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The *BDNF* Val66Met Genotype and Six-Month Remission Rates in Late-Life Depression

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Abstract

Although not observed in younger adult cohorts, in older individuals the *BDNF* Val66Met polymorphism is associated with Major Depressive Disorder (MDD) risk. It is further associated with subjective social support and MRI hyperintense lesions, clinical features independently related to MDD. We examined the relationship between this polymorphism and antidepressant remission rates in an elderly sample with MDD, while also testing for mediation effects of social support and hyperintensities. 229 elderly Caucasian subjects with MDD completed baseline assessments, 1.5T MRI, and *BDNF* genotyping. They received antidepressant medication under a structured treatment algorithm and evaluated for remission at 3- and 6-months. At the 3-month evaluation *BDNF* Val66Met genotype was not associated with remission (Wald $\chi^2 = 2.51$, p = 0.1131). When not controlling for multiple comparisons, Met66 allele carriers were more likely to be remitted at 6-months ($\chi^2 = 4.32$, p = 0.0377) with an odds ratio of 1.82 (95% CI: 1.04, 3.22). This effect persisted after controlling for lesion volume and social support, neither of which mediated this relationship. Thus in this exploratory analysis, the Met66 allele may be associated with increased odds of remission in older subjects, but also with increased time to remission as there was no 3-month effect.

Keywords

BDNF; geriatrics; Major Depressive Disorder; antidepressant response; genetic polymorphism

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Disclosure / Conflicts of Interest

Drs. Taylor, Ashely-Koch, and MacFall, and Mr. McQuoid, and Ms. Bridgers have no conflicts to report. Dr. Steffens reports receiving consultancy fees from TransForm Pharmaceuticals, Inc. and speaking fees from Forest Pharmaceuticals and Wyeth Pharmaceuticals. Dr. Krishnan has received consultancy fees from CeNeRx, Corcept, GlaxoSmithKline, Johnson & Johnson, Merck, Roche, and Sonexa. He has ownership interest in Orexigen, CeNeRx and Sonexa.

INTRODUCTION

Although antidepressant medications may affect serotonin and norepinephrine systems acutely, the observation of the time delay between these changes and treatment response led to the theory that drug response is secondary to adaptive mechanisms such as neurogenesis, plasticity, and modulation of signal transduction and gene expression.[1, 2] Within this hypothesis, one of the most studied targets is brain-derived neurotrophic factor (BDNF), which plays a crucial role in synaptic plasticity, repair, and connectivity.[3–5] Its role in mood disorders has been supported by reports of BDNF levels being decreased in depression [6] and by stress [2] and increased by electroconvulsive therapy [7, 8] and antidepressant treatment.[2, 9] Despite this background, there are only limited data on how polymorphisms of the gene coding for BDNF are related to antidepressant outcomes.

One of the more widely studied functional polymorphisms is the common Val66Met polymorphism found in the 5' signal domain of the *BDNF* gene. The Met66 allele has been associated with abnormal intracellular trafficking and secretion, and is associated with alterations in hippocampal function and morphology.[10, 11] Although recent meta-analyses did not find that this polymorphism is associated with risk of depression,[12, 13] it may play a role in a subgroup of patients, particularly more severely depressed older individuals, where Met66 allele carriers have a greater risk of depression.[14, 15] We subsequently found that the Met66 allele is associated with risk factors for geriatric depression, including greater MRI hyperintense lesion severity[16] and lower levels of reported subjective social support.[17]

This polymorphism may also be related to antidepressant response. Interestingly, the Met allele, which may contribute to vulnerability to depression in older individuals, was associated with better response to an 8-week trial of citalopram in a Korean population.[18] Shorter trials of other selective serotonin reuptake inhibitors in Japanese and Taiwanese populations found evidence for a molecular heterosis effect, wherein heterozygous subjects exhibited a better antidepressant response than the homozygous subjects,[19, 20] but similar relationships were not observed with mirtazapine.[21] These studies suggest that the relationship between depression and this *BDNF* polymorphism is complex, and the Met allele may increase late-life depression risk but hypothetically be associated with better antidepressant outcomes, while the Val allele may be associated with worse treatment outcomes.

Based on these studies, we hypothesized that older depressed individuals who were homozygous for the Val66 allele would be less likely than Met66 allele carriers to achieve remission of depression over three or six months. As we have previously associated the Met66 allele with greater white matter lesion volume[16] and lower levels of subjective social support,[17] we sought to determine if these measures mediated a potential relationship between genotype and rates of remission. We also tested for molecular heterosis as an exploratory, secondary analysis.

METHODS

Sample

Participants were enrolled in the NIMH Conte Center for the Neuroscience of Depression in Late Life, located at Duke University Medical Center. Eligibility was limited to patients aged 60 years or older with a diagnosis of Major Depressive Disorder (MDD). Exclusion criteria included (1) another major psychiatric illness, although coexisting anxiety symptoms considered to be secondary to the depression diagnosis were allowed; (2) history of alcohol or drug dependence; (3) primary neurologic illness, including dementia; and (4) any contraindication to MRI. Subjects were recruited for the study primarily through clinical

referrals to the study, but also through limited advertising at Duke University Medical Center and through self-referral. As we have previously found a racial difference in frequency of the Val66Met polymorphism,[15] this analysis was restricted to Caucasian subjects.

The study protocol was approved by the Duke University Medical Center Institutional Review Board. All subjects provided written informed consent before beginning study procedures. The cohort examined in this study was included in our previous work examining the relationship between the *BDNF* Val66Met polymorphism and its frequency in late-life depression,[15] as well as its relationship with subjective social support[17] and hyperintense lesions.[16]

Clinical Evaluation

A trained interviewer administered the Duke Depression Evaluation Schedule (DDES) to each subject. The DDES, a composite diagnostic interview instrument, includes sections of the NIMH Diagnostic Interview Schedule (DIS)[22] assessing depression, enriched with items assessing sleep problems and the clinical features of melancholia and psychosis, dysthymia, mania, and alcohol abuse or dependence. The DDES also includes the Montgomery-Asberg Depression Rating Scale (MADRS)[23] and questions on age of depression onset, depression history, and family history of psychiatric illness. Functional status, assessed by instrumental activities of daily living (IADL) performance, was measured using a series of questions asking about difficulty in common household activities.[24] All depressed subjects were additionally evaluated by a study geriatric psychiatrist, who reviewed entry criteria, current psychiatric symptoms and psychiatric history, and reviewed their current medical problem severity using the Cumulative Illness Rating Scale (CIRS).[25]

Social support was measured using the Duke Social Support Index (DSSI).[26] This 35-item self-report questionnaire was designed to evaluate several domains of a subject's social environment and perception of that environment. It is divided into four subscales previously derived by factor analysis, including scales assessing frequency of social contacts and availability of assistance with activities of daily living.[26, 27] The current study examined only the Subjective Social Support scale, which includes items referring to how the individual feels understood, useful, and listened to by family and friends, and whether or not they have a close confidant. Higher scores on all scales indicate greater levels of social support, and the scales have been validated.[27]

Subjects were excluded if they had a diagnosis of dementia or if the study geriatric psychiatrist suspected dementia at baseline. The majority of subjects had Mini Mental State Examination (MMSE)[28] scores above 24; some severely depressed individuals had scores below 25. These subjects were followed through the initial three month treatment phase; if the scores remained below 25, they were not included in this study.

Antidepressant Treatment

Subjects were treated according to the Duke Somatic Treatment Algorithm for Geriatric Depression.[29] This algorithm mimics "real world" treatment options rather than adhering to a rigid clinical trial design by providing a stepwise treatment approach while accounting for past treatments and depression severity. Never-treated subjects are initially prescribed a selective serotonin reuptake inhibitor (SSRI). If adequate doses of the SSRI do not bring sufficient response after 8 to 12 weeks, the recommendation is to switch to venlafaxine or augment with bupropion, with other marketed antidepressants serving as further options based on the individual's treatment history. At each stage, doses are increased as tolerated or required, to the maximum approved dose. Electroconvulsive therapy is a treatment option at

each algorithm level, dependent on subject severity, number of failed trials, and subject preference. Subjects were not routinely referred for psychotherapy, although some were already engaged in ongoing psychotherapy at study entry while others were referred for individual and/or group psychotherapy, usually cognitive-behavioral psychotherapy. For this study, an adequate trial was defined of a minimum duration of 4 weeks at the minimum therapeutic dose. Treating clinicians were not aware of genotype results.

Magnetic Resonance Image Acquisition and Analysis

Subjects were imaged using a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radiofrequency coil. MRI acquisition methods and the imaging protocol have been previously described.[30] Likewise, the tissue segmentation protocol has been previously described with documented reliability.[31] This semi-automated method uses multiple MR contrasts to identify different tissue classifications through a 'seeding' process. Both periventricular and deep white matter lesions were combined to provide a measure of WMLs (white matter hyperintense lesions) on the segmented image.

Genotyping

Fresh blood samples were obtained from all participants and DNA was extracted and stored according to methods and quality checks previously reported.[15, 32] An aliquot of DNA was used for genotyping of the *BDNF* Val66Met polymorphism. DNA samples were placed in 96 well plates together with no-template controls and four sample duplicates in an asymmetric pattern to avoid unintended plate-switching. DNA was PCR amplified applying a Taqman by-design assay (Applied Biosystems) that recognized the single nucleotide polymorphism (SNP) which defines the Val66Met polymorphism (rs6265). The samples were examined with an ABI7900 DNA analyzer and the genotypes determined with the SDS software package (Applied Biosystems). Greater than 95% genotyping efficiency was required before data were submitted for further analysis.

Analytic Plan

Due to the small number of Met66 allele homozygous subjects, we used our previous strategy[15] of dichotomizing the study population into those who were homozygous for the Val66 allele, and those who were Met66 allele carriers. In secondary analyses we compared any homozygous subjects (Val66 or Met66) with heterozygous subjects, a similar approach used by studies reporting that homozygous individuals had lower response rates to antidepressants than did heterozygotes.[19, 20]

All statistical analyses were conducted using SAS 9.1 (Cary, NC). Although hypothesis-driven, these analyses were exploratory so we did not make adjustments for Type I error. We used a rigorous definition of remission, a MADRS score of 6 or less, which has been identified as valid cutoff.[33]

As a first step, we tested for differences in key independent variables between subjects who were and were not remitted at both the 3- and 6-month time points. We examined *BDNF* Val66Met genotype, demographic variables, and other potential markers of antidepressant response or remission (such as age of depression onset, MMSE score, baseline depression severity by MADRS, medical comorbidity by the CIRS, and instrumental activities of daily living). We also included subjective social support and WML volume, two measures associated both with *BDNF* genotype, depression, and possibly antidepressant response. Differences were tested using pooled, two-tailed t-tests, or Satterthwaite t-tests for unequal variances. As the subjective social support measure was not normally distributed,[17] we used a log transformation of that measure as the dependent variable. Similarly, we tested for

differences in antidepressant treatment received at each the 3- and 6-month time points between remitting and nonremitting cohorts and genotype groups.

We next created logistic models for the 3- and 6-month data, examining remission as the dichotomous dependent variable. We included *BDNF* genotype, age, and baseline MADRS as independent variables. We also planned to include any additional demographic or clinical variables that were significantly different between remitters and non-remitters, or had a trend for a difference (defined as a t-test with a $p < 0.10$). We did not include subjective social support and WML volume for these initial models as we wished to determine if they mediated any possible effect of the Val66Met polymorphism on remission. To test this, we created new logistic models at each time point which included either subjective social support or WML volume. In these models, we sought to determine if genotype's influence on remission was reduced when subjective support or WML volume was included in the model.[34] As exploratory analyses, we a) examined other definitions of remission and b) created repeated measures models examining MADRS as a continuous variable. Finally, we combined all subjects who were homozygous for either the Val66 or Met66 allele and compared them with heterozygous subjects, and conducted similar analyses.

RESULTS

This study examined 229 depressed Caucasian subjects with genetic and clinical data at the 3-month evaluation. 25 of those subjects withdrew from the study or were lost to follow-up. Six subjects did not attend the 3-month evaluation, but did attend the 6-month evaluation, so data on 210 subjects were included in the 6-month analyses. Of those 25 subjects assessed at 3-months and subsequently lost to follow-up, 15 were Val66 homozygotes and 10 were Met66 allele carriers, with no significant difference in genotypes between subjects who withdrew and those who remained in the study ($\chi^2 = 0.01$, 1 df, $p = 0.9396$). As previously reported,[15] we found no deviation from Hardy-Weinberg equilibrium.

Group Differences at Each Assessment Period

At three months, 31% of subjects (71 of 229) had achieved remission (MADRS ≤ 6). There was no significant difference in mean 3-month MADRS score between *BDNF* genotypes (Met66 carrier = 12.8, SD=9.1; Val66 homozygotes = 11.5, SD = 8.6; 227 df, $t = -1.15$, $p = 0.2526$). We observed remission in 24% of Met66 carriers (22 of 90) and 35% of Val66 homozygotes (49 of 139; $\chi^2 = 2.98$, 1 df, $p = 0.0842$).

Univariate analyses found that only subjective social support was associated with three-month remission (Table 1). During this period, the majority of subjects were treated with SSRI monotherapy (47.8%, N =109). We did not observe significant differences in the frequency of treatments used between remitters and nonremitters (Table 2), except a greater proportion of remitters (15.5%, or 11 of 71) received ECT than did nonremitters (7.0%, or 11 of 158). We found no differences in what treatment was provided based on *BDNF* genotype.

204 subjects were assessed both at 3- and 6-months. Subjects who did not achieve remission at 3-months were significantly more likely to have their antidepressant treatment changed (22.6%, 31 of 137) than remitting subjects (3%, 2 of 67; Fisher's exact, $p = 0.0002$). When regimen changes occurred, it was either a swap to another antidepressant medication (N = 23) or using an augmentation strategy (adding ECT = 1, adding a second antidepressant = 9). *BDNF* genotype was not significantly related to changes in antidepressant treatment (Val/Val: 17.8% or 22 of 124 subjects had regimen changes, compared with 13.8% or 11 of 80 Met allele carriers; $\chi^2 = 0.57$, $p = 0.4497$).

At six months 40% of subjects (85 of 210) were remitted, which was associated with both subjective social support and the *BDNF* Val66Met genotype (Table 3). There was no significant difference in 6-month mean MADRS scores by genotype (Met66 carrier = 9.7, SD=8.6; Val66 homozygotes = 10.6, SD = 7.6; 208 df, t = 0.80, p = 0.4268). However, we observed remission in 49% of Met66 carriers (40 of 82) and 35% of Val66 homozygotes (45 of 128; $\chi^2 = 3.85$, 1 df, p = 0.0497).

We did observe some significant differences in the frequency of treatments used between remitters and nonremitters during this period (Table 4). The observed difference at the 3-month assessment in ECT use was no longer significant, which likely reflects that ECT was discontinued in some subjects after the 3-month assessment, primarily those who remitted. We now found that only 36% (45 of 125) of nonremitting subjects were on SSRI monotherapy at the 6-month assessment, in contrast to 52% of remitted subjects (44 of 85; $\chi^2 = 5.15$, 1df, p = 0.0233). Additionally, use of combination antidepressant therapy was more frequent in the nonremitted population (16%, 20 of 125) than the remitted population (5%, 4 of 85; Fisher's exact, p = 0.0140). These findings suggest there was a move away from SSRI monotherapy for nonresponders, wherein at least some subjects received combination therapy. We continued to find no differences in what treatment was provided based on *BDNF* genotype.

Primary Models Predicting Remission

When examined in the planned models controlling for age and baseline depression severity, *BDNF* genotype was not associated with 3-month remission but was significantly associated with 6-month remission (Table 5). At 6-months, carrying the Met66 allele resulted in increased odds of remission, with an odds ratio of 1.82 (95% CI: 1.04 – 3.22). In models testing for mediation, the log transformation of subjective social support was significantly associated with remission at each assessment, while white matter lesion volume was not. The addition of the transformed subjective social support measure or WML volume in the 6-month models did not substantially affect the significance level of the *BDNF* polymorphism, so it appears that these measures did not mediate the effect of *BDNF* genotype on 6-month remission. These results did not appreciably change when we excluded subjects with inadequate antidepressant trials due to inadequate dose or duration over each period.

Alternative Models

To determine the stability of our findings, we examined alternative definitions of remission, including a more (MADRS ≤ 3) and less rigorous (MADRS ≤ 9) definition, selected as these are respectively a 50% decrease and increase in the cutoff used in our main analyses. Using the more rigorous definition, *BDNF* genotype continued to be significantly associated with 6-month remission rates (Met carrier: 32.9% remitted, 27 of 82; Val/Val: 20.3% remitted, 26 of 128 1 df, $\chi^2 = 4.22$, p = 0.0401), but not 3-month remission rates (Met carrier: 17.8% remitted, 16 of 90; Val/Val: 21.6% remitted, 30 of 139; 1 df, $\chi^2 = 0.49$, p = 0.4827). Using the less rigorous definition, *BDNF* genotype was not significantly associated with either 3- (Met carrier: 40.0% remitted, 36 of 90; Val/Val: 42.5% remitted, 59 of 139; 1 df, $\chi^2 = 0.13$, p = 0.7137) or 6-month (Met carrier: 54.9% remitted, 45 of 82; Val/Val: 49.2% remitted, 63 of 128; 1 df, $\chi^2 = 0.64$, p = 0.4234) remission rates.

In an alternative approach, we conducted repeated measures analyses, where we examining genotype effect on MADRS as a continuous variable, while controlling for age, baseline MADRS, and assessment period. We additionally included a genotype by assessment period interaction term. In this model, we did not find a statistically significant direct effect for *BDNF* genotype or for the genotype by assessment interaction (data not shown).

Based on previous findings,[19, 20] we examined exploratory models testing for a molecular heterosis effect, we did not find a relationship between being homozygous for either Val66Met allele and remission. This was true for models controlling for age and baseline depression severity at both 3- (Wald $\chi^2 = 3.01$, 1 df, $p = 0.0830$) and 6-months (Wald $\chi^2 = 3.52$, 1 df, $p = 0.0605$). Due to the small number of Met66 homozygous individuals, there was not a sizable shift in group numbers: only 9 subjects were Met66 homozygous in the 3-month analyses, and only 8 subjects in the 6-month analyses.

Finally, given reports of epistasis between the *5-HTTLPR* and *BDNF* polymorphisms,[35] we conducted exploratory analyses based on our primary models wherein we included *5-HTTLPR* genotype and an interaction between *BDNF* and *5-HTTLPR* genotypes. In those models, there was not a statistically significant relationship between 3- and 6-month remission and either the *5-HTTLPR* genotype or for the gene-gene interaction term (data not shown).

DISCUSSION

The primary finding of this study is that *BDNF* Val66Met genotype is not associated with 3-month rates of remission, but that Met66 allele carriers are more likely to achieve remission at six months, with an odds ratio of 1.82 (95% CI: 1.04 – 3.22). Thus older depressed Met66 allele carriers have almost double the odds of achieving remission at 6-months than do Val66 homozygous individuals. It appears this relationship holds for more rigorous definitions of remission, as there was not a significant relationship between genotype and remission when a broader definition was used. We further found that neither WML volume nor subjective social support mediated this relationship, which was important as both these measures are associated with both late-life depression[27, 30] and the *BDNF* Val66Met polymorphism.[16, 17]

The difference between our findings at 3- and 6-months is intriguing. It is possible that individuals who are Met66 allele carriers are more likely to remit than Val/Val individuals, but require a period longer than 3 months to achieve remission. Although the majority of subjects who remit to an antidepressant do so in the first 12 weeks of treatment, over 10% of remitters require a longer period,[36] so some of this variability may be explained by *BDNF* polymorphisms. Unfortunately we lack data between each three-month assessment period, so we cannot more definitively test this hypothesis. However, such a theory could explain discrepancies in the literature about which allele if either is associated with poorer chance of remission, given how most published trials are of 8- to 12-week duration or less.

Importantly, the relationship between genotype and remission was only evident when we examined more rigorous definitions of remission. We neither find a significant relationship using less rigorous definitions nor examining change in depression severity. Thus the Met66 allele may have some value for predicting full remission of depression, which is the goal of antidepressant therapy as residual symptoms are associated with disability and risk of relapse. However, at this point the evidence does not support it guiding treatment decisions.

Our finding that Val66 homozygous subjects were less likely to remit is similar to findings from a Korean study which examined this polymorphism's effect within an 8-week trial of citalopram,[18] except for the observed difference in time to remission. In contrast, a Japanese study comparing six weeks of fluvoxamine with milnacipran a serotonin-norepinephrine reuptake inhibitor found that the Val/Met heterozygous subjects exhibited greater reduction of MADRS scores than either homozygous group[19] while a Korean study found no relationship between this polymorphism and mirtazapine response.[21] Two issues complicate the comparison of our current report with these past studies: the older age of our sample and

the observation that these studies examined Asian populations, which have a higher frequency of the Met66 allele than occurs in our Caucasian, North American population. Despite these issues, it does appear the Val66Met polymorphism may be related to antidepressant response, particularly response to SSRIs which was the primary antidepressant drug class used in this study.

This report may inform current hypotheses associating antidepressant response with *BDNF* expression and neurogenesis. Chronic antidepressant administration is associated with elevated *BDNF* transcript levels in the brain[8] and elevated BDNF expression in the periphery.[6] This effect appears to persist with aging, although there may be regional differences in where BDNF is expressed in older individuals.[37] It is not clear to what degree antidepressant effects are mediated through changes in BDNF signaling, and there is some suggestion that there may be differences between the antidepressants on their effect on serum BDNF levels.[38]

This study has a number of limitations, the most notable being that it is not generalizable to a younger or midlife adult population and that it focuses only on a single polymorphism, while other *BDNF* gene variants likely also contribute to depression risk or affect remission.[39] Additionally, there are other factors, not assessed in the current study, which may be associated with antidepressant remission rates, including economic or social inequities[40] or more comprehensive assessments of depression history or lifetime depression duration. Our population, despite being limited to a Caucasian sample, may also suffer from hidden population stratification in original ethnic origin, which could affect our results if those populations have different allele frequencies. It should also be emphasized that this is a prospective algorithm-based observational study and not a rigid controlled trial, and as described, inherently includes variability in medication use and dosing strategies. However, it does allow for a “real world” picture of remission. Unfortunately, we did not have data on medication side effects, which would affect decisions to withdraw from the study or change antidepressant medications, and thus would also affect outcomes.

In conclusion, this study found that older depressed subjects who carried the Met66 allele were more likely than Val66 homozygotes to achieve remission at six months. Although this finding provides clues about heterogeneity in the antidepressant response, it would be premature to assume it has clinical utility. The Met66 allele carriers did have higher rates of six-month remission, but we found no differences in the treatment they received, so they should continue to be treated as clinically warranted regardless of genotype. Importantly, other factors not assessed in the current study may also be related to both *BDNF* genotype and antidepressant outcomes, such as executive dysfunction.[41, 42] Future work should include a more rigid design guiding antidepressant administration, more frequent assessments of antidepressant response, broader interrogation of the *BDNF* gene,[39] and serum BDNF measures. This report should guide future studies in older adult depressed subjects and would benefit from correlations with structural and functional imaging studies examining neuroanatomic correlates of antidepressant response.

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Table 1

Demographics by remission status at 3-months

	Remitted N = 71	Nonremitted N = 158	Test value	p value
BDNF (% Met/*)	31.0 % (22/71)	43.0% (68/158)	$\chi^2 = 2.98$	0.0842
Age	68.8 (7.2)	69.7 (7.5)	t = 0.82	0.4133
Age of onset	44.4 (18.7)	44.5 (21.2)	t = 0.04	0.9664
Sex (% Female)	66.2% (47/71)	62.0% (98/158)	$\chi^2 = 0.37$	0.5446
Education	13.9 (2.9)	13.7 (2.7)	t = 0.70	0.4855
MMSE	28.3 (2.1)	28.1 (2.2)	t = 0.39	0.6999
MADRS, baseline	26.7 (8.2)	27.0 (7.8)	t = 0.24	0.8078
CIRS	4.1 (3.1)	4.5 (3.1)	t = 0.90	0.3707
IADL score	2.9 (4.5)	3.7 (4.7)	t = 1.17	0.2443
Subjective SS (Unadjusted)	24.3 (3.6)	22.6 (4.1)	t = 2.92	0.0039
Subjective SS (Log)	3.2 (0.2)	3.1 (0.2)	t = 3.12	0.0021
WML volume	6.1 (12.3)	7.6 (10.9)	t = 0.76	0.4460

All comparisons of continuous variables used pooled, two-tailed t-tests with 227 df, except for analyses of subjective social support which used a Satterthwaite t-test with 162 df due to unequal variances. Age and education variables presented in years, white matter hyperintense lesion (WML) volume presented in milliliters.

Table 2

Three-Month Remission Status and Genotype by Treatment

	Remit N = 71	Nonremit N = 158	Test statistic	P value	*BDNF* v/v N = 139	*BDNF* met N = 90	Test statistic	P value
SSRI (N = 109)	33.0% (36)	67% (73)	$\chi^2 = 0.40$	0.5281	65.1% (71)	34.9% (38)	$\chi^2 = 1.72$	0.1899
TCA (N = 14)	35.7% (5)	64.3% (9)	FE	0.7673	64.3% (9)	35.7% (5)	FE	1.0000
Venlafaxine (N = 12)	25% (3)	75% (9)	FE	0.7586	58.3% (7)	41.7% (5)	FE	1.0000
Bupropion (N = 23)	30.4% (7)	69.6% (16)	FE	1.0000	56.5% (13)	43.5% (10)	FE	0.6600
Other (N = 14)	14.3% (2)	85.7% (12)	FE	0.2356	50% (7)	50% (7)	FE	0.4108
Combination (N = 18)	16.7% (3)	83.3% (15)	FE	0.1968	55.6% (10)	44.4% (8)	FE	0.6264
Inadequate trial (N = 17)	23.5% (4)	76.5% (13)	FE	0.5939	64.7% (11)	35.3% (6)	FE	0.8014
ECT (N = 22)	50.0% (11)	50.0% (11)	$\chi^2 = 4.11$	0.0427	50.0% (11)	50.0% (11)	$\chi^2 = 1.17$	0.2799

Columns display the percentage (number) of individuals who received a given treatment, then did or did not remit, and were or were not *BDNF* met allele carriers. All drug categories represent monotherapy and treatment with multiple antidepressants was categorized as “combination” therapy. The “Other” category included mirtazapine (N = 8), nefazodone (N = 5), and phenelzine (N = 1). Subjects who received ECT were not included in drug categories, only the ECT category. FE = Fisher’s exact test, tests had 1 degree of freedom.

Table 3

Demographics by remission status at 6-months

	Remitted N = 85	Nonremitted N = 125	Test value	p value
BDNF (% Met/*)	47.1% (40/85)	33.6% (42/125)	$\chi^2 = 3.85$	0.0497
Age	69.6 (7.8)	69.4 (7.1)	t = 0.22	0.8242
Age of onset	47.2 (19.0)	43.3 (21.4)	t = 1.32	0.1898
Sex (% Female)	65.9% (56/85)	60.8% (76/125)	$\chi^2 = 0.41$	0.5244
Education	13.8 (2.7)	13.9 (2.7)	t = 0.19	0.8524
MMSE	28.1 (2.3)	28.2 (2.2)	t = 0.17	0.8664
MADRS, baseline	27.4 (8.6)	26.4 (7.5)	t = 0.89	0.3733
CIRS	4.1 (3.4)	4.3 (2.9)	t = 0.39	0.6994
IADL score	2.9 (4.3)	3.8 (4.7)	t = 1.52	0.1289
Subjective SS (Unadjusted)	24.0 (3.4)	22.1 (4.0)	t = 2.09	0.0380
Subjective SS (Log)	3.2 (0.2)	3.1 (0.2)	t = 2.35	0.0198
WML volume	6.1 (11.6)	6.7 (9.9)	t = 0.36	0.7166

All comparisons of continuous variables used pooled, two-tailed t-tests with 208 df, except for analyses of subjective social support which used a Satterthwaite t-test with 198 df due to unequal variances. Age and education variables presented in years, white matter hyperintense lesion (WML) volume presented in milliliters.

Table 4

Six-Month Remission Status and Genotype by Treatment

	Remit N = 85	Nonremit N = 125	Test statistic	P value	*BDNF* v/v N = 128	*BDNF* met N = 82	Test statistic	P value
SSRI (N = 89)	49.4% (44)	50.6% (45)	$\chi^2 = 5.15$	0.0233	61.8% (55)	38.2% (34)	$\chi^2 = 0.05$	0.8295
TCA (N =16)	43.8% (7)	56.3% (9)	FE	0.7961	62.5% (10)	37.5% (6)	FE	1.0000
Venlafaxine (N = 14)	21.4% (3)	78.6% (11)	FE	0.1653	71.4% (10)	28.6% (4)	FE	0.5728
Bupropion (N = 21)	42.9% (9)	57.1% (12)	FE	0.8187	57.1% (12)	42.9% (9)	FE	0.8144
Other (N = 16)	31.3% (5)	68.7% (11)	FE	0.5978	62.5% (10)	37.% (6)	FE	1.0000
Combination (N = 24)	16.7% (4)	83.3% (20)	FE	0.0140	66.7% (16)	33.3% (8)	FE	0.6586
Inadequate trial (N = 17)	41.2% (7)	58.8% (10)	FE	1.0000	58.8% (10)	41.2% (7)	FE	1.0000
ECT (N = 13)	46.1% (6)	58.9% (7)	FE	0.7728	38.5% (5)	61.5% (8)	FE	0.1393

Columns display the percentage (number) of individuals who received a given treatment, then did or did not remit, and were or were not *BDNF* met allele carriers. All drug categories represent monotherapy and treatment with multiple antidepressants was categorized as “combination” therapy. The “Other” category included mirtazapine (N = 9), nefazodone (N = 6), and phenelzine (N = 1). Subjects who received ECT were not included in drug categories, only the ECT category. FE = Fisher’s exact test, tests had 1 degree of freedom.

Table 5

Remission Models

	3-month remission			6-month remission		
	Estimate (SE)	**Wald Chi-Square**	**P value**	**Estimate (SE)**	**Wald Chi-Square**	**P value**
Model 1a:						
BDNF	0.24 (0.15)	2.51	0.1131	−0.30 (0.14)	4.32	0.0377
Model 1b:						
Subjective Social Support (log)	2.43 (0.93)	6.76	0.0093	1.86 (0.88)	4.47	0.0344
Model 1c:						
WML volume	−0.01 (0.02)	0.29	0.5909	−0.01 (0.02)	0.26	0.6075
Model 2:						
BDNF	0.18 (0.16)	1.39	0.2388	−0.32 (0.15)	4.50	0.0338
Subjective Social Support (log)	2.54 (0.95)	7.13	0.0076	2.10 (0.88)	5.75	0.0165
Model 3:						
BDNF	0.21 (0.17)	1.45	0.2293	−0.36 (0.16)	4.85	0.0277
WML volume	−0.01 (0.02)	0.11	0.7347	−0.01 (0.02)	0.47	0.4940

All models controlled for age and baseline MADRS score. SE = standard error, WML = white matter lesion