ABCB1 Genetic Effects on Antidepressant Outcomes: A Report From the iSPOT-D Trial

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Objective: The ABCB1 gene encodes P-glycoprotein, which limits brain concentrations of certain antidepressants. ABCB1 variation has been associated with antidepressant efficacy and side effects in small-sample studies. Cognitive impairment in major depressive disorder predicts poor treatment outcome, but ABCB1 genetic effects in patients with cognitive impairment are untested. The authors examined ABCB1 genetic variants as predictors of remission and side effects in a large clinical trial that also incorporated cognitive assessment.

Method: The authors genotyped 10 ABCB1 single-nucleotide polymorphisms (SNPs) in 683 patients with major depressive disorder treated for at least 2 weeks, of whom 576 completed 8 weeks of treatment with escitalopram, sertraline, or extended-release venlafaxine (all substrates for P-glycoprotein) in a large randomized, prospective, pragmatic trial. Antidepressant efficacy was assessed with the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR), and side effects with a rating scale for frequency, intensity, and burden of side effects. General and emotional cognition was assessed with a battery of 13 tests.

Results: The functional SNP rs10245483 upstream from ABCB1 had a significant effect on remission and side effect ratings that was differentially related to medication and cognitive status. Common homozygotes responded better and had fewer side effects with escitalopram and sertraline. Minor allele homozygotes responded better and had fewer side effects with venlafaxine, with the better response most apparent for patients with cognitive impairment.

Conclusions: The functional polymorphism rs10245483 differentially affects remission and side effect outcomes depending on the antidepressant. The predictive power of the SNP for response or side effects was not lessened by the presence of cognitive impairment.

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Antidepressant efficacy and side effects may depend on the concentrations of the medication in the brain. Serum concentration is not a good predictor of treatment outcome for newer antidepressants (1, 2). This may be due to active transport of antidepressants from the brain by blood-brain barrier transporters, so that serum concentrations do not accurately reflect brain concentrations. Among blood-brain barrier transporter proteins, P-glycoprotein transports several commonly prescribed antidepressants (3, 4).

Genetic variation at the ABCB1 (MDR1) locus, which encodes P-glycoprotein, has been studied as a predictor of treatment outcomes for several medications (5, 6). The primary hypothesis has been that genetic variants affecting P-glycoprotein abundance or function could alter brain concentrations of substrate medications. Substrate brain antidepressant levels have been shown to be higher in mice lacking P-glycoprotein function than in mice with normal P-glycoprotein function (4). Several ABCB1 single-nucleotide polymorphisms (SNPs) may be clinical predictors of antidepressant efficacy (7–10) or side effects (11), but results have not been consistent (12). Some studies have shown no predictive value for ABCB1 SNPs, particularly earlier studies that explored exonic alleles in medical disorders (13–17). These varying accounts may be explained by clinical heterogeneity among patient samples (e.g., inpatients versus outpatients), differing interactions of substrate medications with P-glycoprotein, specific alleles explored, and sample size. Also, ABCB1 genotypes have not been assessed in large-scale prospective clinical trials in which DNA was collected before treatment.

Cognitive impairment is common in patients with major depressive disorder (18) and may be assessed using behavioral performance tests (19, 20, 21). In the International Study to Predict Optimized Treatment in Depression (iSPOT-D), we observed that performance on pretreatment behavioral tests of general and emotional cognition predicted posttreatment outcomes (21, 22). However, it is unknown whether pharmacogenetic prediction can be used to

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TABLE 1. Demographic and Clinical Characteristics of Patients With Major Depressive Disorder at Pretreatment Baseline (N=683)

Characteristic		
	Mean	SD
Age (years)	38.6	12.8
Education (years)	14.2	3.5
Age at first episode (years)	23.3	12.1
Duration of major depressive disorder (years)	14.9	12.5
	N	%
Female	392	57.4
Race[a]		
White	424	62.1
Nonwhite	256	37.5
Family history of major depressive disorder	154	22.5
Age at first episode ≤18 years	321	47.0
Prior treatment failure	191	28.0
Recurrent major depressive disorder	593	86.6
	Mean	SD
Symptom severity[b]		
Hamilton Depression Rating Scale (17-item)	21.7	4.1
Quick Inventory of Depressive Symptomatology–Self Report (16-item)	14.5	3.8
Depression, Anxiety, Stress Scale		
Depression subscale	22.4	9.4
Anxiety subscale	8.7	6.6
Stress subscale	18.1	8.6
Functional capacity[c]		
Social Functioning and Adjustment Scale	56.6	9.4
Satisfaction With Life Scale	11.5	5.3
World Health Organization Quality of Life scale		
Physical subscale	51.5	14.8
Psychological subscale	34.5	13.9
Social subscale	38.7	20.2
Environmental subscale	52.4	15.9
Emotion Regulation Questionnaire		
Reappraisal subscale	4.3	1.2
Suppression subscale	4.1	1.3

[a] Race was unknown for three participants.
[b] Higher scores on these scales indicate greater symptom severity.
[c] Higher scores on these scales indicate better functioning.

improve treatment outcome in depressed patients with cognitive changes.

We examined whether 10 ABCB1 SNPs are predictors of remission and side effects in treatment with three commonly prescribed antidepressants in patients from the iSPOT-D cohort who provided DNA. We also examined the effects of ABCB1 SNPs in patients with intact and impaired cognition.

METHOD

Overview

iSPOT-D is a multiple-phase, multisite randomized controlled trial that explores biomarker predictors of outcomes in 1,008 participants with major depressive disorder randomly assigned to receive escitalopram, sertraline, or extended-release venlafaxine. Details of the study design and response and remission rates for the sample have been described previously (22, 23). In the present study, we tested whether specific SNP alleles, chosen based on associations reported in the literature, predict acute response to antidepressants and/or moderate a differential response to specific types of antidepressants. We studied 888 participants with MDR1 genotypes, of whom 683 completed at least 2 weeks of treatment (the modified intent-to-treat sample), 84% of whom (N=576) completed the full 8 weeks of treatment (the per-protocol sample) (see Figure S1 in the data supplement that accompanies the online edition of this article). Given the potential bias from the per-protocol sample, we focused on the modified intent-to-treat sample and then tested whether results were consistent in the per-protocol sample. Participants were recruited from eight academic and nine private sites in five countries (mean enrollment per site, N=56, SD=96) and had ABCB1 genotypes and cognitive testing at pretreatment baseline.

Study Participants

The study enrolled adults (18–65 years old) who had a diagnosis of current, single-episode, or recurrent nonpsychotic major depressive disorder and whose treating clinician approved treatment with an antidepressant drug. See Figure S2 in the data supplement for inclusion and exclusion criteria (22). Psychiatric inclusion and exclusion criteria were based on the Mini International Neuropsychiatric Interview (24), the 17-item Hamilton Depression Rating Scale (HAM-D) (25) to assess severity (a score ≥16 was required for inclusion), and a urine toxicology screen. The Mini International Neuropsychiatric Interview was also used to assess comorbid psychiatric disorders. Race and ethnicity were assessed by self-report as part of a computerized questionnaire using standard World Health Organization formats (Table 1).

Written informed consent was obtained from all participants after the procedures had been fully explained. The study was approved by institutional or ethical review boards at each site, and its protocols were in compliance with International Conference on Harmonization and Good Clinical Practice principles, the U.S. Food and Drug Administration Code of Federal Regulations, and country-specific guidelines.

Study Treatments

Participants were randomly assigned to receive escitalopram, sertraline, or extended-release venlafaxine. Randomization was undertaken centrally using Phase Forward's validated web-based Interactive Response Technology application to implement a blocked randomization procedure (block size of 12, across sites). Investigators, raters, and participants were not blind to treatment assignment. Medications were prescribed and dosages adjusted by treating clinicians according to routine clinical practice, but following the recommended dosage ranges. Psychotropic medication was discontinued prior to randomization except for occasional (i.e., ≤1 dose/week) use of sleep aids, anxiolytics, and medications to manage antidepressant-induced side effects (e.g., nausea), which are commonly used in practice. Treatments

for concurrent general medical conditions were allowed and recorded.

TABLE 2. Position, Allelic Distribution, and Role of ABCB1 Single-Nucleotide Polymorphisms[a]

Polymorphism	Position	Minor Allele (Major Allele)	Minor Allele Frequency[b] (%)	Hardy-Weinberg p	Role
rs10245483	89475544	T(g)	46.2	1.00	Approximately 2.4 Mb upstream of ABCB1
rs3213619	87068129	C(t)	5.0	0.21	5′UTR (exon 2)
rs2214102	87067437	A(g)	5.2	0.88	5′UTR (exon 3)
rs2235015	87037500	T(g)	21.6	0.64	Intron 5
rs10276036	87018134	G(a)	39.5	0.05[c]	Intron 10
rs2032588	87017379	T(c)	8.3	0.01[c]	Intron 13
rs2235033	87017079	C(t)	49.3	0.73	Intron 14
rs28381916	87013077	A(g)	1.0	1.00	Intron 16
rs2032583	86998497	C(t)	13.0	0.94	Intron 22
rs7793196	86960783	G(a)	27.0	0.003[c]	10 kb downstream from ABCB1

[a] Relative positions on chromosome 7 are taken from the National Center for Biotechnology Information, genome build 36.3.
[b] All have a number of chromosomes of 1,776.
[c] No deviation from Hardy-Weinberg equilibrium in the white subsample.

Outcome Measures

We focused on two planned outcome measures: remission, defined as a score ≤5 on the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR) (26), and the sum of the three items of the Frequency, Intensity, and Burden of Side Effect Rating (FIBSER) scale (27) (referred to here as the FIBSER sum score). The QIDS-SR and the FIBSER were the only outcome measures to be collected at baseline, at the 8-week posttreatment follow-up, and during treatment-phase telephone monitoring sessions (at weeks 1, 2, 4, and 6).

Behavioral Tests of General and Emotional Cognition

At baseline, participants completed a computerized test battery that evaluated 13 cognitive and emotional capacities, including response speed, decision speed, processing speed, attention/working memory, cognitive flexibility, response inhibition, verbal memory, executive function, emotion identification, and the implicit priming of simple decision by emotion (28, 29). To create summary measures of each test, we followed our previously established procedure for normalizing each measure to the benchmark from 336 healthy controls (i.e., as standardized z-scores relative to a control mean of 0) and averaged normalized measures (e.g., accuracy and reaction time) within each test. Values on each measure were aligned such that positive indicated better performance and negative indicated worse performance.

Heterogeneity in Cognitive and Emotional Test Performance

Consistent with our previous report (21), participants fell into two clusters of cognitive and emotional test performance: an "intact" cluster who performed on average within the healthy range of $z > -0.5$, and an "impaired" cluster who performed on average well below the healthy norm, at $z < -0.5$. This clustering method was reproducible using alternative assumption-free classification methods such as latent class analysis (21). In the modified intent-to-treat sample, 494 participants were intact and 189 were impaired. In the per-protocol sample, 418 were intact and 158 were impaired.

Genetic Analysis

We genotyped 10 SNPs in or near the ABCB1 gene (Table 2), chosen based on previously reported associations with ABCB1 function or on pharmacogenetic studies of ABCB1 substrate drug treatment outcomes (7–9, 11, 13, 30–33). Four of these have been investigated for predicting antidepressant response or remission: rs2032583 (7, 8, 11, 34, 35), rs2235033 (8), rs2235015 (7, 8, 11), and rs10245483 (7). Others have been studied in other diseases (e.g., rs10276036, rs2214102, and rs32313619 in cancer risk) (36, 37).

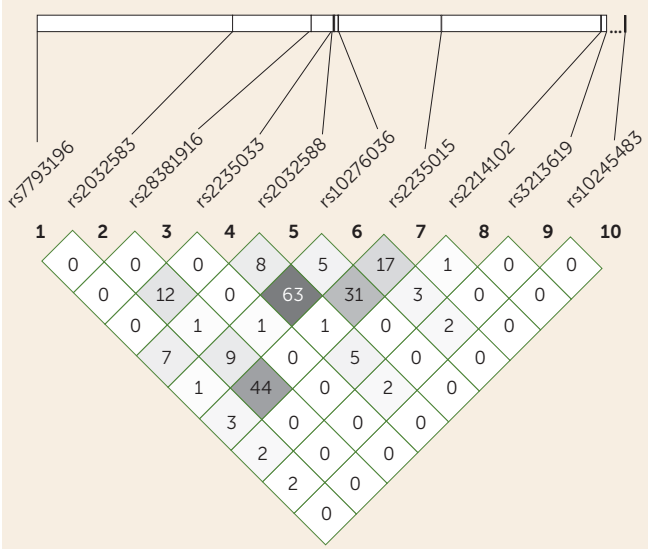
DNA extraction was performed from EDTA-treated blood using the Puregene DNA method (Qiagen, Valencia, Calif.). Genotyping was performed using the Illumina VeraCode Golden Gate SNP genotyping platform (Illumina, Hayward, Calif.) by Covance, Inc. (Seattle). To screen for genotyping errors, we checked for deviation from Hardy-Weinberg equilibrium (38). Because the sample was ethnically heterogeneous, and population stratification can result in deviation from Hardy-Weinberg equilibrium, we also tested for Hardy-Weinberg equilibrium in participants with self-reported white ethnicity. Haploview, version 4.2 (39), was used to calculate p values for Hardy-Weinberg equilibrium deviation and to calculate linkage disequilibrium among SNPs.

Statistical Analysis

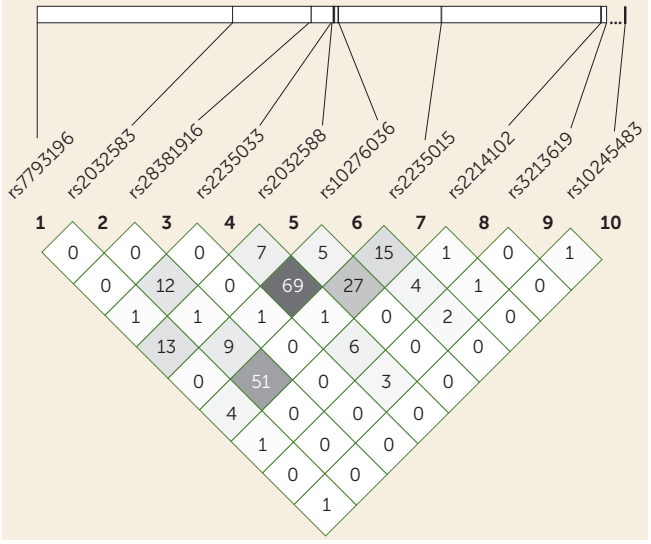
Logistic regression analyses were performed with remission (defined by QIDS-SR score) as the binary dependent outcome measure. We tested for effects of individual ABCB1 SNPs and the effects of SNP-by-treatment interactions on remission. Thus, predictors in the model were ABCB1 SNPs entered simultaneously (and with each SNP coded by number of minor alleles as 0, 1, and 2 using an additive allelic model), treatment defined as a categorical variable, and the interaction of these predictors. We did not include rs3213619 in analyses because of the absence of minor allele carriers for this SNP, and thus the analyses were undertaken with nine SNPs in total. Site was included as a covariate in the regression model. Potential confounders included pretreatment symptom severity, age, and treatment duration. When one or more of these variables contributed to remission status, we included them in the regression model as additional covariates. Within the overall regression model, the Wald statistic (W) was used to assess the significance of the contribution of each predictor. To account for the testing of multiple SNPs, SNP p values of

FIGURE 1. Linkage Disequilibrium Maps for the Full Genotyped Sample (N=888) and for White Participants in the Genotyped Sample (N=546)

A. Full Genotyped Sample (N=888)



B. White Participants in Full Genotyped Sample (N=546)



0.05/18 ≤0.0028 were considered significant using a Bonferroni correction for nine SNPs, each tested for one main effect and one interaction effect. All p values <0.05 are reported for completedness, because of the possibility of false negative results at this significance level. Based on the exponential beta values in the regression models, we generated the odds ratio for each significant effect. The odds ratio for interaction terms reflects how much greater or lower the likelihood of remission or side effects is in a multiplicative sense between treatment arms according to number of minor alleles. To assess potential clinical applicability we computed the number needed to treat for significant SNP effects. To account for genotype frequencies, we also calculated the numbers needed to screen (40).

Linear regression analyses were run with FIBSER sum score as the linear dependent outcome measure. Predictors were again the number of minor alleles for each SNP, treatment, and the SNP-by-treatment interaction. The t statistic was used to assess the significance of the contribution of each predictor.

In a second set of logistic (for QIDS-SR-based remission) and linear (for FIBSER sum score) regressions, cognitive status (impaired, intact) was included as an additional predictor to assess SNP-by-cognition interactions. We again tested the overall regression model, the individual contributions of SNP-by-cognition and SNP-by-treatment-by-cognition interactions, and the odds ratio for significant effects.

Our sample size was powered to achieve at least 89% power to detect even small effects for the nine SNP predictors of interest and interactions with treatment at p<0.05. This power calculation applied to the smaller per-protocol subsample from our two analytic samples. Our analytic models were designed to identify each SNP's unique predictive contributions while taking account of the effects of other SNPs. Because genetic effects can depend on ethnic background, we examined the full sample and the subsamples of self-reported whites and nonwhites.

We compared baseline characteristics of the impaired and intact cognition groups in the modified intent-to-treat and per-protocol cohorts using t tests and chi-square tests. Similar analyses were performed comparing the demographic and clinical characteristics of the modified intent-to-treat and per-protocol samples with those patients excluded from genetic analyses.

RESULTS

The sample's baseline demographic and clinical characteristics are summarized in Table 1.

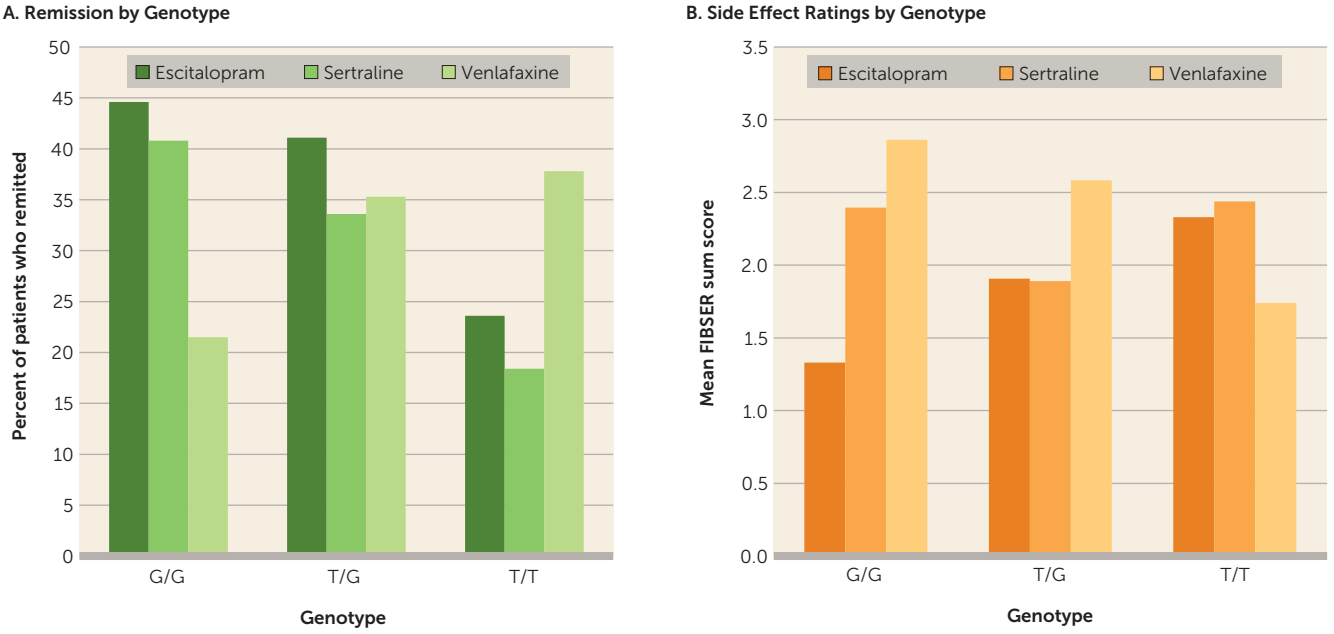
The genotype distributions in the complete sample (N=888) were in Hardy-Weinberg equilibrium for all SNPs except rs7793196, rs10276036, and rs2032588 (Table 2). In the white subsample, none of these deviated from Hardy-Weinberg equilibrium. Some variants were in moderate but not complete linkage disequilibrium in our cohort (Figure 1). Of note, rs10245483 was unrelated to any markers genotyped.

Modified Intent-to-Treat Sample

Remission. In the modified intent-to-treat sample, age (p=0.01) and baseline QIDS-SR score (p<0.001) were significant predictors of remission. Hence, genetic analyses were performed covarying for both.

Within the significant overall model (χ^2=67.58, df=29, p<0.001) only rs10245483 contributed significantly to prediction of remission. For rs10245483, there was a significant main effect on remission using multiple testing correction (W=12.64, p<0.001; main effect odds ratio=3.48) and a significant interaction by treatment arm (W=11.18, p=0.001; interaction odds ratio=1.73) (Figure 2A). Common allele homozygotes for rs10245483 responded significantly better to escitalopram (p=0.032) and sertraline (p=0.020) than did minor allele homozygotes. Minor allele homozygotes responded significantly

FIGURE 2. Interaction of ABCB1 rs10245483 Genotype With Remission and Side Effect Ratings, by Antidepressant Medication, in the Modified Intent-to-Treat Sample (N=683)[a]



[a] The modified intent-to-treat sample included those of the 888 genotyped patients who completed ≥2 weeks of antidepressant treatment. Remission was defined as a score ≤5 on the 16-item Quick Inventory of Depressive Symptomatology. The side effect measure was the sum of the three items of the Frequency, Intensity, and Burden of Side Effect Rating (FIBSER) scale. Carriers of the rs10245483 major allele with intact cognition were most likely to remit with escitalopram; minor allele homozygotes with impaired cognition were most likely to remit with venlafaxine.

better to venlafaxine (p=0.018). There were no effects noted in the heterozygotes. The specific contribution of rs10245483 as a predictor of remission was also verified in univariate models assessing each SNP one at a time.

The effect was similar in whites and nonwhites. In white participants in the modified intent-to-treat sample (N=423), within the significant overall model (χ^2=61.51, df=29, p<0.001) rs10245483 had a significant main effect on remission (W=7.22, p=0.007; main effect odds ratio=3.54) and a significant interaction by treatment arm (W=6.99, p=0.008; interaction odds ratio=1.78), which did not pass the multiple testing threshold. For nonwhites, within the significant overall model (χ^2=55.79, df=28, p=0.001), there was a main effect of rs10245483 on remission (W=11.42, p=0.001; main effect odds ratio=14.38) and a significant interaction between rs10245483 and treatment (W=9.81, p=0.002; interaction odds ratio=3.54) that met the multiple testing correction threshold.

To assess clinical utility for predicting efficacy, we calculated number needed to treat for the genotype groups within the overall modified intent-to-treat sample (Table 3). The number needed to treat, as computed by comparing remission rates in minor allele homozygotes (G/G) treated with escitalopram or sertraline versus venlafaxine, was 5. In contrast, T/T subjects were more likely to remit with venlafaxine than with escitalopram or sertraline, with a number needed to treat of 6. In the heterozygotes, there was no advantage for genotyping (number needed to treat=50). Thus, for the homozygotes, genotyping five or six subjects yields one additional remitter. To account for genotype frequencies, we calculated number needed to screen (40) for the three genotypes; for G/G, it was 18; for T/G, 100; and for T/T, 27. Thus, screening 18 subjects would yield one more G/G patient attaining remission. Combining the homozygote groups, the number needed to screen was 10. Thus, screening 10 subjects yields one additional patient (either G/G or T/T) attaining remission.

Side effects. There was a significant overall prediction model for side effects (FIBSER sum score) (F=1.77, df=26, 628, p=0.012). Again, only rs10245483 contributed significantly to prediction. For rs10245483, there was a significant main effect on side effects using multiple testing correction (t=3.55, p<0.001; main effect odds ratio=3.07) and a significant interaction by treatment arm (t=−3.83, p<0.001; interaction odds ratio=1.76) (Figure 2B). Major allele carriers had fewer side effects with escitalopram (p=0.037), whereas minor allele homozygotes had fewer side effects with venlafaxine (p=0.017).

The effect for side effects was similar in whites and nonwhites. In white participants in the modified intent-to-treat sample, the omnibus model was not significant. For rs10245483, there was a significant main effect on side effects for whites (t=2.52, p=0.012; main effect odds ratio=2.82) and a significant interaction by treatment type (t=−2.44, p=0.015; interaction odds ratio=1.59) that did not meet the multiple testing correction threshold. For nonwhites, there was a significant main effect for rs10245483 on side effects (t=2.92, p=0.004; main effect odds ratio=5.15) and a significant interaction for rs10245483 by treatment arm (t=−3.35, p=0.001; interaction odds ratio=2.70) that did not meet the multiple testing correction threshold.

TABLE 3. Remission Rate for Each Antidepressant and Number Needed to Treat and to Screen for Patients With Major Allele Homozygote (G/G), Heterozygote (T/G), and Minor Allele Homozygote (T/T) Status on ABCB1 rs10245483

	Genotype		
Measure	G/G (N=192)	T/G (N=342)	T/T (N=149)
Remission rate	%	%	%
Total sample	28	50	22
Escitalopram group	45	41	24
Sertraline group	45	34	18
Venlafaxine group	22	35	38
	N	N	N
Number needed to treat, escitalopram and sertraline versus venlafaxine	5	50	6
Number needed to screen[a], escitalopram and sertraline versus venlafaxine	18	100	27

[a] Number needed to screen is computed as number needed to treat divided by genotype frequency.

Per-Protocol Sample

Remission. In the per-protocol sample, we observed a significant effect of age (p=0.003) and baseline QIDS-SR score (p<0.001) on remission. Thus, age and baseline QIDS-SR score were again included as covariates.

Within the significant overall model for the per-protocol sample (χ^2=70.18, df=29, p<0.001), only the rs10245483 SNP contributed significantly to prediction of remission. For rs10245483, there was a significant main effect on remission (W=11.90, p<0.001; main effect odds ratio=3.70) and a significant interaction by treatment using multiple testing correction (W=10.43, p=0.001; interaction odds ratio=1.77). Common rs10245483 homozygotes responded comparatively better to sertraline (p=0.010)—as well as to escitalopram, although this comparison did not reach statistical significance (p=0.056)—while minor allele homozygotes were more likely to remit with venlafaxine (p=0.007). The results for remission were similar for whites and nonwhites.

Side effects. Within the significant overall prediction model for side effects assessed by the FIBSER sum score (F=1.98, df=25, 532, p=0.003), rs10245483 also showed a significant main effect on side effects (t=3.13, p=0.002; main effect odds ratio=2.80) and a significant interaction by treatment arm (t=−3.47, p=0.001; interaction odds ratio=1.09) using multiple testing correction. Minor allele carriers had fewer side effects with venlafaxine (p=0.019); major allele homozygotes had fewer side effects with escitalopram, although this difference did not reach statistical significance (p=0.09). The results for side effects were similar for whites and nonwhites.

Cognition and ABCB1 SNPs

Remission. There was a significant overall model for the interaction of SNPs with cognitive status in the modified intent-to-treat sample (χ^2=84.57, df=30, p<0.001). The rs10245483 SNP contributed significantly to prediction of remission as a function of cognitive status and of treatment arm using multiple testing correction (W=9.57, p=0.002; interaction odds ratio=1.53). The greater likelihood of remission for major allele homozygotes with escitalopram was most apparent for participants with intact cognition (p=0.047), whereas the greater rate of remission in minor allele homozygotes with venlafaxine was most apparent for participants with impaired cognition (p=0.033). This interaction was significant for whites and nonwhites considered separately.

Side effects. For FIBSER sum score, there was a significant overall model for prediction by SNPs and cognition (F=1.84, df=33, 653, p=0.004). Within the model, rs10245483 showed a significant main effect using multiple testing correction (t=3.33, p=0.001; main effects odds ratio=3.01) and a significant interaction with cognitive status that did not meet the correction threshold (t=−2.86, p=0.004; interaction odds ratio=1.48). In the impaired cognition group, minor allele homozygotes had fewer side effects than major homozygotes (p=0.021), whereas there were no differences in the intact cognition group.

Other Clinical Considerations

The modified intent-to-treat and per-protocol groups were not markedly different from the overall genotyped sample. Participants in the modified intent-to-treat group were significantly older on average than the excluded participants (N=205), but only by half a year. There were no other significant differences between the two groups in baseline clinical measures (see Table S1 in the online data supplement) or genotype frequencies for rs10245483. There were no significant differences in dosage within each treatment among the rs10245483 genotype groups.

There were no differences in baseline clinical measures between per-protocol and excluded participants (N=312), and there were no significant differences in genotype frequencies for rs10245483 between the two groups.

DISCUSSION

Our results demonstrate novel effects of the rs10245483 variant, which is approximately 2.5 Mb upstream of the ABCB1 locus, on antidepressant outcomes. The T minor allele has been reported to result in higher P-glycoprotein expression in a lymphoblast cell line model (31) when found in combination with minor alleles of the rs28656907/rs28373093 dinucleotide pair. Cell line models for ABCB-1 have been shown to be have limited predictive value for in vivo activity (41). We observed a clinical predictive effect for rs10245483 without genotyping the rs28656907/rs28373093 dinucleotide pair. Increased P-glycoprotein expression could result in enhanced clearance of antidepressants from the brain, which could explain why rs10245483 T allele homozygotes

demonstrated significantly poorer responses to escitalopram and sertraline. It is not apparent why T homozygotes did well on venlafaxine. Possibly the difference in the drugs' monoaminergic activity, with escitalopram and sertraline being selective serotonin reuptake inhibitors and venlafaxine a mixed norepinephrine-serotonin reuptake inhibitor, play a role. The association of cognitive impairment with a better response to venlafaxine in the T/T homozygotes would be in keeping with a particular need for a noradrenergic effect (i.e., the noradrenergic effect of venlafaxine may specifically improve cognition in subjects with poor cognition).

In contrast, rs10245483 had opposite actions on side effects depending on medication. Minor allele carriers who demonstrated lower efficacy with escitalopram also experienced greater side effects. We recently observed similar reciprocal prediction of efficacy versus side effects for variants of rs2235040 in a study of chronic depression (34). MDR1 variants that predict lower antidepressant response but greater side effects could reflect nonresponding patients being treated with higher dosages that produce greater peripheral side effects resulting from higher tissue concentrations where P-glycoprotein is not expressed. In contrast, greater efficacy and lower side effects with venlafaxine were observed in minor allele carriers. Although escitalopram, sertraline, and venlafaxine are P-glycoprotein substrates (4, 42–44), they may differ in their relative induction versus inhibition effects on the P-glycoprotein pump, much as agents can be not only substrates but also inducers or inhibitors of P4502D6 enzymes. Sertraline inhibits P-glycoprotein activity at the blood-brain barrier (45), such that chronic treatment increases sertraline brain levels. This could offset the minor allele increased efflux effect. Escitalopram is neutral in its activity. Venlafaxine induces P-glycoprotein expression (46), and chronic treatment could induce P-glycoprotein and lower brain (and perhaps serum) concentrations. However, at the dosages used in our study, P-glycoprotein induction by venlafaxine may be negligible (46). We did find that among venlafaxine-treated participants, rs10245483 had a significant effect on side effects, but whether this is related to the P-glycoprotein-inducing properties of the drug remains unknown. Further study, using measures of central drug concentration, efficacy, and side effects, is required to better understand the differences in genetic prediction among the three agents.

Little else is known about the clinical effects of rs10245483. Our study in an elderly depressed sample (7) found no evidence of an effect of rs10245483 on paroxetine or mirtazapine efficacy. Other ABCB1 antidepressant pharmacogenetic studies have not assessed this variant (8, 11, 13, 32).

The minor C allele for the intronic SNP rs2032583 has been associated with shorter time to remission on substrate medications (7, 8) but greater antidepressant side effects (11). However, we recently reported it to be associated with greater remission and lower side effect burden in a chronic depression cohort treated primarily with escitalopram or sertraline (34, 35), although that finding did not withstand correction for multiple testing. In the present study, we found no evidence for a significant effect of this SNP on remission. We did note significant prediction of response for the minor allele (data not shown). Given these findings, rs2032583 seems a less robust predictor of outcome.

SNP rs2235033 has been associated with likelihood of remission (8), a finding not replicated in the present sample. Similarly, rs2235015 has been shown to predict remission (8), but it was not predictive in this sample, which is in agreement with other studies (7, 11).

In the full cohort of iSPOT-D completers, we recently reported that impairment on tests of cognitive and emotional function predicted poorer antidepressant outcomes (21). Patients with cognitive impairment and major depression may represent a distinct population with unique clinical characteristics and possibly a different response to treatment (18). For example, patients with depression and cognitive impairment tend to be older and have a longer duration of illness, as we found in the present sample; however, our sample was by design not elderly, and the effect of age on remission was included in the analyses.

Another explanation is that the cognitively impaired nonelderly participants represent what is classically referred to as suffering from a significant depression, in contrast to patients with milder depression who often barely meet criteria for major depressive disorder and are often recruited into clinical trials. Thus, the cognitively impaired may represent a distinct endophenotype for depression defined by these impairments and associated disruptions to cognitive brain circuitry. We are following up our studies on cognition with other biomarkers to better understand the neurobiology of these patients.

From a pharmacogenetic perspective, it may be that because of age-associated changes in impaired patients, differences in brain concentrations due to altered P-glycoprotein function have a more pronounced effect in older than in younger individuals. Certainly, greater sensitivity to a variety of medications has been associated with aging (47, 48), and the function of the P-glycoprotein pump declines with age (49). In the present study, there was a strong overall association between age and remission, with older patients showing less frequent response than younger ones. Even after controlling for age, we observed a significant interaction of cognition and rs10245483 on treatment response.

Our study had several limitations that must be considered. We only included patients who completed at least 2 weeks of treatment. There could be pharmacogenetic effects that affected those who dropped out early. ABCB1 is a large gene, and we assessed a limited number of SNPs. There could be other ABCB1 pharmacogenetic markers that we did not test, in particular the rs28656907/rs28373093 dinucleotide pair that modulates the effect of rs10245483. Although dosages were similar across cohorts and genotypes, we did not determine serum antidepressant concentrations, which could affect outcomes. Because iSPOT-D is a real-world outcomes study that includes primary care providers, the dosages used were somewhat lower than those used in traditional clinical drug trials. Higher dosages might have resulted in different pharmacogenetic effects.

In conclusion, we found that the functional SNP rs10245483, located upstream from the ABCB1 gene, affects antidepressant medication efficacy and side effects. The effect depended on the specific medication. Our results suggest that ABCB1 variation is drug specific and that further study is needed to understand the differences among the agents. The results also suggest that other pharmacogenetic cohorts should be examined for effects in cognitively impaired subgroups.

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REFERENCES

1. DeVane CL: Pharmacokinetics of the newer antidepressants: clinical relevance. Am J Med 1994; 97(6A):13S–23S
2. Mitchell PB: Therapeutic drug monitoring of non-tricyclic antidepressant drugs. Clin Chem Lab Med 2004; 42:1212–1218
3. Doran A, Obach RS, Smith BJ, et al: The impact of P-glycoprotein on the disposition of drugs targeted for indications of the central nervous system: evaluation using the MDR1A/1B knockout mouse model. Drug Metab Dispos 2005; 33:165–174
4. Uhr M, Grauer MT, Holsboer F: Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. Biol Psychiatry 2003; 54:840–846
5. Zhou SF: Structure, function, and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica 2008; 38: 802–832
6. Chinn LW, Kroetz DL: ABCB1 pharmacogenetics: progress, pitfalls, and promise. Clin Pharmacol Ther 2007; 81:265–269
7. Sarginson JE, Lazzeroni LC, Ryan HS, et al: ABCB1 (MDR1) polymorphisms and antidepressant response in geriatric depression. Pharmacogenet Genomics 2010; 20:467–475
8. Uhr M, Tontsch A, Namendorf C, et al: Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. Neuron 2008; 57:203–209
9. Singh AB, Bousman CA, Ng CH, et al: ABCB1 polymorphism predicts escitalopram dose needed for remission in major depression. Transl Psychiatr 2012; 2:e198
10. Lin KM, Chiu YF, Tsai IJ, et al: ABCB1 gene polymorphisms are associated with the severity of major depressive disorder and its response to escitalopram treatment. Pharmacogenet Genomics 2011; 21:163–170
11. de Klerk OL, Nolte IM, Bet PM, et al: ABCB1 gene variants influence tolerance to selective serotonin reuptake inhibitors in a large sample of Dutch cases with major depressive disorder. Pharmacogenomics J 2013; 13:349–353
12. Perlis RH, Fijal B, Dharia S, et al: Failure to replicate genetic associations with antidepressant treatment response in duloxetine-treated patients. Biol Psychiatry 2010; 67:1110–1113
13. Peters EJ, Slager SL, Kraft JB, et al: Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PloS One 2008; 3(4):e1872
14. Kato M, Fukuda T, Serretti A, et al: ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:398–404
15. Mihaljevic Peles A, Bozina N, Sagud M, et al: MDR1 gene polymorphism: therapeutic response to paroxetine among patients with major depression. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:1439–1444
16. Laika B, Leucht S, Steimer W: ABCB1 (P-glycoprotein/MDR1) gene G2677T/a sequence variation (polymorphism): lack of association with side effects and therapeutic response in depressed inpatients treated with amitriptyline. Clin Chem 2006; 52:893–895
17. Menu P, Gressier F, Verstuyft C, et al: Antidepressants and ABCB1 gene C3435T functional polymorphism: a naturalistic study. Neuropsychobiology 2010; 62:193–197
18. Papakostas GI: Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. J Clin Psychiatry 2014; 75:8–14
19. Gotlib IH, Joormann J: Cognition and depression: current status and future directions. Annu Rev Clin Psychol 2010; 6:285–312
20. Snyder HR: Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull 2013; 139:81–132
21. Etkin A, Patenaude B, Song YJ, et al: A cognitive-emotional biomarker for predicting remission with antidepressant medications: a report from the iSPOT-D trial. Neuropsychopharmacology (Epub ahead of print, Dec 30, 2014)
22. Williams LM, Rush AJ, Koslow SH, et al: International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials 2011; 12:4
23. Saveanu R, Etkin A, Duchemin A-M, et al: The International Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment. J Psychiatr Res 2015; 61:1–12
24. Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(suppl 20):22–33
25. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
26. Rush AJ, Trivedi MH, Ibrahim HM, et al: The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003; 54:573–583

27. Wisniewski SR, Rush AJ, Balasubramani GK, et al: Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006; 12:71–79
28. Clark CR, Paul RH, Williams LM, et al: Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. Arch Clin Neuropsychol 2006; 21: 449–467
29. Williams LM, Mathersul D, Palmer DM, et al: Explicit identification and implicit recognition of facial emotions, I: age effects in males and females across 10 decades. J Clin Exp Neuropsychol 2009; 31:257–277
30. Noordam R, Aarts N, Hofman A, et al: Association between genetic variation in the ABCB1 gene and switching, discontinuation, and dosage of antidepressant therapy: results from the Rotterdam Study. J Clin Psychopharmacol 2013; 33:546–550
31. Loeuillet C, Weale M, Deutsch S, et al: Promoter polymorphisms and allelic imbalance in ABCB1 expression. Pharmacogenet Genomics 2007; 17:951–959
32. Dong C, Wong ML, Licinio J: Sequence variations of ABCB1, SLC6A2, SLC6A3, SLC6A4, CREB1, CRHR1, and NTRK2: association with major depression and antidepressant response in Mexican-Americans. Mol Psychiatry 2009; 14:1105–1118
33. Uher R, Perroud N, Ng MY, et al: Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. Am J Psychiatry 2010; 167:555–564
34. Schatzberg AF: ABCB-1: antidepressant response in geriatric depression and chronic depression. Biol Psychiatry 2014; 75(suppl):23S
35. Ray A, Tennakoon L, Keller J, et al: ABCB1 (MDR1) predicts remission on P-gp substrates in chronic depression. Pharmacogenomics J (Epub ahead of print, Dec 9, 2014)
36. Weissfeld JL, Diergaarde B, Nukui T, et al: Inherited variation in the ATP-binding cassette transporter ABCB1 and survival after chemotherapy for stage III–IV lung cancer. J Thorac Oncol 2014; 9:1264–1271
37. Lu PH, Wei MX, Yang J, et al: Association between two polymorphisms of ABCB1 and breast cancer risk in the current studies: a meta-analysis. Breast Cancer Res Treat 2011; 125:537–543
38. Hosking L, Lumsden S, Lewis K, et al: Detection of genotyping errors by Hardy-Weinberg equilibrium testing. Eur J Hum Genet 2004; 12: 395–399
39. Barrett JC, Fry B, Maller J, et al: Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005; 21:263–265
40. Holmes MV, Harrison S, Talmud PJ, et al: Utility of genetic determinants of lipids and cardiovascular events in assessing risk. Nat Rev Cardiol 2011; 8:207–221
41. Rebbeck TR, Spitz M, Wu X: Assessing the function of genetic variants in candidate gene association studies. Nat Rev Genet 2004; 5:589–597
42. O'Brien FE, O'Connor RM, Clarke G, et al: The P-glycoprotein inhibitor cyclosporin A differentially influences behavioural and neurochemical responses to the antidepressant escitalopram. Behav Brain Res 2014; 261:17–25
43. Karlsson L, Carlsson B, Hiemke C, et al: Altered brain concentrations of citalopram and escitalopram in P-glycoprotein deficient mice after acute and chronic treatment. Eur Neuropsychopharmacol 2013; 23:1636–1644
44. Karlsson L, Schmitt U, Josefsson M, et al: Blood-brain barrier penetration of the enantiomers of venlafaxine and its metabolites in mice lacking P-glycoprotein. Eur Neuropsychopharmacol 2010; 20:632–640
45. Kapoor A, Iqbal M, Petropoulos S, et al: Effects of sertraline and fluoxetine on P-glycoprotein at barrier sites: in vivo and in vitro approaches. PLoS ONE 2013; 8:e56525
46. Bachmeier C, Levin GM, Beaulieu-Abdelahad D, et al: Effect of venlafaxine and desvenlafaxine on drug efflux protein expression and biodistribution in vivo. J Pharm Sci 2013; 102:3838–3843
47. Bowie MW, Slattum PW: Pharmacodynamics in older adults: a review. Am J Geriatr Pharmacother 2007; 5:263–303
48. Trifirò G, Spina E: Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metab 2011; 12:611–620
49. Toornvliet R, van Berckel BN, Luurtsema G, et al: Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C]verapamil and positron emission tomography. Clin Pharmacol Ther 2006; 79:540–548