1 Study

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The P-glycoprotein efflux pump, encoded by the *ABCB1* gene, has been shown to alter concentrations of various antidepressants in the brain. In this study, we conducted a systematic review and meta-analysis to investigate the association between six *ABCB1* single-nucleotide polymorphisms (SNPs; rs1045642, rs2032582, rs1128503, rs2032583, rs2235015, and rs2235040) and antidepressant treatment outcomes in individuals with major depressive disorder (MDD), including new data from the Canadian Biomarker and Integration Network for Depression (CAN-BIND-1) cohort. For the CAN-BIND-1 sample, we applied regression models to investigate the association between *ABCB1* SNPs and antidepressant treatment response, remission, tolerability, and antidepressant serum levels. For the meta-analysis, we systematically summarized pharmacogenetic evidence of the association between *ABCB1* SNPs and antidepressant treatment outcomes. Studies were included in the meta-analysis if they investigated at least one *ABCB1* SNP in individuals with MDD treated with at least one antidepressant. We did not find a significant association between *ABCB1* SNPs and antidepressant treatment outcomes in the CAN-BIND-1 sample. A total of 39 studies were included in the systematic review. In the meta-analysis, we observed a significant association between rs1128503 and treatment response (T vs. C-allele, odds ratio = 1.30, 95% confidence interval = 1.15–1.48, *P* value (adjusted) = 0.024, *n* = 2,526). We did not find associations among the six SNPs and treatment remission nor tolerability. Our findings provide limited evidence for an association between common *ABCB1* SNPs and antidepressant outcomes, which do not support the implementation of *ABCB1* genotyping to inform antidepressant treatment at this time. Future research, especially on rs1128503, is recommended.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ P-glycoprotein is encoded by the *ABCB1* gene and regulates the active transport of some antidepressants across the blood brain barrier. *ABCB1* single nucleotide polymorphisms (SNPs) affect the expression and/or function of the p-glycoprotein but associations between *ABCB1* SNPs and antidepressant treatment outcomes have been mixed.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Are six commonly examined *ABCB1* SNPs (rs1045642, rs1128503, rs2032582, rs2032583, rs2235015, and rs2235040) associated with antidepressant treatment response, remission, or tolerability?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We conducted a systematic review and meta-analysis examining the association among six *ABCB1* SNPs and antidepressant treatment outcomes including a new sample from the Canadian Biomarker Integration Network in Depression (CAN-BIND-1). Although our meta-analysis revealed that carriers of the rs1128503 T allele had 30% greater odds of achieving antidepressant treatment response relative to C allele carriers, we found no evidence of an association between the examined *ABCB1* SNPs and antidepressant treatment remission or tolerability.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our findings do not support the use of *ABCB1* genotyping to inform antidepressant treatment at this time.

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Major depressive disorder (MDD) is a common, yet complex, mood disorder that stems from a combination of biological, environmental, and sociological factors. Although antidepressant medications are a first line treatment for depression, only 40–60% of patients with MDD respond to an initial antidepressant treatment, and < 40% achieve symptom remission.[1] A recent meta-analysis on the efficacy of antidepressant compared with placebo indicated that a clinically relevant treatment heterogeneity across randomized clinical trials (RCTs) is very small.[2] However, one possible factor contributing to the inadequate treatment efficacy could be the interindividual variability with respect to the serum levels of antidepressants. Notably, pharmacogenetic studies showed that gene polymorphisms in drug metabolizing enzymes (e.g., CYP2C19 and CYP2D6) result in variability in enzyme function and contribute to interindividual differences in antidepressant serum concentration and treatment outcome.[3] Although drug concentrations in the serum have been used as a proxy for estimating drug concentrations in the brain, there are yet significant differences between these two compartments due to the blood–brain barrier (BBB).[4,5] Therefore, genetic factors influencing BBB mechanisms might significantly influence therapeutic drug concentrations reaching the brain. In this context, the active transport of antidepressants from the brain by the p-glycoprotein (P-gp), a BBB efflux transporter, has received much attention in the past.[6]

P-gp is part of the ATP binding cassette (ABC) superfamily and is encoded by the *ABCB1* gene, which is located on the chromosomal region 7q21 and includes 28 exons.[7] P-gp at the BBB acts as a protective mechanism against toxins and foreign substances and enhances the active excretion of substrates from the brain.[8] Antidepressants of various classes are P-gp substrates, with various affinities for the transporter as shown in preclinical models using *abcb1* knockout (KO) mice.[6] Antidepressants with high P-gp affinity include citalopram, escitalopram (ESC), fluvoxamine, paroxetine, and venlafaxine, whereas mirtazapine is not substrate of the P-gp.[6] As for fluoxetine and sertraline, the P-gp substrate status is not entirely clear, with some studies reporting higher drug concentrations in the brain of KO mice compared with wild-type mice, whereas others did not observe such a significant difference.[9,10] In addition, aripiprazole (ARI), which is an atypical antipsychotic commonly used for antidepressant treatment augmentation, has also been reported to be a substrate of the P-gp.[11]

Single nucleotide polymorphisms (SNPs) in the *ABCB1* gene have been shown to affect the expression and/or function of the P-gp in *in vitro*, *in vivo*, and *in silico* models.[12,13] Carriers of the TT genotype of the exonic *ABCB1* SNP rs1045642, which leads to lower P-gp expression and reduced substrate efflux,[14] required lower ESC doses to achieve remission, compared with noncarriers.[15] This indicates that changes in P-gp expression or function could alter therapeutic brain concentrations of relevant substrates, leading to variations in antidepressant treatment outcomes.[12,16] However, the association between *ABCB1* SNPs and antidepressant treatment outcomes (i.e., efficacy and tolerability) have been mixed. Although several studies that examined exonic SNPs (i.e., rs1045642, rs2032582, and rs1128503) showed no associations,[17,18] a 2013 meta-analysis[19] demonstrated a weak association between the SNP rs2032582 and antidepressant response. Furthermore, Uhr *et al.*[20] reported an association among three intronic SNPs (rs2235040, rs2032583, and rs2235015) with remission to antidepressant treatment.[20] Nonetheless, a number of subsequent studies failed to replicate these findings.[21,22] The most recent meta-analysis, conducted in 2015, showed a significant association between two intronic SNPs (rs2032583 and rs2235015) and treatment outcomes in inpatient samples only.[23] These findings indicate that existing *ABCB1* studies are methodologically heterogenous, leading to unclear conclusions of the association between *ABCB1* SNPs and antidepressant treatment outcomes.

As numerous studies have been published since the last meta-analysis, we conducted an updated systematic review and meta-analysis of the association among six *ABCB1* SNPs (rs1045642, rs2032582, rs1128503, rs2235040, rs2032583, and rs2235015) and antidepressant treatment outcomes (i.e., response, remission, and tolerability) among individuals with MDD, including results from the well-characterized Canadian Biomarker Integration Network for Depression Study-1 (CAN-BIND-1). We focused on controlling heterogeneity among included studies through incorporating subgroup stratification by study design, admission status (i.e., inpatient vs. outpatient), type of antidepressant used, and ancestry in our meta-analyses.

Based on previous literature, we had two main hypotheses: (1) carriers of alleles in each of the six *ABCB1* SNPs that lead to lower P-gp expression or function will be predominant among responders/remitters and would show higher treatment-related side effects in the CAN-BIND-1 sample and in the meta-analysis, and (2) this association between *ABCB1* SNPs and treatment outcomes would be stronger in inpatient samples, and in studies were antidepressants with high-affinity P-gp substrates was used in the meta-analysis.

METHODS

CAN-BIND-1 association study

Clinical sample and treatment protocol. The CAN-BIND-1 is a multicenter discovery study designed to identify predictors of treatment response in MDD participants (ClinicalTrials.gov identifier: NCT01655706). A detailed description of the CAN-BIND-1 protocol, study design, inclusion, and exclusion criteria are available elsewhere.[24-26] Briefly, the sample consisted of 211 participants (18–61 years old) recruited at 6 clinical centers across Canada. Participants were diagnosed with MDD in a current major depressive episode according to the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV-TR; American Psychiatric Association, 2000) using the Mini International Neuropsychiatric Interview (MINI). In addition, all participants were: (1) free of psychotropic medications for at least 5 half-lives prior to the start of the study, (2) experiencing a current major depressive episode of ≥ 3 months, and (3) had a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 24 at the time of screening. 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.

The study involved a 16-week (phase I and II) protocol. During phase I (weeks 0 to 8), participants were treated with open-label escitalopram (ESC) (10–20 mg/day, flexible dosage) for 8 weeks. At week 8, participants were classified as "responders" if they achieved 50% or greater reduction on the MADRS from baseline. During phase II (weeks 8–16), responders continued ESC, whereas nonresponders had ESC treatment augmented with aripiprazole (ARI)(2–10 mg/d, flexible dosage) for the second 8 weeks, see **Figure S1**.

Using the CAN-BIND-1, we aim to test whether these six *ABCB1* SNPs (rs1045642, rs2032582, rs1128503, rs2032583, rs2235015, and rs2235040) are associated with antidepressant (1) response and remission, (2) treatment-related side effects, and (3) serum levels.

Genotyping. Genomic DNA was extracted from venous blood samples collected at week 4 and was genotyped at the Centre for Addiction and Mental Health Biobank and Molecular Core Facility (Toronto, Canada). The following 6 SNPs were genotyped in the *ABCB1* gene using assays listed in **Table S1**: rs1045642 (C3435T), rs2032582 (G2677T/A), rs2032583, and rs2235015. For SNPs rs2235040 and rs1128503 (C1236T), genotypes were extracted from available CAN-BIND-1 genomewide association study data. SNPs were chosen based on previously reported associations between *ABCB1* substrates and treatment outcomes. Genotyping results were reviewed by two laboratory staff who were blinded to clinical data. All *ABCB1* SNPs were checked for deviation from Hardy–Weinberg equilibrium in participants with self-reported European ethnicity, as they comprise the largest ancestral group. Haploview version 4.2 was used to calculate *P* values for Hardy–Weinberg equilibrium deviation and to calculate linkage disequilibrium (D′) and correlation (r^2) between SNPs.

Outcome measures. The following planned outcomes were assessed:

1. Treatment response, remission, and change in symptom severity over time

Response was defined as a MADRS score reduction of ≥ 50% from baseline. Remission was defined as a score of ≤ 10 on the MADRS. Both response and remission status as dichotomous measures of outcome (responders vs. nonresponders, and remitters vs. nonremitters) were assessed on the last visit of phases I (week 8) and II (week 16), refer to the **Supplementary Material** for a detailed description. Change in symptom severity was defined as the percent mean MADRS change across phases I and II using the formula presented in the **Supplementary Material**.

2. Treatment-related side effects

Antidepressant side effects was assessed with the Toronto Side Effects Scale (TSES), which was administered on weeks 2, 4, 10, 12, and 16. TSES is a clinical instrument which assesses the intensity of treatment-related side effects by measuring its frequency and severity on a 5-point Likert scale.[27] The items assessed were broadly categorized into four categories: (1) central nervous system (CNS) side effects, (2) gastrointestinal (GI) side effects, (3) sexual side effects, and (4) weight gain (**Table S2**). Side effects was measured 2 ways: (1) absence or presence of side effects within the 4 categories at week 8 (end of phase I) and week 16 (end of phase II), and (2) the intensity (range = 1–25) of each side effect category across visits during each phase.

3. Antidepressant serum exposure

Drug exposure of ESC was assessed using dose-adjusted serum concentrations of ESC, its primary metabolite S-didemethylcitalopram (S-DCT) and the S-DCT/ESC ratio at weeks 2, 10, and 16. For those receiving ESC and ARI during phase II, an assessment of ARI exposure was also conducted using dose-adjusted serum concentrations of ARI, its metabolite dehydroaripiprazole (DHA) and the DHA/ARI ratio at weeks 10 and 16.

Statistical analysis. Logistic regression models were used to simultaneously assess the association among each of the six *ABCB1* SNPs and dichotomous outcome measures (responder vs. nonresponder, remitter vs. nonremitter, and present vs. absent side effects) at the end of phase I (week 8) and phase II (week 16). Given the availability of biweekly MADRS scores and multiple timepoints for TSES, continuous measures of response (change in symptom severity over time) and side effects (intensity of each category of side effects) were assessed using linear mixed-effects models. Linear mixed-effects models were tested for effects of individual *ABCB1* SNPs and effect of SNP-by-time interaction, with recruitment site and participant as random effects variables. For drug exposure, linear regression models were used to assess the association between *ABCB1* SNPs and dose-adjusted serum concentration of the drug, its corresponding metabolite, and the metabolite/drug ratio at weeks 2, 10, and 16. Common covariates in all models included age, sex, and ancestry. We also investigated the interaction between *ABCB1* SNPs and *CYP2C19* and *CYP2D6* metabolizer status on dichotomous outcome measures at the end of phases I and II. Considering that ARI dose at week 16 differed among participants (**Table 1**), we included dose as a covariate in the dichotomous outcome measures, response and remission status, and the presence and absence of side effects. For all analyses, genotypes of these 4 SNPs: rs2032582, rs2235015, rs2235040, and rs2032583, were grouped together when one genotype group contained 8 or less participants to enable sufficient sample sizes for meaningful statistical comparisons (see **Table 1**).

All analyses were conducted using R version 4.1.3. (R Foundation for Statistical Computing Platform, 2021) and RStudio version 2021.09.01 (RStudio Inc, 2021). The normality of variables was tested using the Shapiro–Wilk test. Descriptive statistics for demographic and clinical characteristics by each genotype of the six *ABCB1* SNPs were generated using the chi-squared test for categorical variables and the Kruskal-Wallis's rank sum test for continuous variables. Given the different treatments in phase II and different metabolizing enzymes of the administered drugs (i.e., ESC mainly metabolized by CYP2C19, and ARI mainly metabolized by CYP2D6[26]), treatment arms were analyzed

Table 1 CAN-BIND-1 sample demographics and clinical information

	All	ABCB1 rs1045642 (C3435T)				ABCB1 rs2032583			ABCB1 rs2235015		
	(*N* = 178)	TT (*N* = 52)	CT (*N* = 78)	CC (*N* = 47)	*P* value[a]	TT (*N* = 142)	CT/CC (*N* = 36)	*P* value[a]	GT/TT (*N* = 58)	GG (*N* = 120)	*P* value[a]
Characteristics	*N* (%)	*N* (%)	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	χ^2
Sex											
Female	110 (61.8%)	33 (63.5%)	45 (57.7%)	31 (66.0%)	0.640	88 (62.0%)	22 (61.1%)	0.924	34 (58.6%)	76 (63.3%)	0.544
Ancestry											
Admixed	12 (6.7%)	2 (3.8%)	6 (7.7%)	4 (8.5%)	0.196	12 (8.5%)	0 (0%)	0.229	1 (1.7%)	11 (9.2%)	**0.035***
African	4 (2.2%)	0 (0%)	1 (1.3%)	3 (6.4%)		4 (2.8%)	0 (0%)		0 (0%)	4 (3.3%	
American	9 (5.1%)	3 (5.8%)	4 (5.1%)	2 (4.3%)		8 (5.6%)	1 (2.8%)		2 (3.4%)	7 (5.8%)	
East Asian	18 (10.1%)	5 (9.6%)	5 (6.4%)	8 (17.0%)		15 (10.6%)	3 (8.3%)		4 (6.9%)	14 (11.7%)	
European	129 (72.5%)	38 (73.1%)	61 (78.2%)	29 (61.7%)		97 (68.3%)	32 (88.9%)		51 (87.9%)	78 (65.0%)	
South Asian	6 (3.4%)	4 (7.7%)	1 (1.3%)	1 (2.1%)		6 (4.2%)	0 (0%)		0 (0%)	6 (5.0%)	
Arm											
ESC	81 (45.5%)	21 (40.4%)	38 (48.7%)	22 (46.8%)	0.641	67 (47.2%)	14 (38.9%)	0.372	29 (50.0%)	52 (43.3%)	0.403
ESC+ARI	97 (54.5%)	31 (59.6%)	40 (51.3%)	25 (53.2%)		75 (52.8%)	22 (61.1%)		29 (50.0%)	68 (56.7%)	
ESC dose at week 2											
10 mg	177 (99.4%)	52 (100%)	77 (99%)	47 (100%)	1	141 (99%)	36 (100%)	1	58 (100%)	119 (99.2%)	1
20 mg	1 (0.6%)	0 (0%)	1 (1.3%)	0 (0%)		1 (0.7%)	0 (0%)		0 (0%)	1 (0.8%)	
ESC dose at week 16											
10 mg	16 (9.0%)	5 (9.6%)	7 (9.9%)	4 (8.5%)	1	13 (9.2%)	3 (8.3%)	1	5 (8.6%)	11 (9.2%)	1
15 mg	2 (1.1%)	1 (1.9%)	1 (1.3%)	0 (0%)		2 (1.4%)	0 (0%)		0 (0%)	2 (1.7%)	
20 mg	145 (81.5%)	42 (80.8%)	63 (80.8%)	39 (83%)		115 (81.0%)	31 (83.3%)		48 (82.8%)	97 (80.8%)	
ARI dose at week 16											
2 mg	33 (18.5%)	10 (19.2%)	16 (20.5%)	6 (12.8%)	0.436	28 (19.7%)	5 (13.9%)	0.081	7 (12.1%)	26 (21.7%)	0.171
5 mg	35 (19.7%)	14 (26.9%)	11 (14.1%)	10 (21.3%)		26 (18.3%)	9 (25.0%)		11 (19.0%)	24 (20.0%)	
10 mg	14 (7.9%)	3 (5.8%)	6 (7.7%)	5 (10.6%)		11 (7.7%)	3 (8.3%)		5 (8.6%)	9 (7.5%)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**H**	**Mean (SD)**	**Mean (SD)**	**H**	**Mean (SD)**	**Mean (SD)**	**H**
Age (years)	35.4 (12.8)	37.2 (12.3)	35.0 (12.9)	34.4 (13.1)	0.446	35.7 (13.0)	34.5 (12.0)	0.729	35.5 (11.8)	35.4 (13.2)	0.728

(Continued)

Table 1 (Continued)

	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	H	Mean (SD)	Mean (SD)	H	Mean (SD)	Mean (SD)	H
Baseline MADRS score	30.0 (5.5)	29.6 (5.7)	30.5 (5.1)	29.7 (5.9)	0.348	29.9 (5.50)	30.5 (5.6)	0.510	30.3 (5.5)	29.8 (5.5)	0.551
%Δ in MADRS score from baseline at week 8	45.8 (31.8)	45.8 (31.5)	47.6 (32.1)	42.8 (32.3)	0.744	46.8 (31.5)	41.7 (33.0)	0.351	47.6 (33.1)	44.9 (31.2)	0.602
%Δ in MADRS score from baseline at week 16	65.3 (27.2)	68.2 (27.1)	66.1 (26.6)	60.0 (28.2)	0.308	65.3 (26.5)	65.2 (29.8)	0.812	67.6 (27.7)	64.1 (26.9)	0.332

	ABCB1 rs2032582 (G2677T/A)				ABCB1 rs1128503 (C1236T)				ABCB1 rs2235040		
	GG (*N* = 45)	GT/GA (*N* = 87)	TT/TA/AA (N = 43)	*p*-value[a]	CC (*N* = 48)	CT (*N* = 83)	TT (*N* = 31)	*p*-value[a]	AA/AG (*N* = 33)	GG (*N* = 130)	*p*-value[a]
Characteristics	*N* (%)	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	χ^2
Sex											
Females	27 (60.0)	54 (62.1)	27 (62.8)	0.958	29 (60.4)	46 (55.4)	23 (74.2)	0.189	20 (60.6)	79 (60.8)	1
Ancestry											
Admixed	5 (11.1)	3 (3.4)	4 (9.3)	0.078	3 (6.2)	6 (7.2)	2 (6.5)	0.272	0 (0)	11 (8.5)	0.276
African	3 (6.7)	1 (1.1)	0 (0)		2 (4.2)	2 (2.4)	0 (0)		0 (0)	4 (3.1)	
American	2 (4.4)	4 (4.6)	3 (7.0)		2 (4.2)	5 (6.0)	1 (3.2)		1 (3.0)	7 (5.4)	
East Asian	1 (2.2)	10 (11.5)	7 (16.3)		3 (6.2)	7 (8.4)	8 (25.8)		3 (9.1)	15 (11.5)	
European	34 (75.6)	65 (74.7)	27 (62.8)		38 (79.2)	58 (69.9)	19 (61.3)		29 (87.9)	87 (66.9)	
South Asian	0 (0)	4 (4.6)	2 (4.7)		0 (0)	5 (6.0)	1 (3.2)		0 (0)	6 (4.6)	
Arm											
ESC	23 (51.1)	39 (44.8)	18 (41.9)	0.693	23 (47.9)	39 (47.0)	15 (48.4)	0.989	13 (39.4)	65 (50.0)	0.276
ESC+ARI	22 (48.9)	48 (55.2)	25 (58.1)		25 (52.1)	44 (53.0)	16 (51.6)		20 (60.6)	65 (50.0)	
ESC Dose at Week 2											
10 mg	45 (100)	86 (98.9)	43 (100)	1	48 (100)	82 (98.8)	31 (100)	1	33 (100)	129 (99.2)	1
20 mg	0 (0)	1 (1.1)	0 (0)		0 (0)	1 (1.2)	0 (0)		0 (0)	1 (0.8)	
ESC Dose at Week16											
10 mg	3 (6.7)	9 (10.3)	4 (9.3)	0.931	4 (8.3)	5 (6.0)	6 (19.4)	0.286	2 (6.1)	13 (10.0)	0.833
15 mg	1 (2.2)	1 (1.1)	0 (0)		1 (2.1)	1 (1.2)	0 (0)		0 (0)	2 (1.5)	
20 mg	37 (82.2)	68 (78.2)	37 (86.0)		40 (83.3)	66 (79.5)	24 (77.4)		28 (84.8)	103 (79.2)	

(Continued)

Table 1 (Continued)

	ABCB1 rs2032582 (G2677T/A)				ABCB1 rs1128503 (C1236T)				ABCB1 rs2235040		
	GG (*N* = 45)	GT/GA (*N* = 87)	TT/TA/AA (N = 43)	*p*-value[a]	CC (*N* = 48)	CT (*N* = 83)	TT (*N* = 31)	*p*-value[a]	AA/AG (*N* = 33)	GG (*N* = 130)	*p*-value[a]
Characteristics	*N* (%)	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	*N* (%)	χ^2	*N* (%)	*N* (%)	χ^2
ARI Dose at Week 16											
2 mg	4 (8.9)	16 (18.4)	12 (27.9)	0.252	4 (8.3)	12 (14.5)	12 (38.7)	**0.009***	4 (12.1)	24 (18.5)	0.076
5 mg	8 (17.8)	16 (18.4)	10 (23.3)		9 (18.8)	17 (20.5)	2 (6.5)		8 (24.2)	20 (15.4)	
10 mg	6 (13.3)	7 (8.0)	1(2.3)		7 (14.6)	7 (8.4)	0 (0)		3 (9.1)	11 (18.5)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**H**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**H**	**Mean (SD)**	**Mean (SD)**	**H**
Age (years)	33.2 (11.7)	36.2 (13.1)	35.8 (13.2)	0.529	34.8 (12.4)	36.3 (12.7)	34.6 (14.2)	0.661	33.8 (11.5)	35.9 (13.2)	0.567
Baseline MADRS score	29.3 (6.2)	30.4 (4.8)	29.7 (5.9)	0.177	29.3 (6.2)	30.7 (5.0)	29.9 (5.5)	0.159	30.5 (5.8)	30.0 (5.4)	0.747
%Δ in MADRS Score from Baseline at Week 8	45.5 (35.3)	45.8 (28.8)	45.2 (35.1)	0.983	42.3 (32.2)	47.3 (30.2)	51.3 (33.4)	0.443	41.2 (32.6)	48.0 (31.0)	0.276
%Δ in MADRS Score from Baseline at Week16	61.0 (31.2)	68.0 (23.1)	62.3 (30.0)	0.615	58.8 (31.2)	67.1 (24.3)	73.3 (26.0)	0.083	65.7 (30.5)	65.8 (26.3)	0.788

ARI, aripiprazole; CAN-BIND-1, Canadian Biomarker and Integration Network for Depression-1; ESC, escitalopram; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation. *(bold) $P<0.05$.
[a]Fisher's exact test for categorical variables and Kruskal-Wallis rank sum test for continuous variables. Categories for ancestry are adapted from the International Genome Sample Resource 1,000 Genomes Project: (http://www.internationalgenome.org/category/population/).

separately for phase II (ESC-only arm and ESC + ARI arm). The false discovery rate approach[28] was used to control for multiple comparisons in the analysis of each subsample (i.e., total sample for phase I, and by treatment arms for phase II) with a significance threshold of $q < 0.05$. For *post hoc* comparisons, $P < 0.05$ was considered significant. Our sample size was powered to achieve at least 82% power to detect the effect for the 6 SNP of interest at $P < 0.05$.[29]

Systematic review and meta-analyses

Identification of data through public databases and registers. A systematic literature search of published articles was conducted using PubMed, Clinicaltrials.gov, and Web of Science from January 2000 to May 2022 by two reviewers (authors L.M. and M.C.). The search strategy was: ((ABCB1 or P-gp or P-glycoprotein or MDR1) AND (Antidepressant OR **NameOfTheDrug**) AND (Pharmacogenetics OR variants OR SNPs)). Bibliographies of included research articles were hand-searched for additional references not identified in our primary searches. This systematic review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting recommendations.

Identification of data through author collaboration. Three datasets included in the systematic review and meta-analyses which were obtained through author collaborations are: STAR*D (Peters *et al.*[17]), IRL-GREY,[30] and Scherf-Clavel *et al.*[31] The STAR*D (Sequenced Treatment Alternatives to Relieve Depression: NCT00021528) is a multisite clinical study which included participants diagnosed with MDD and received prospective treatment with citalopram for at least 6 weeks. The IRL-GREY (Incomplete Response in Late-Life Depression: Getting to Remission; NCT00892047) sample consisted of adults ≥ 60 years. We included IRL-GREY participants who received open-label venlafaxine for 12 weeks.[30] The cohort study by Scherf-Clavel *et al.*[31] investigated the association between antidepressant treatment outcomes (response and remission) and three *ABCB1* SNPs (rs1045642, rs2032582, and rs1128503) in individuals with MDD treated for a duration of 7 weeks. For this study, we included individuals who were treated with mirtazapine, amitriptyline, or venlafaxine. For CAN-BIND-1, we used response and remission status from week 8 of treatment (phase I end point) before individuals received augmentation therapy with ARI.

Data selection. Articles were included if they were: (1) RCTs, cohort studies, or case reports, (2) published in English between January 2000 and May 2022, (3) investigated the association of *ABCB1* SNPs with antidepressants' treatment outcomes (response, remission, tolerability, and serum levels), (4) included individuals diagnosed primarily with MDD, (5) included individuals treated with at least one antidepressant, and (6) genotyping of *ABCB1* SNPs were conducted and results were reported.

Data extraction. All articles identified by the search strategy were assessed for eligibility independently by both reviewers (authors L.M. and M.C.). Articles for which a consensus between the two reviewers was not obtained were evaluated by a third reviewer (author C.H.). Information extracted from each eligible article included: (1) author names, study design, and publication year; (2) sample size; (3) patients' characteristics (i.e., age, sex, and ethnicity/ancestry); (4) type of antidepressant investigated; (5) diagnosis; (6) phenotype assessed (response, remission, tolerability, or serum levels); (7) SNPs assessed; and (8) main findings of the study. When information was missing or incomplete for an eligible study, a request for additional information was made to the corresponding author of the eligible study.

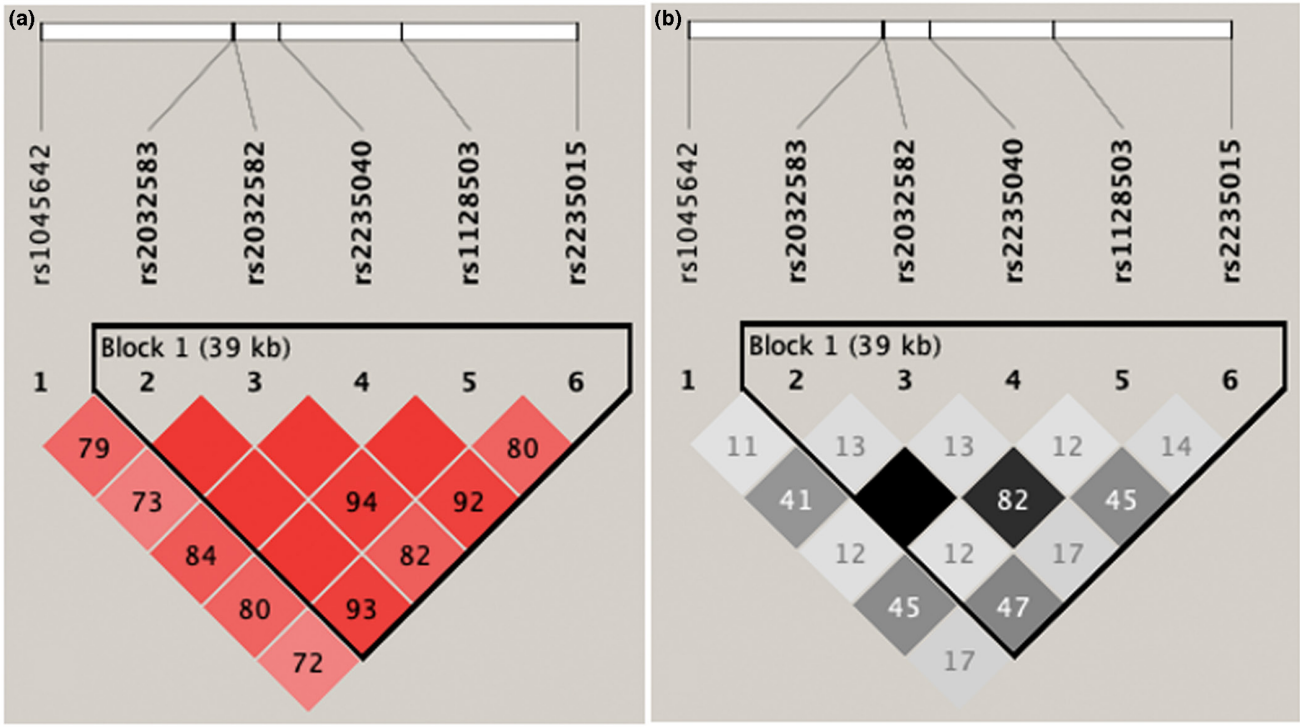

Figure 1 HaploView plot composed of selected SNPs using the CAN-BIND-1 sample of European ancestry showing LD indicated by D′ in (**a**) and correlation indicated by r^2 in (**b**) SNPs rs2032583, rs2032582, rs2235040, and rs1128503 were in strong LD (D′ =0.94–1, r^2 = 0.84–1). CAN-BIND-1, Canadian Biomarker and Integration Network for Depression-1; LD, linkage disequilibrium; SNPs, single-nucleotide polymorphisms.

Table 2 Position, allelic distribution, and role of *ABCB1* single-nucleotide polymorphisms

dbSNP ID	Position[a]	Minor allele (Major allele)	MAF	Hardy–Weinberg p[b]	Role
rs1045642	87,509,329	C(T)	0.49	1.000	Exon 27
rs1128503	87,550,285	T(C)	0.45	0.596	Exon 13
rs2032582	87,531,302	T/A(G)	0.44/ 0.05	0.381	Exon 22
rs2032583	87,531,245	C(T)	0.11	0.482	Intron 22
rs2235015	87,570,248	T(G)	0.19	0.815	Intron 5
rs2235040	87,536,434	A(G)	0.11	0.717	Intron 21

MAF, minor allele frequency.
[a]Relative position on chromosome 7 are taken from the National Center for Biotechnology Information, genome build 38. [b]No deviation from Hardy–Weinberg equilibrium in the European subsample.

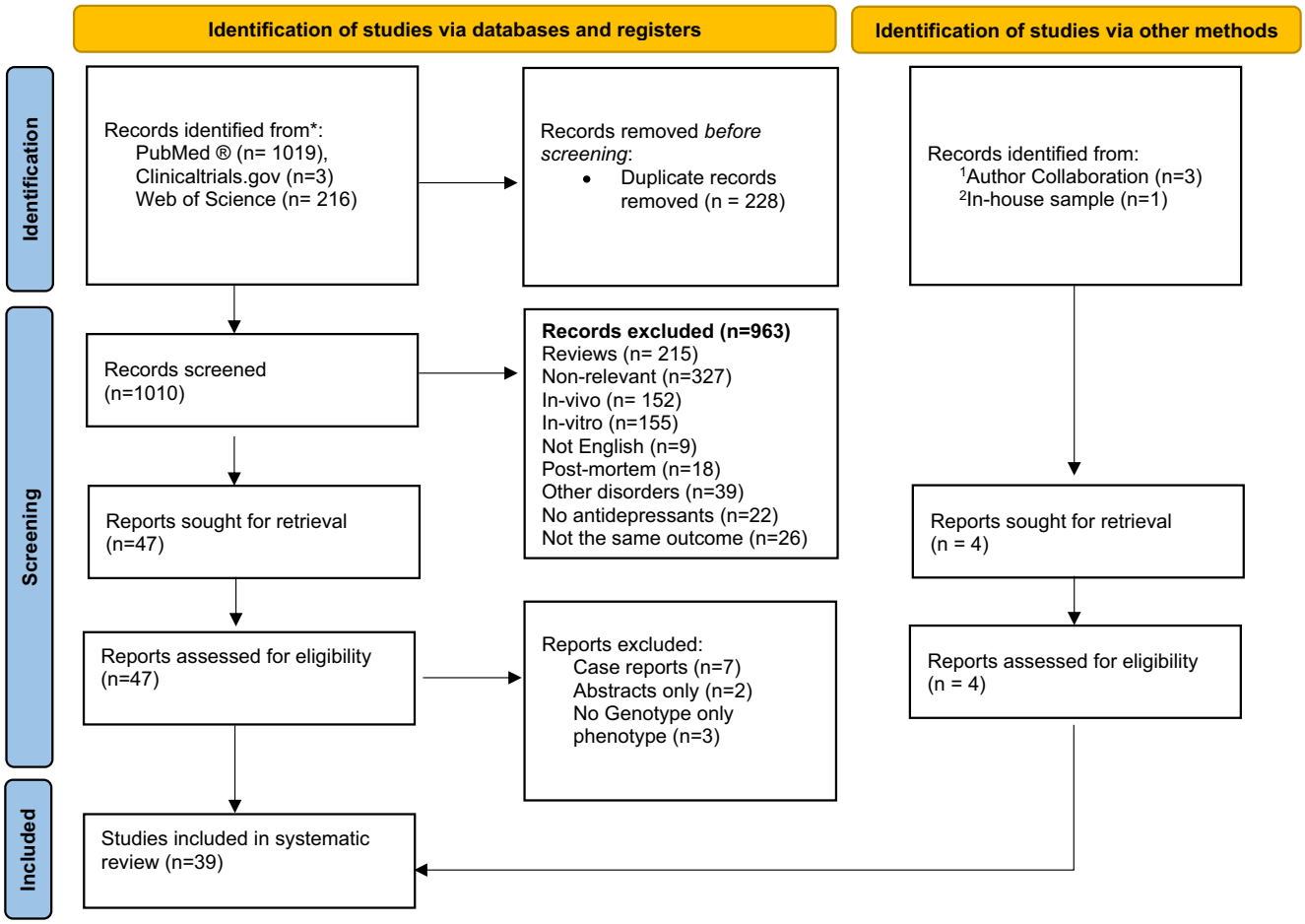

Figure 2 PRISMA flow diagram of article selection including searches of databases, registers, and other sources. (1) Records identified through author collaboration include IRL-GREY,[30] STAR*D,[17] and the sample provided by Scherf-Clavel *et al*.[31]; (2) In house sample: CAN-BIND-1. CAN-BIND-1, Canadian Biomarker and Integration Network for Depression-1; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Quality assessment. An assessment of study quality was conducted independently by two reviewers (authors L.M. and C.H.). Six domains were assessed using the standardized Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I)[32] tool after the initial selection. These six domains assessed bias due to confounding, participant selection, intervention classification, missing data, measurement of outcomes, and selection of reported results. An overall risk of bias (low, moderate, severe, or critical) across all domains was reported for each study, see **Supplementary Material**.

Data analysis. Meta-analyses were performed using the "meta" package in R version 4.1.3. Meta-analyses for *ABCB1* SNPs and a specific phenotype were performed and represented graphically if three or more studies met the inclusion criteria. The odds ratio (OR) was used as the primary effect size estimator for response and remission by contrasting the number of individuals who were classified as responders/nonresponders or remitters/nonremitters (defined by each included study as exceeding a specific threshold decrease in symptom severity)

or tolerability (defined as the presence of one or more assessed side effects) within each of the *ABCB1* SNPs genotype groups. Additionally, standard mean difference (Hedges' g) of percent change in rating scale scores at study end point from baseline between each *ABCB1* genotype was also used as a secondary effect size estimator (see **Supplementary Material** for additional explanation). Percent change measured with standard depression rating scales (Hamilton Rating Scale for Depression (HAMD), MADRS, or Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)) from all studies was used. Three genetic models were examined, which included the allelic model (A vs. B), dominant model (AA vs. AB/BB), and the recessive model (AA/AB vs.BB). Genotype counts from each study were reported separately based on the antidepressant subgroup used: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCA's), and atypical antidepressants or mixed.

The pooled ORs were calculated using a random-effects model for dichotomous data, using the Mantel–Haenszel method. Heterogeneity in effect sizes between studies was tested using the Cochran Q test (with $P < 0.10$ indicating significant heterogeneity), and its magnitude was quantified using the I-squared statistic, which is an index that describes the percentage of variability in effect size due to heterogeneity and is independent of the number of studies included in the meta-analysis and the metric of the effect size. Analyses were repeated using the fixed-effects model when no significant heterogeneity was detected. Influential case analysis was performed to determine studies which had the largest influence on direction or magnitude of effect size. Finally, publication bias was evaluated using funnel plots, Peter's regression for binary outcomes and Egger's regression test for continuous outcomes. Following the recommendations of Dalton *et al*.[33] a test for funnel plot asymmetry was only conducted if the number of studies was 10 or greater. These practices are in line with the guidelines for conducting a meta-analysis outlined in the Cochrane Handbook.[34]

For all SNPs, subgroup analysis by ancestry, study design, setting, and type of antidepressant used was performed. In addition, moderator analysis for age of participant, proportion of female participants, and year of publication were conducted using meta-regression with the restricted maximum likelihood estimator (REML) mixed-effects model. Subgroup and moderator analyses were only performed when the total number of included studies were > 10 for each SNP, according to Bornstein and colleagues, 2011.[35]

RESULTS

CAN-BIND-1 results

Sample characteristics. Participant flow is detailed in **Figure S1**. We excluded 31 participants who dropped out prior to week 8 and therefore lacked MADRS scores for phases I and II. Dropouts were not over-represented in any of the genotypes for the six *ABCB1* SNPs (see **Table S3**). For the dropouts for whom MADRS scores at week 2 were available, there were no significant differences in change in symptom severity between genotypes of each of the six *ABCB1* SNPs (see **Figure S2**). Two additional participants were also excluded as genotype data for all SNPs was not available.

A total of 178 participants were included in the study out of 211 recruited participants. All participants were considered adherent to treatment during phase I based on serum drug concentrations at week 2. During phase II, seven participants were suspected of treatment nonadherence based on undetectable serum drug concentrations at both weeks 10 and 16, therefore they were not included in phase II analyses.

Table 3 Summary characteristics of the included studies in the systematic review

Overall (*N* = 39 studies)	
Age, mean (SD)	42.0 (10.8)
Sample size, mean (SD)	161 (144)
Proportion female, mean (SD)	64.3 (13.6)
Outpatients, *n* (%)	28 (71.8%)
Response, *n* (%)	26 (66.7%)
Remission, *n* (%)	19 (48.7%)
Tolerability, *n* (%)	18 (46.2%)
Serum levels, *n* (%)	10 (25.6%)
Ancestry	
European	24 (61.5%)
East Asian	6 (15.4%)
American	1 (2.6%)
Mixed	8 (20.5%)
ABCB1 SNPs	
rs1045642	30 (76.9%)
rs2032582	25 (64.1%)
rs1128503	15 (38.5%)
rs2235040	11 (28.2%)
rs2235015	14 (35.9%)
rs2032583	15 (38.5%)
Phenotype measure	
HAMD-17	14 (35.9%)
HAMD-21/24	13 (33.3%)
MADRS	5 (12.8%)
QIDS-SR	2 (5.1%)
Study medication	
Citalopram	30 (76.9%)
Escitalopram	25 (64.1%)
Fluoxetine	14 (35.9%)
Paroxetine	10 (25.6%)
Desvenlafaxine	14 (35.9%)
Duloxetine	15 (38.5%)
Amitriptyline	3 (7.7%)
Mirtazapine	14 (35.9%)
Nortriptyline	12 (30.8%)
Clomipramine	1 (2.6%)
Desipramine	4 (10.3%)
Venlafaxine	15 (38.5%)

HAMD, Quick Inventory of Depressive Symptomatology-Self Report; MADRS, Montgomery–Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; SNPs, single-nucleotide polymorphisms.

Analyses were conducted on the included participants ($n = 178$) following exclusions with a mean age of 35.4 years (SD = 12.8, range of 18–61 years) of which 110 (62%) were women. Overall, 42% of participants were treated with an antidepressant at least once previously (range 1–5), whereas 58% were treatment naïve for their current major depressive episode (see **Table 1**). For the

Table 4 Characteristics of studies included in the systematic review and meta-analysis on antidepressant response, remission, and tolerability

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Roberts *et al*. 2002[49]	Randomized clinical trial	160	White	58.1	31.8 (11.2)	MDD	SSRI: Fluoxetine *n* = 82 TCA: Nortriptyline *n* = 78	Response: Change in MADRS and HAM-D scores after 3 and 6 weeks. Side effects: Clinical history. Drug exposure: Steady-state serum concentrations.	**rs1045642**	No significant effect of the investigated SNP on antidepressant response. For nortriptyline: TT carriers more likely than CC or CT to develop postural hypotension (*P* value = 0.042). Measured serum concentrations were similar across genotypic groups.
Laika *et al*. 2006[36]	Prospective cohort	50	White	56	50.6 (12.1)	Medium grade MDE	TCA: Amitriptyline	Response: Change on the HAM-D21 after 3 weeks from baseline. Side effects: Dosage record and treatment emergent symptoms scale (DOTES) after 3 weeks.	**rs2032582**	No significant effect of the P-gp polymorphism on therapeutic response or side effects.
Gex-Fabry *et al*. 2008[50]	Prospective cohort	71	Mixed White (81.7%)	53.5	37.5 (9.05)	Moderate or severe depression	SSRI: Paroxetine	Response: Change by >50% on the MADRS until remission was reached (2–18 weeks). Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582** rs9282564	Persistent response was not significantly associated with *ABCB1* genotypes and the 3-marker haplotypes in univariate model. In the multivariate model: rs9282564 were associated with persistent response (*P* value = 0.043). Paroxetine concentration did not significantly differ according to *ABCB1* genotypes.
Kato *et al*. 2008[62]	Clinical trial	68	Japanese	45.6	45.1 (15)	MDD	SSRI: Paroxetine	Response: Change by >50% on the HAM-D21 after 6 weeks from baseline.	**rs1045642** **rs2032582** **rs1128503**	**rs2032582**: TT/TA/AA carriers showed greater reduction of depression scores than GT/GA or GG carriers in HAM-D21 at week 6 (*P* value = 0.011, *P* value corrected = 0.033). No significant association of HAM-D score change with the SNPs rs1045642 or rs1128503 was found. The C–G–T haplotype was significantly associated with lower HAM-D21 change (*P* value = 0.006).

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Nikisch *et al*. 2008[63]	Prospective cohort	15	White	46.7	36.2 (8.3)	MDD	SSRI: Citalopram	Response: Change by >50% on the HAM-D21 after 4 weeks from baseline. Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582**	For **rs2032582**: GG/GT had more responders than TT (*P* value = 0.001), and significantly influenced citalopram concentrations. The **rs1045642** SNP was not associated with a significantly better treatment response.
Mihaljevic Peles *et al*. 2008[21]	Open-label clinical trial	127	White	53.5	52 (11)	MDD	SSRI: Paroxetine	Response: Change by >50% on the HAM-D17 weekly until week 6.	**rs1045642** **rs2032582**	No effect of genotype or allele frequency on response, percent change scores or weekly depression scores.
Peters *et al*. 2008[17] (STAR*D)	Pragmatic clinical trial	333	White	52.3	42.8 (13.6)	MDD	SSRI: Citalopram	Response: Reduction in QIDS-SR score of at least 50% after 42 days of treatment. Remission: A score of 5 or less on the QIDS-SR score after 42 days. Tolerance: Global rating of side effect frequency, intensity and global burden. All participants who continued with citalopram at the end of treatment were considered tolerant.	**rs1045642** **rs1128503** **rs2032583** **rs2235015** **rs2235040**	No robust association found in the validation sample.
Uhr, *et al*. 2008[20] (Subset of MADRS cohort)	Prospective cohort	112	White	N/A	48.3 (2.1)	MDE	SSRI: Citalopram Paroxetine SNRI: Venlafaxne TCA: Amitriptyline Atypical: Mirtazapine P-gp substrate (*n* = 133) P-gp non-substrate (*n* = 98)	Remission: A score of 10 or less on the HAM-D21 after 4, 5, and 6 weeks	**95 SNPs** **rs1045642** **rs2032582** **rs1128503** **rs2032583** **rs2235015** **rs2235040**	P-gp substrates only: For **rs2032583**: C-allele carriers have high relative risk of remission after 4 weeks of treatment of P-gp substrates. **rs2235040** and **rs2235015**: T-allele carriers associated with better outcome than noncarriers (*P* value = 0.000065 for remission). No significant effect for non-P-gp substrate group.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Dong *et al.* 2009[37]	Randomized clinical trial	142	Mexican American	66.2	38 (10)	MDD	SSRI: Fluoxetine *n* = 74 TCA: Desipramine *n* = 68	Response: Change by >50% on the HAM-D21 after 8 weeks Remission: A score on the HAM-D21 of 8 or less after 8 weeks.	**81 SNPs** **rs1128503** **rs2032583** **rs2235015** **rs2235040** rs2032588 rs28401781 rs3747802 rs9282564 rs2235057 rs10276036 rs28381916 rs2235033 rs2214102 rs17064 rs3842 rs221403 rs2235020	For Fluoxetine **rs1128503**: G-allele frequency was higher in remitters compared with nonremitters (*P* value = 0.02), but did not withstand *P* value correction for multiple testing. For Desipramine: **rs17064**: A-allele frequency was higher in remitters compared with nonremitters, but *P* value did not withstand correction for multiple testing. For both drugs **rs3842** C-allele frequency was higher in remitters compared with nonremitters, but *P* value did not withstand correction for multiple testing. **rs2214103** CC carriers have higher change in HAM-D21 score compared with CG patients, but *P* value did not withstand correction for multiple testing.
Menu *et al.* 2010[22]	Naturalistic prospective cohort	117	White	74.4	45.4 (14.5)	MDE	P-gp substrate (*n* = 57) SSRI: Citalopram *n* = 2 Escitalopram *n* = 10 Paroxetine *n* = 12 Fluoxetine *n* = 16 SNRI: Venlafaxine *n* = 31 TCA: Clomipramine *n* = 25 Amitriptyline *n* = 2 Dosulepine *n* = 1 Imipraminen *n* = 2 Atypical: Mirtazepine *n* = 14	Response: Change by >50% on the HAM-D17 after 28 days from baseline. Side effects: Percent weight change and antidepressant tolerability (CGI-therapeutic index score).	**rs1045642**	No association of rs1045642, neither in the total sample nor in the subsample of P-gp substrate-treated patients.
Perlis *et al.* 2010[38]	Randomized clinical trial	250	White	79	44.2 (12.6)	MDD	SNRI: Duloxetine	Response: Change by >50% on the HAM-D17 from baseline.	**rs2032583** **rs2235040** **rs10280101** **rs7787082**	None of the investigated polymorphisms showed a significant association with response to duloxetine treatment in patients with MDD.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Sarginson *et al*. 2010[64]	Double-blind clinical trial	246	Mixed White (92%)	51.2	72 (5.5)	MDD	SSRI: Paroxetine *n* = 124 Atypical: Mirtazapine *n* = 122	Remission: A score on the HAM-D21 of 10 or less after 4, 6, and 8 weeks.	**rs1045642** **rs2032582** **rs2032583** **rs2235040** **rs2235015** rs2032588 rs9282564 rs10276036 rs10245483 rs28381916 rs2235033 rs2214102 rs3213619 rs2229109 rs2235063	Paroxetine only: For **rs2032583**, carriers of the C allele remitted faster than those with the TT genotype. For **rs2235040**, carriers of the A-allele remitted more quickly than those with the GG genotype. However, none of the analyses were statistically significant after multiple testing correction. Mirtazapine only: No effect of these variants on time to remission were observed.
Lin *et al*. 2011[18]	Open-label clinical trial	100	Han Chinese	81	42	MDD	SSRI: Escitalopram	Response: Change by >50% on the HAM-D21 after 8 weeks from baseline. Remission: A score of <10 on the HAM-D21 scale after 8 weeks. Side effects: Treatment emergent symptom scale and the Arizona Sexual Experiences Scale over 8 week period.	**20 SNPs** **rs1045642** **rs1128503** rs1922242 rs2235046 rs1202184 rs1882478 rs10256836	Associated with response: rs1922242 rs2235046 **rs1128503** rs1202184 Associated with remission: rs1882478: Lower frequency of the T-allele in remitters vs. nonremitters (*P* value = 0.037). **rs1045642**: Lower frequency of the C-allele in remitters than nonremitters (*P* value = 0.045). rs10256836: Higher frequency of the C-allele in remitters vs. nonremitters (*P* value = 0.021). Associated with side effects: rs1882478: T-allele carriers had more severe insomnia symptoms than the C-allele carriers (*P* value = 0.002) at week 1. rs1922242: T-allele carrier had stronger symptoms of depression than the A-allele carriers (*P* value = 0.0054) at week 2.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Perroud *et al*. 2011[65]	Open-label clinical trial	74	European	N/A	36.7 (10.8)	Moderate or severe depression	SSRI: Paroxetine SNRI: Venlafaxine TCA: Clomipramine Sequential treatment of antidepressants Add on therapy: Lithium, Triiodothyronine	Response: Change by >50% on the MADRS from baseline. Remission: A score of 10 or less on the MADRS at 12 weeks. Side effects: Suicide attempts using MADRS 10th item. Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582**	None of the polymorphisms predicted antidepressant response or remission. rs2032582: Carriers of the minor T-allele had a higher rate of treatment increasing suicidal ideation with an OR of 1.07 compared with the GG, GT, and TT genotypes (*P* value = 0.003). There was a significant association between SNP rs2032582 and desmethylclomipramine concentrations.
Crisafulli *et al*. 2012[46]	Case–control	145	Korean	48.3	41.4 (14.1)	MDD	SSRIs: Paroxetine *n* = 40 Fluoxetine *n* = 23 SNRIs: Venlafaxine *n* = 35 Atypical: Mirtazapine *n* = 21 Other (*n* = 26)	Response: Change by >50% on the HAM-D17 after 4 weeks of treatment from baseline. Remission: A score of 7 or less on the HAM-D17 after 4 weeks of treatment.	rs2235047 rs2229107 rs6961419 rs1922241 rs1202167 rs3789243	No significant association between the investigated SNPs and related haplotypes with the diagnosis of MDD or clinical response to treatment in the present study.
Singh *et al*. 2012[15]	Open-label clinical trial	98	Mixed White (73%)	61.2	39.5 (9.19)	MDD	SSRI: Escitalopram *n* = 57 SNRI: Venlafaxine *n* = 41	Response: Change by >50% on the HAM-D17 after 8 weeks from baseline. Remission: A score of 7 or less on the HAM-D17 after 8 weeks.	**rs1045642** **rs2032582** **rs1128503**	**rs1045642**: TT genotype had higher remission than other genotypes in the venlafaxine group only (*P* value = 0.006). **rs2032582**: TT genotype had higher remission than other genotypes in the venlafaxine group only (*P* value = 0.018).
Bly *et al*. 2013[66]	Prospective cohort	43	Mixed White (91%)	100	24.9 (5)	MDD	P-gp substrates only SSRI: Escitalopram *n* = 19 Citalopram *n* = 3 Sertraline *n* = 16 Paroxetine *n* = 5	Side effects: Self-administered CSFQ Sexual dysfunction determined by falling below sex-specific thresholds on the total score (<41 for women).	**rs1045642** **rs2032582** **rs1128503** **rs2235015**	**rs1128503**: CC genotype has the highest CSFQ scores, followed by those with the CT genotype and the lowest scores observed in the TT genotype group (*P* value = 0.005).

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
De Klerk *et al*. 2013[44] (NESDA sample)	Naturalistic cohort	424	European	68.6	41 (11.8)	MDD	SSRI: Citalopram (*n* = 106) Paroxetine *n* = 151 Fluvoxamine *n* = 42 Sertraline *n* = 38 SNRI: Venlafaxine *n* = 87	Side effects: The AASEC-12 Self-report questionnaire. Serotonergic, cholinergic, and histaminergic side effects.	**rs1045642** **rs2032582** **rs1128503** **rs2032583** **rs2235015** **rs2235040**	Two SNPs were significantly associated with the number of side effects: **rs2235040** A-allele (*P* value = 0.002; OR = 2.29) and **rs2032583** C-allele (*P* value = 0.001, OR = 2.41). **rs2235040** A-allele and **rs2032583** C-allele also associated with serotonergic side effects, rs2235040 (*P* value = 0.003; OR = 1.85); rs2032583 (*P* value = 0.002; OR = 1.95).
Huang *et al*. 2013[47]	Cohort	290	Han Chinese	51.4	36 (13.2)	MDD	SSRI: Paroxetine *n* = 81 Fluoxetine *n* = 103 Citalopram *n* = 68 Sertraline *n* = 38	Response: Change by >50% on the HAM-D21 after 6weeks from baseline.	rs6946119 rs28401781 rs4148739 rs3747802 rs182694	**rs28401781**: A-allele is higher in responders than nonresponders (*P* value = 0.0297) but nonsignificant *P* value after correction. **rs4148739**: G-allele is higher in responders than nonresponders (*P* value = 0.0360), but nonsignificant *P* value after correction.
Breitenstein *et al*. 2014[39] A subset of the MADRS cohort	Case–control	58	White	55.2	48.5 (15.2)	MDD+ bipolar, MDD with psychosis	SSRI: Sertraline Citalopram Paroxetine Escitalopram Fluoxetine SNRI: Venlafaxine. TCA: Amitriptyline Nortriptyline Imipramine Trimipramine Doxepin Atypical: Mirtazapine Bupropion Trazodone	Clinical application of genotypes into practice Remission: A score of 10 or less on the HAM-D21 rating scale	**rs2032583** **rs2235015**	Patients whose *ABCB1* test result was received during hospital stay were more likely to be remitted at discharge compared with patients whose test results were unknown at the time of treatment (*P* value = 0.005), and had lower HAM-D scores at discharge (*P* value = 0.0195), as compared with patients without *ABCB1* testing.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Gasso *et al.* 2014[40]	Naturalistic cohort	83	White	68.7	14.7 (1.7)	MDD (majority)	SSRI: Fluoxetine	Remission: Change on the Clinical Global Impression-Severity Scale (CGI-S and CGI-I) after 8 and 12 weeks. Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582**	**rs2032582** Patients carrying the 2677T-allele showed a higher reduction in depressive symptoms, anxiety and obsessive or compulsive symptoms, as well as a higher improvement in clinical global impression. **rs1045642**: Higher scores in the CGI-I scale were observed in T-allele carriers (*P* value = 0.03). No associations with serum concentrations were found.
Ray *et al.* 2014[41]	Open-label clinical trial	83	Mixed White (78.3%)	59.0	47.3 (10.8)	Chronic major depression for 2 years	SSRI: Sertraline *n* = 65 Escitalopram *n* = 13 SNRI: Venlafaxine *n* = 5	Remission: A score of 10 or less on the HAM-D24 after 12 weeks. Global side effect scale: Sum of the three items of the Frequency, Intensity, and Burden of Side Effect Rating (FIBSER) scale at 4 weeks and 12 weeks. Side effect: Organ-specific side effect was measured using the patient-rated intensity of side effects after 12 weeks.	**rs1045642** **rs2032582** **rs2032583** **rs2235015** **rs2235040** rs9282564	Carriers of minor alleles at **rs2235040** or **rs9282564** experienced significantly higher remission rates (*P* value = 0.008 and *P* value = 0.021) and lower average side effects on the FIBSER scale at 12 weeks than did major homozygotes, (*P* value = 0.003 and *P* value = 0.017, respectively). At 4 weeks only: Carriers of minor allele of **rs2032583** demonstrated significantly lower average other side effects (insomnia and nervousness) than did major homozygotes (*P* value = 0.003).
Ozbey *et al.* 2014[51]	Case–control	54	Turkish	79.6	39.4 (13.4)	MDD	SSRI: Citalopram	Response: Change by >50% on the HAM-D17 after 6 weeks of treatment from baseline.	**rs1045642**	The HAM-D scores did not show any statistically significant differences according to genotype, (*P* value = 0.279). No significant difference in distribution of C-allele carriers between responders and nonresponders (*P* value 1.000). Distribution of CC genotype and C-allele frequency were higher in patients than in the control group (*P* value = 0.006, *P* value = 0.020, respectively).

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Blazquez *et al.* 2015[67]	Naturalistic cohort	46	White	78.3	15 (1.74)	MDD (majority)	SSRI: Fluoxetine	Remission: Defined as a relatively asymptomatic period of at least 14 days. Children's Depression Inventory (CDI) Clinical Global Impression-Severity Scale (CGI-S) Global Assessment of Functioning (GAF) Scale Suicide attempts	**rs1045642** **rs2032582**	Polymorphisms were not associated with remission or recovery. A significant association was found between the rs2032582 polymorphism and suicide attempts (*P* value = 0.01).
Chang *et al.* 2015[68]	Randomized clinical trial	112	Taiwanese	73.2	39.7 (12.4)	MDD	SSRI: Fluoxetine *n* = 58 SNRI: Venlafaxine *n* = 54	Response: Change by >50% on the HAM-D21 after 6 weeks.	**rs1045642** **rs2032582** **rs1128503**	rs2032582 MDD patients with the G/G genotype had a worse antidepressant treatment response defined by a lower percent change of HAM-D scores over 6 weeks (*P* value = 0.002).
Schatzberg *et al.*, 2015[42] iSPOT-D trial	Randomized controlled trial	683	Mixed White (62.1%)	57.4	38.6 (12.8)	MDD	SSRI: Sertraline Escitalopram SNRI: Venlafaxine	Remission: A score of 5 or less on the 16-item QIDS-SR after 8 weeks. Side effects: Sum of the three items of the Frequency, Intensity, and Burden of Side Effect Rating (FIBSER) scale after 8 weeks.	**rs2235015** **rs2032583** rs10245483 rs2032588 rs10276036 rs2214102 rs2235033 rs28381916 rs7793196	rs10245483 is a predictor of remission. G-allele homozygotes responded better to escitalopram and sertraline (*P* value = 0.032, 0.020, respectively). T-allele homozygotes responded better to venlafaxine (*P* value = 0.018). rs10245483 is a predictor of side effects (*P* value = 0.001) and a significant interaction by treatment arm (*P* value = 0.001). Major allele (G) carriers had fewer side effects with escitalopram. Minor allele (T) homozygotes had fewer side effects with venlafaxine.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Jeleń *et al*. 2015[69]	Prospective cohort	90	White	64.4	42.6 (11.1)	Recurrent depressive disorder	SSRI, SNRIs, TCA's and agomelatine	Response: Change on the HAM-D21 rating scale from baseline.	**rs1045642**	**rs1045642**: Patients with CC genotype had higher initial HAM-D scores (more depressive symptoms), (*P* value = 0.0106). Patients with CC genotype also had greater change in HAM-D scores (*P* value = 0.0301). Patients with the T-allele have a significantly lower severity of symptoms (*P* value = 0.0026) and decreased therapy effectiveness (*P* value = 0.0142) than C-allele carriers.
Breitenstein *et al*., 2016[16]	Randomized clinical trial	73	White	47.9	47.4 (15.3)	MDD+ Bipolar	SSRI: Citalopram *n* = 6 Escitalopram *n* = 15 Paroxetine *n* = 3 Sertraline *n* = 6 SNRI: Venlafaxine *n* = 30 TCA: Amitriptyline = 1 Amitriptylinoxide *n* = 6 Nortriptyline *n* = 2 Trimipramine *n* = 4	Response: Change by >50% on the HAM-D17 after 4weeks from baseline. Side effects: Somatic symptoms scale of the AMDP interview.	**rs2032583** rs2235015	ABCB1 genotype alone was not associated with treatment outcomes measured by HAM-D-17.
Bet *et al*. 2016[45] (NESDA sample)	Naturalistic cohort	557	European	66.6	42 (12)	MDD	P-gp substrates only SSRI: Paroxetine Sertraline Citalopram Fluvoxamine Escitalopram Fluoxetine SNRI: Venlafaxine Duloxetine TCA: Clomipramine Amitriptyline Impramine Maprotiline Nortriptyline Mianserin Atypical: Mirtazapine	Side effects: The ASEC-12 Self-report questionnaire after 1 and 2years of follow-up.	**rs1045642** **rs1128503** **rs2032582** **rs2032583** rs2032588 rs10276036 rs10808072 rs2188526 rs13233308	rs2032588: A-alleles were nominally associated with a lower number of side effects (mainly serotonergic) in patients in P-gp dependent antidepressants only, (*P* value = 4.6×10^{-3}, after covariate and multiple correction adjustment).

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
CAN-BIND-1 (2016)	Open-label clinical trial	178	Mixed European (72.5%) (72.5%)	62	35.4 (12.7)	MDD	SSRI: Escitalopram	Response: Change by >50% on the MADRS after 8 weeks of treatment from baseline. Remission: A score of 10 or less on the MADRS after 8 weeks. Side effect: Toronto side effect scale (TSES). Drug exposure: Steady-state serum concentrations.	**rs1045642 rs2032582 rs1128503 rs2032583 rs2235015 rs2235040**	No significant effect of investigate SNP on antidepressant response, remission, serum drug levels, or tolerability.
Ozbey *et al.* 2017[70]	Open-label clinical trial	52	Turkish	82.7	38.1 (10.8)	MDD	SNRI: Venlafaxine	Response: Change by >50% on the HAM-D17 after 6 weeks from baseline. Side effects: Clinically assessed in the first, second, and sixth weeks Drug exposure: Steady-state serum concentrations.	**rs1045642 rs2032582**	HAM-D17 total scores did not show any statistically significant difference for the rs1045642 (*P* value = 0.850) and rs2032582genotypes (*P* value = 0.577). For **rs1045642 and rs2032582, the TT genotypes** were reported significantly more frequently in patients with akathisia (*P* value = 0.003, 0.029, respectively). Measured blood concentrations were similar across genotypic groups.
Bousman *et al.* 2017[71]	Open-label clinical trial	119	White	56.3	49 (13)	MDD	SNRI: Desvenlafaxine	Remission: A score of 7 or less on the HAM-D17 after 10 weeks.	**rs1045642**	The use of CNS Dose tool at the start of desvenlafaxine treatment has the potential to shorten the time to remission
Vancova *et al.* 2018[48]	Prospective cohort	61	White	65.6	40.8 (12.8)	Depressive disorders Single or recurrent depressive episodes	SSRI: Paroxetine	Response: Change by >50% on the HAM-D21 score after 6 weeks from baseline. Remission: A HAM-D21 score of 7 or less after 6 weeks. Side effects: Utvalg for Kliniske Undersogelser rating scale (UKU) for nausea and sexual dysfunction.	**rs2032582**	The difference in allele frequencies between the responders and the nonresponders was statistically significant at weeks 4 and 6. Increased chance of treatment response in patients carrying at least one T-allele at week 4, *P* value = 0.049; and at week 6, *P* value = 0.001 for codominant model (GG vs. GT) and *P* value = 0.003 for recessive model. No significant differences between the occurrence of these two side effects were found in samples differentiated by the genotype and allele frequencies of the rs2032582 SNP.

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Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Shan *et al*. 2019[56]	Case- control	253	Han Chinese	50.6	30.9 (10.9)	MDD	SSRI: Paroxetine *n* = 50 Sertraline *n* = 11 Escitalopram *n* = 86 SNRI: Venlafaxine *n* = 65 Duloxetine *n* = 41	Response: Change by >50% on the HAM-D17 after 6weeks of treatment from baseline.	**rs1045642** **rs2032582** **rs1128503** **rs2032583** **rs2235040** **rs2235015**	For **rs2032583**: The T allele frequency and TT genotype were significantly increased in the responders compared with nonresponders (*P* value = 0.033, 0.027, respectively). **For SNRIs**: The HAM-D17 scores of the **rs2032583** TT genotype are lower than those of the CT genotype, with higher decreased score (*P* value = 0.016), and reducing score rate, (*P* value = 0.003). The GG genotypes of **rs2235040** have lower HAM-D17 scores than AG genotypes and higher decreased score (*P* value = 0.041) and reducing score rate than AG genotypes (*P* value = 0.011). The GG genotype of **rs2235015** have lower HAM-D17 scores than those of the GT genotypes and higher in decreased score (*P* value = 0.029) and reducing score rate than those of the GT genotypes (*P* value = 0.009). For SSRIs: The HAM-D17 score was significantly different across genotypes of the **rs2235040** (*P* value = 0.039).

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Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Magalhaes *et al.* 2020[43]	Cross-sectional observational study	79	White	92.4	54.8 (12.1)	MDD	SSRI: Fluoxetine	Remission: A score on the HAM-D17 of 7 or less. Side effects: Antidepressant Side Effect Checklist (ASEC), the Global Adverse Reaction Severity Index (GARSI) and the Positive Side Effect Distress Index (PSEDI). Drug exposure: Steady state serum concentrations (CSS).	**rs1045642** **rs2032582** **rs1128503**	Carriers of the TTT-haplotype showed a higher likelihood to be remitters compared with the non-TTT and TTT-TTT haplotypes, (*P* value = 0.003). Carriers of the TTT-haplotype presented an ASEC-GARSI score 1.7- and 2.0-fold lower than carriers of the non-TTT and TTT-TTT haplotypes, respectively (*P* value = 0.05). TTT-haplotype presented an ASEC-PSEDI score 1.3- and 1.4-fold lower than those with non-TTT and TTT-TTT haplotypes, respectively (*P* value = 0.02). No statistically significant predictors were found for the concentrations of active portion (fluoxetine and metabolite; *P* value >0.05).
Simoons *et al.* 2020[57]	Prospective	81	Mixed White (59.3%)	66.7	43.9 (1.57)	MDD	SSRI: Paroxetine	Response: Absolute decrease and 50% decrease on the HAM-D17 after 6 weeks from baseline. Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582** **rs1128503** **rs2235040**	No association between ABCB1 genotype and clinical response to 6-weeks of paroxetine (*P* value ≥0.13 in responders and *P* value ≥0.34 in nonresponders). **rs2235040**: carriers of the variant A-allele had lower serum concentration than noncarriers (*P* value <0.01).
Geers *et al.* 2022[72]	Cohort	152	White	88.2	49.7 (10.5)	MDD	SSRI: *n* = 92 SNRI: *n* = 14 TCA: *n* = 23 Atypical: Mirtazapine NaSSa: Mianserin *n* = 11	Response: Change by >50% on the HAMD-17 after 4 weeks from baseline.	**rs1045642** **rs2032582** **rs2032583** **rs2235040** **rs2235015** rs4148739 rs28401781 rs9282564	The SNP **rs2235040** A-allele has a significant positive relation with the change in HAM-D17 score at 2 weeks but a significant negative influence on the change in HAM-D17 score at 4 weeks. The rs4148739 G-allele has a significant negative influence on the change in HAM-D17 score at two score but a significant positive influence on the change in HAM-D17 score at 4 weeks. The SNP **rs2235015** T-allele is negatively related to the change in HAM-D17 score at 4 weeks.

(Continued)

Table 4 (Continued)

Study	Study Design	*N*	Ethnicity/ Ancestry	Female (%)	Age [Mean (SD), years]	Diagnosis	Drug used	Phenotype measure	SNPs[a]	Findings
Scherf-Clavel *et al.*, 2022[31]	Naturalistic cohort	277	White	54.2	45 (14.03)	MDD	SNRI: Venlafaxine *n* = 134 TCA: Amitriptyline *n* = 68 Atypical Mirtazapine *n* = 75	Response: Change by >50% on the HAMD-17 after 4weeks from baseline. Remission: A score on the HAM-D21 of 7 or less. Drug exposure: Steady-state serum concentrations.	**rs1045642** **rs2032582** **rs1128503**	No association between ABCB1 genotype and response, remission, or drug exposure.

ASEC, antidepressant side effect checklist; CAN-BIND-1, Canadian Biomarker and Integration Network for Depression; CNS, central nervous system; CSFQ, changes in sexual functioning questionnaire: HAM-D, Hamilton Rating Scale for Depression; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; NaSSa, noradrenergic and specific serotonergic antidepressants; OR, odds ratio; QIDS, Quick Inventory of Depressive Symptomatology; SNPs, single-nucleotide polymorphisms; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TCA, tricyclic antidepressants.
[a]Bolded SNPs are included in the meta-analysis.

use of concomitant medicines, ~71.3% (n = 127) of participants reported taking ongoing comedications up until study completion (week 16), 18.6% discontinued comedications prior to week 8 completion, whereas 10.1% (n = 18) reported no concomitant medication use, including herbal and multivitamins during all phases of the study period, see **Table S4** for a complete list of participant comedications.

Linkage disequilibrium (LD) plots composed of the selected SNPs are shown below in **Figure 1**. The genotype distributions in the European sample (n = 129) were in Hardy–Weinberg equilibrium for all SNPs (see **Table 2**). SNPs rs2032582, rs1128503, rs2032583, and rs2235040, were in strong LD (D′ =0.94–1, r^2 = 0.84–1).

Association of *ABCB1 SNPs* with antidepressant response and remission. The frequency of genotypes in the six SNPs among responders and remitters during phases I and II are presented in **Tables S5** and **S6**. The analyses of the association of each *ABCB1* SNP and response, remission, and percent change in MADRS scores are presented in **Tables S7-S12** and **Figures S3-S5**. The overall response and remission rates were, respectively, 47% (83/178) and 30% (54/178) at the end of phase I, and 74.5% (123/165) and 59.4% (98/165) at the end of phase II. None of the investigated *ABCB1* SNPs were significantly associated in the discrete outcome analysis (response vs. nonresponse and remission vs. nonremission) or in the percent change in MADRS scores from baseline (change in symptom severity) during phase I and phase II.

Association of *ABCB1 SNPs* with antidepressant tolerability. The frequency of at least one CNS, GI, sexual functioning, or treatment-related weight-gain side effect was 77.8%, 65.0%, 37.8%, and 12.2% at the end of phase I, and 64.2%, 45.1%, 27.7%, and 23.1% at the end of phase II, respectively. The most frequent CNS, GI, and sexual functioning specific side effects at the end of phase I were drowsiness, decreased appetite, and decreased libido, respectively. The most frequent CNS, GI, and sexual functioning specific side effects at the end of phase II were weakness and fatigue, increased appetite, and anorgasmia, respectively. Analyses of the associations of each *ABCB1* SNP with the absence or presence of each side effect category are presented in **Tables S13-S15**. No associations between the presence or absence of side effects with *ABCB1* SNPs remained significant after multiple testing corrections were applied (see also **Figures S6-S9**).

Analyses of the associations of each *ABCB1* SNP with the intensity of CNS, GI, sexual side effects, and treatment-related weight gain during phases I and II are presented in **Tables S16-S19**. No associations between the intensity of side effects across timepoints with *ABCB1* SNPs were observed.

Association of *ABCB1 SNPs* with drug exposure. For the dose-adjusted serum levels of ESC, S-DCT, and S-DCT/ESC ratio, there were no significant associations between these serum levels and any of the investigated *ABCB1* SNPs at weeks 2, 10, and 16, see **Tables S20-S22**.

As for the dose-adjusted serum levels of ARI, DHA, and DHA/ARI ratio, we observed a trend between the SNP rs1128503 and

Table 5 Visual representation of investigated SNP in each study and whether an association was found with response, remission or tolerability indicated by: Yes/No

Study	rs2032583	rs2235015	rs2235040	rs1045642	rs1128503	rs2032582	rs2032588	rs28401781	rs4148739	rs3747802	rs7787082	rs9282564
Roberts *et al.* 2002[49]				**Yes**								
Laika *et al.* 2006[36]						No						
Peles *et al.* 2008[21]				No		No						
Kato *et al.* 2008[62]				**Yes**	**Yes**	**Yes**						
Gex-Fabry *et al.* 2008[50]				No		No						**Yes**
Nikisch *et al.* 2008[63]				No		**Yes**						
Uhr *et al.* 2008[20]	**Yes**	**Yes**	**Yes**	No	No	No	No	No	**Yes**	No	**Yes**	No
Peters *et al.* 2008[17]	No	No	No	No	No							
Dong *et al.* 2009[37]	No	No	No		No		No	No		No		No
Perlis *et al.* 2010[38]	No		No								No	
Menu *et al.* 2010[22]				No								
Sarginson *et al.* 2010[64]	**Yes**	No	No	No		No	No					No
Lin *et al.*, 2011[18]				**Yes**	**Yes**							
Perroud *et al.* 2011[65]				No		**Yes**						
De Klerk *et al.* 2013[44]	**Yes**	No	**Yes**	No	No	No						
Bly *et al.* 2013[66]		No		No	**Yes**	No						
Singh *et al.* 2012[15]				**Yes**	No	No						
Huang *et al.*, 2013[47]								No	No	No		
Breitenstein *et al.*, 2014[39]	**Yes**	**Yes**										
Ray *et al.*, 2014[41]	**Yes**	No	**Yes**	No		No						**Yes**
Ozbey *et al.* 2014[51]				No								
Gasso *et al.* 2014[40]				**Yes**		**Yes**						
Chang *et al.* 2015[68]				No	No	**Yes**						
Schatzberg *et al.*, 2015[42]	No	No					No					
Jeleń *et al.*, 2015[69]				**Yes**								
Blazquez *et al.* 2015[67]				No		**Yes**						
Bet *et al.* 2016[45]	No			No	No	No	**Yes**					

(Continued)

Table 5 (Continued)

Study	rs2032583	rs2235015	rs2235040	rs1045642	rs1128503	rs2032582	rs2032588	rs28401781	rs4148739	rs3747802	rs7787082	rs9282564
Breitenstein *et al*. 2016[16]	No	No										
CAN-BIND-1	No	No	No	No	No	No						
Ozbey *et al*., 2017[70]				**Yes**		**Yes**						
Bousman *et al*. 2017[71]				**Yes**								
Vancova *et al*. 2018[48]						**Yes**						
Shan *et al*. 2019[56]	**Yes**	**Yes**	**Yes**	No	No	No						
Simoons *et al*. 2020[57]			No	No	No	No						
Magalhaes *et al*. 2020[43]				**Yes**	**Yes**	**Yes**	No					
Geers *et al*., 2022[72]	No	**Yes**	**Yes**	No		No		No	**Yes**			**Yes**
Scherf-Clavel *et al*., 2022[31]				No	No	No						

CAN-BIND-1, Canadian Biomarker and Integration Network for Depression; CNS, central nervous system; SNP, single-nucleotide polymorphism. Green shade (Yes) denoting a significant association with either response, remission or tolerability. Red shade (No) denotes no sigificant association found.

the DHA/ARI ratio at week 16 ($F(2, 55) = 9.26$, P value = 0.0008, q value = 0.07), see **Table S23**. Participants with the TT genotype showed higher mean ARI/DHA ratios compared with the CT genotype ($B = 0.12$, 95% confidence interval (CI) = 0.04, −0.19; see **Figure S10**).

Interaction with CYP2C19 and CYP2D6 metabolizer status. The interaction between each *ABCB1* SNP and CYP2D6 and CYP2C19 metabolizer status on dichotomous outcome measures (response and remission status, and presence or absence of side effects) at the end of phases I and II were also nonsignificant, see **Tables S24-S27**.

Systematic review and meta-analyses

The systematic search produced a total of 1,238 articles. A summary of the article selection process is presented in the PRISMA flow diagram (Figure 2). After title, abstract, and full text screening, a total of 39 articles were eligible for inclusion in this systematic review. Four of these included articles were studies that were identified through author collaborations: CAN-BIND-1, STAR*D,[17] IRL-GREY,[30] and Scherf-Clavel[31] *et al*. Characteristics of available reported data from each article are presented in **Table 3**, and a detailed summary of each study are presented in **Tables 4** and **5** and **Table S30**.

For meta-analyses, 17 (43.6%) studies were included for response, 11 (28.2%) studies for remission, 12 (30.8%) studies for percent mean change in rating scale scores, and 9 (23.1%) studies for tolerability. Excluded studies ($n = 12$) in meta-analyses were either due to insufficient data[16,20,36–45] or investigated other *ABCB1* SNPs ($n = 2$) than those listed in **Table 2**.[46,47] Data were deemed insufficient if the number of patients within each outcome of interest according to each genotype of each *ABCB1* SNP was not obtained.

Treatment response/remission *Exonic SNPs: rs1045642, rs2032582, and rs1128503.* Most of the studies ($n = 27$, 2,635–3,453 participants, range: 15–333) investigated the genetic association between 2 SNPs rs2032582 and rs1045642 and antidepressant response and/or remission in individuals with depression. Twelve studies (1,833 participants, range: 68–333) investigated rs1128503. The majority of studies for all SNPs (> 50%) included individuals of European ancestry. Symptom severity scales used were mainly HAMD-17/21/24. For detailed information on studies included in this systematic review and meta-analysis, see **Table 4**.

For rs1045642 and rs2032582, a total of 24 and 17 subgroups, respectively, were used to calculate the pooled ORs using the random effects model for the three genetic models (allelic, dominant, and recessive), see **Figures S11-S18**. The pooled OR showed no significant association between either of the two SNPs and antidepressant response, remission, or percent change in outcome scores from baseline under any of the three genetic models. Similar results were obtained when stratifying analyses by type of antidepressant, ancestry, setting, and study design or when performing meta-regressions, see **Tables S31** and **S32**. For SNP rs2032582, one study was detected to be an outlier and had the greatest influence on effect size for treatment response (Vancova *et al*.[48]), but removal of this study did not change the direction of the overall result (OR = 0.93, 95% CI = 0.80; 1.09, P value = 0.362; see **Figure S38**). No significant publication bias was detected using Peter's regression test for treatment response for both SNPs, rs1045642 (P value = 0.785), and rs2032582 (P value = 0.143), see **Figures S43, S44** for funnel plots. Similar results were obtained using the fixed-effects model (**Figures S53, S54**).

For rs1128503, a total of 11 subgroups were used to calculate the pooled ORs using the random effects model for the three genetic models (allelic, dominant, and recessive). The pooled ORs showed a significant association between the SNP rs1128503 using the allelic model only and antidepressant response, with T allele carriers having greater odds of response compared with C-allele carriers (OR = 1.30, 95% CI = 1.15–1.48, P value = 0.001, q value = 0.024; see **Figure 3**). All studies using SSRIs (OR = 1.27, 95% CI = 1.09–1.48) or SNRIs (OR = 1.58, 95% CI = 1.25–2.00) as antidepressants favored the T-allele for better treatment response. The TCA subgroup was not significant (OR = 0.85, 95% CI = 0.42–1.72), see **Figures S19-S21**. This effect was also more robust in clinical trial studies (OR = 1.36, 95% CI = 1.12–1.64), and among outpatients (OR = 1.31, 95% CI = 1.12–1.54). In contrast, no significant association between this SNP and antidepressant remission was observed (see **Figure 3**). The CAN-BIND-1 study was detected to be most influential on pooled effect size (**Figure S39**). The adjusted OR after removing this influential study increased modestly (OR = 1.34, 95% CI = 1.17–1.54). No significant publication bias was detected using Peter's regression test for treatment response (P value = 0.822; **Figure S45**). Similar results were obtained using the fixed-effects model (**Figure S55**).

Intronic SNPs: rs2235040, rs2235015, and rs2032583. Fewer studies ($n = 10$ to 13) comprising 1850–2,901 (range: 58–333) participants investigated the genetic association among the SNPs rs2235040, rs2235015, and rs2032583 and antidepressant response and/or remission, respectively. A majority of those studies included individuals of European ancestry (**Table 4**).

A total of six subgroups were used to calculate the pooled ORs using the random effects model for the three genetic models (allelic, dominant, and recessive) for the three SNPs (**Figures S25-S36**). The pooled ORs showed no significant association among the three SNPs and antidepressant response, remission, or percent change in outcome scores from baseline. When stratifying analysis by type of antidepressant used, no robust findings were detected (**Table S31**). Not enough subgroups were available to perform meta-regression analysis ($n = 6$). No significant publication bias was detected visually in the funnel plots (**Figures S46, S47**). Not enough studies were available to test for publication bias using Peter's regression method regarding treatment response or remission. Similar results were obtained using the fixed-effects model (**Figures S56-S58**).

Treatment tolerability. Among the 18 included studies that investigated the 6 *ABCB1* SNPs and treatment-related side effects, only 9 were included in the meta-analyses, as data were not readily available from the excluded studies ($n = 9$). The majority of studies ($n = 17/18$) included individuals of European ancestry. For detailed information on those included studies (**Tables 4, 5**). None of the investigated SNPs (rs1045642, rs2032582, rs1128503, rs2235040,

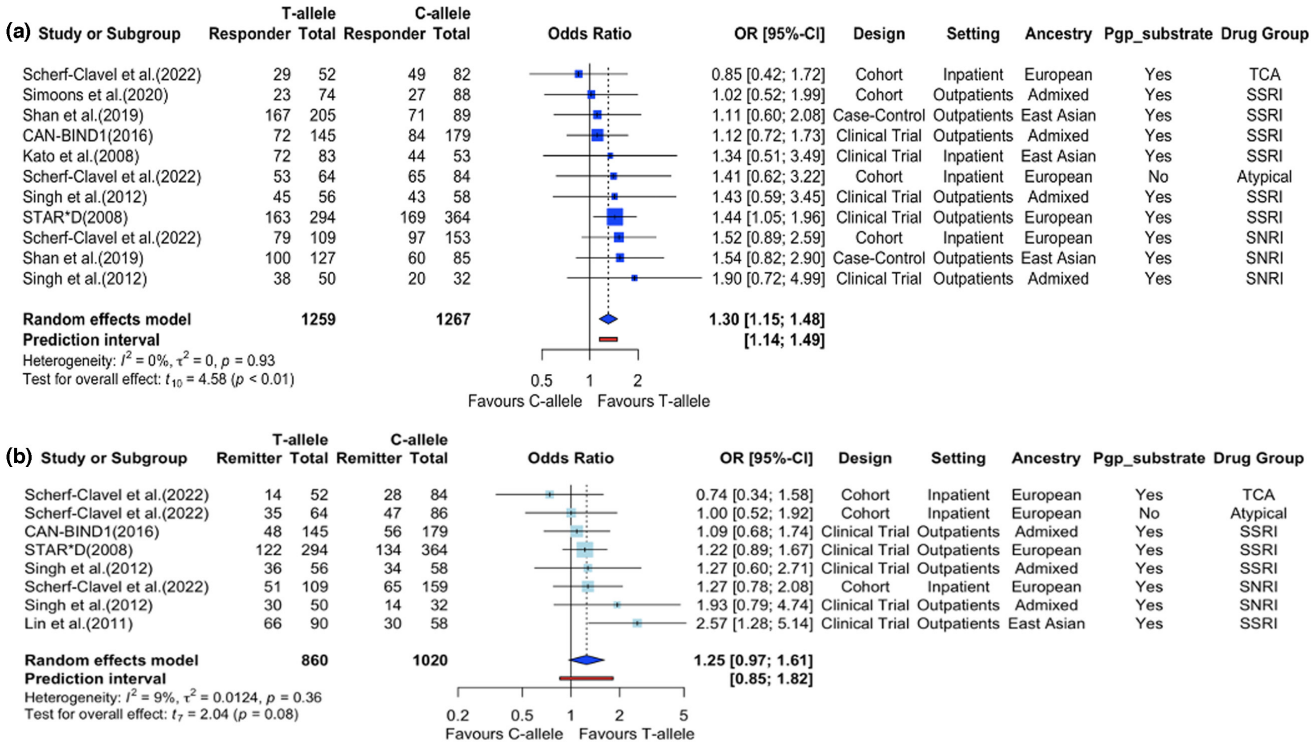

Figure 3 Forest plot of rs1128503 SNP using the allelic model (C vs. T) and (**a**) response, and (**b**) remission, as dichotomous measures. *For response status, adjusted *P* value = 0.024. CI, confidence interval; OR, odds ratio; SNPs, single-nucleotide polymorphisms; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

rs2235015, and rs2032583) showed significant association with treatment tolerability, measured by the presence of at least one treatment-related side effects (**Figures S48-S52**).

Drug exposure. There were 10 studies that examined the influence of *ABCB1* SNPs on antidepressant serum levels, measured by the steady-state concentration of the drug and its respective active metabolite, see **Table 4**. The majority of those studies reported nonsignificant findings.[31,40,43,49–51] There were insufficient studies for each antidepressant medication type to conduct a meta-analysis.

DISCUSSION

This updated and, so far, largest meta-analysis systematically reviewed existing literature, including new and unpublished data from the CAN-BIND-1 sample, summarized and evaluated the pharmacogenetic evidence of the association between *ABCB1* polymorphisms and antidepressant treatment outcomes.

Results revealed that rs1045642 (C3435T), rs2032582 (G2677T/A), rs1128503 (C1236T), rs2032583, rs2235015, and rs2235040 were the most frequently investigated *ABCB1* variants. The first three are exonic SNPs (rs1045642, rs2032582, and rs1128503; i.e., located in the protein-coding region of the gene), and have been previously associated with variations in P-gp expression and activity.[14,52] In contrast, the last three SNPs (rs2032583, rs2235015, and rs2235040) are intronic, although it is unclear whether these variants modulate P-gp expression or function, Uhr *et al.*[20] was the first to report a strong association between these variants and antidepressant treatment outcomes in a large inpatient sample. Based on these findings, subsequent studies aimed to replicate the findings by Uhr *et al.*[20] and incorporated these three intronic SNPs in their investigations.

No significant associations were detected with either treatment remission or tolerability with any of the six SNPs in either in- or outpatients treated with antidepressant medications. Nonetheless, our meta-analysis showed a significant association between the exonic SNP rs1128503 (C1236T) and response, with the T-allele associated with 30% greater odds of achieving response compared with the C-allele for both, in- or outpatients. Given the heterogeneity of studies, we also performed subgroup analyses. We noted our association was more robust for those patients treated with either SSRIs or SNRIs, as opposed to TCAs. The increased robustness among SSRI and SNRI studies would be supported by previous work that showed SSRIs and SNRIs are stronger P-gp substrates than TCAs.[6] The SNP rs1128503 is a synonymous polymorphism, located on exon 12 and encodes the transmembrane-6 (TM6) region of the P-gp which is important for substrate binding.[53] Although the SNP rs1128503 does not involve an amino-acid change, it has been shown to affect P-glycoprotein mRNA stability[13] and protein folding.[54,55] The frequency of the T-allele, which is the minor allele in most ancestral populations, ranges from 14% in Africans to ~40% in Europeans and Americans (www.ensembl.org). The frequency of the T-allele in the CAN-BIND-1 European subsample was found to be 45%, which is consistent with previous published reports. However, our significant finding of rs1128503 with antidepressant response is inconsistent with the finding in the most recent meta-analysis conducted in 2015 by Breitenstein *et al.*[23]

which found no significant association between this SNP and antidepressant treatment response. This discrepancy could possibly be due to differences in the study selection. In addition to the studies that were included by the 2015 meta-analysis, except for Uhr *et al*.[20] and Dong *et al*.[37] we added new data from the CAN-BIND-1 and IRL-GREY,[30] and from 3 other studies published after 2016.[31,56,57]

Our analyses of the other five *ABCB1* SNPs (rs1045642, rs2032582, rs2032583, rs2235015, and rs2235040) did not reveal significant associations with any of the examined antidepressant treatment outcome variables in outpatients. These negative findings in outpatients remain consistent with meta-analysis by Breitenstein *et al*.[23] who reported a significant association between rs2032583 and rs2235015 and antidepressant treatment outcomes in inpatients only. Inpatient status typically represents more severe forms and/or treatment resistant forms of depression,[58] where the *ABCB1* gene variants might have stronger effects on treatment outcomes. However, for these two SNPs (rs2032583 and rs2235015), we were unable to analyze inpatients and outpatients separately as we had no detailed information available from those respective studies. Our inclusion criteria required data from articles to be in a format where allele or genotype counts were available for effect size (OR) calculations. If the data were not available in this explicit format, corresponding authors were contacted for detailed information. Although this was successful for most articles, we were not able to obtain data from selected studies which were included in Breitenstein *et al*. 2015.[19,35,56] As such, our meta-analysis for intronic SNPs (rs2032583 and rs2235015) included outpatient samples only.

One factor contributing to the potential effects of *ABCB1* SNPs on antidepressant response and tolerability is likely variation in serum concentrations of antidepressants. This was shown in a prospective clinical trial of 73 inpatients with a diagnosis of depression randomized to standard- or high-dose treatment with antidepressants that are P-gp substrates.[16] These findings indicated a significant interaction between plasma levels of antidepressants and *ABCB1* genotypes, where minor alleles carriers (C-allele carriers at SNP rs2032583 or T-allele carriers at SNP rs2235015) showing better treatment outcomes at study end point in the normal plasma group, compared with the high plasma group. Interestingly, among noncarriers of the minor allele (TT homozygous at SNP rs2032583 or GG homozygous at SNP rs2235015), there was no improvement in clinical outcomes, either with normal or high plasma levels groups.[16] In the CAN-BIND-1 study, we did not find significant differences among the six *ABCB1* SNPs and dose-adjusted serum concentrations of both ESC and its corresponding metabolite. Furthermore, no significant interactions between the *ABCB1* genotypes and serum concentrations on antidepressant response, remission, and tolerability were found. The results of our systematic review show that only a limited number of studies have investigated the association of *ABCB1* gene variants and antidepressant serum concentrations and a meta-analysis could not be conducted. As such, we cannot rule out the potential role of drug serum concentrations in our study outcomes. Therefore, we strongly recommend including serum levels in future pharmacogenomic assessing antidepressant treatment outcomes.

There are several limitations in our meta-analysis that should be kept in mind. First, we used a random-effects model, as well as subgroup and meta regression analyses to control for ancestry, study design, clinical setting, and proportion of women included to reduce heterogeneity. However, we were unable to adjust for treatment duration, presence of comedications and comorbidities, which could have affected the results. Second, our meta-analysis on antidepressant treatment tolerability was limited by the number of studies available and our negative findings may represent a type II error due to insufficient power. Nonetheless, our studies do not suggest that any of the examined SNPs would have large effect sizes individually. Finally, whereas we have differentiated the type of medications with respect to three classes SSRI, SNRI, and TCA, we and others[19,23] could not distinguish between single medications and their individual affinity for the *ABCB1* gene, which should be addressed in future studies.

CONCLUSION, CLINICAL APPLICATION, AND FUTURE DIRECTIONS

Our systematic review and meta-analysis identified only one modest association with SNP rs1128503 and response, which would not justify clinical implementation of *ABCB1* genotyping to inform antidepressant treatment. Nonetheless, we believe that our study is important because neither the expert groups (e.g., Clinical Pharmacogenetic Implementation Consortium) nor drug regulatory agencies (e.g., US Food and Drug Administration (FDA)) have published *ABCB1* genotype-guided prescribing guidelines for antidepressants to date. However, *ABCB1* genetic variants are currently included on several commercial pharmacogenetic laboratories' testing panels,[59] on which some show clinical utility in smaller randomized controlled trials.[16,60,61] Therefore, our findings are informative as they do not support the use of those *ABCB1* gene variants for broader clinical use across antidepressants at the present time. Future studies should focus on increasing sample size, broader examination of the *ABCB1* gene, accounting for P-gp substrate affinity, using population stratification, controlling for confounders such as dose, serum levels, comedications, and comorbidity, and finally examining a well-defined disease phenotype with validated outcome measures.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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AUTHOR CONTRIBUTIONS

L.M., C.H., and M.C. performed the literature search, created the tables and figures, and wrote and revised the manuscript. L.M. analyzed CAN-BIND-1 and meta-analysis data in R software. L.M., F.H., V.M., C.C.Z., and C.A.B. designed and supervised analysis plan for CAN-BIND-1. L.M., C.C.Z., and C.A.B. designed statistical plan for meta-analysis. R.Z. assisted in the literature search. R.S.G. created Table 5 for systematic review. X.M. and M.S.C. contributed samples for meta-analysis. B.N.F., R.M., C.N.S., S.V.P., S.H., V.H.T., F.L., P.B., R.W.L., G.T., and D.J.M. conducted the site lead for the CAN-BIND-1 clinical trial, patient recruitment. F.P., S.C.S., F.F., J.A.F., and S.H.K. designed and

implemented the CAN-BIND-1 clinical trial. S.R. served as the CAN-BIND-1 clinical trial manager. S.K. assisted in the methodological design of the research plan. S.H.K. was the principal investigator for the CAN-BIND-1 clinical trial, and designed and implemented the clinical trial. D.K. and J.K. revised drafts of the manuscript. D.J.M. was the project principal investigator, and grant holder. All authors approved the revised drafts of the manuscript.

CONFLICTS OF INTEREST

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