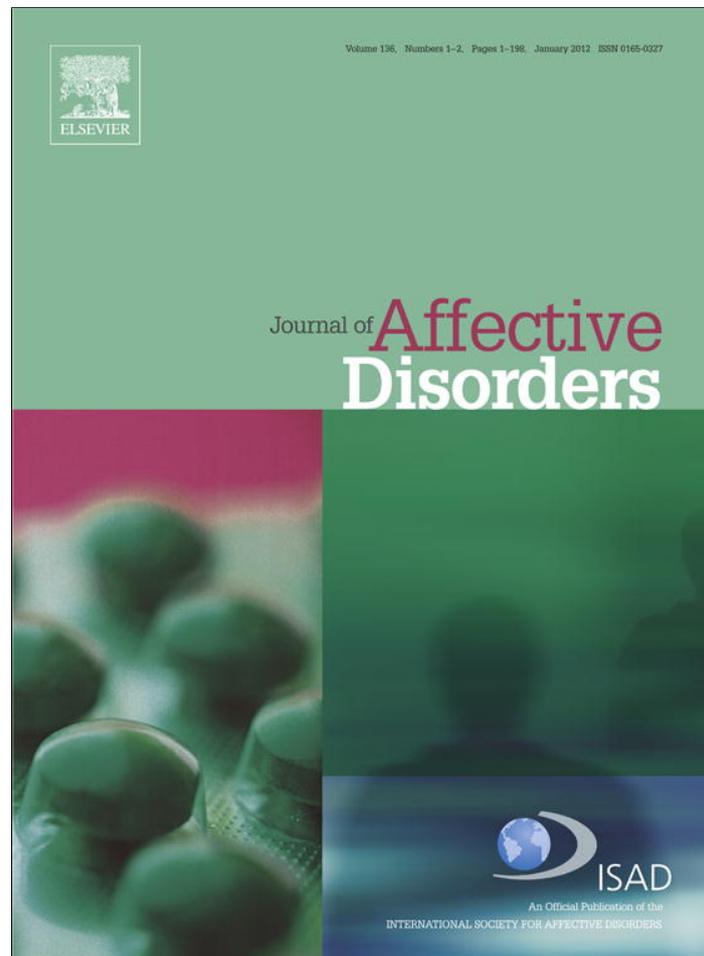


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Journal of Affective Disorders

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## Research report

# Brain-derived neurotrophic factor Val66Met polymorphism and 6-month antidepressant remission in depressed Caucasian patients



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## ARTICLE INFO

## Article history:

Received 24 November 2014

Received in revised form

9 January 2015

Accepted 12 January 2015

Available online 21 January 2015

## Keywords:

BDNF

Val66Met polymorphism

Antidepressant

Major depressive disorder

Response

Remission

## ABSTRACT

**Background:** Whether the Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism can predict antidepressant drug efficacy in depressed patients remains unclear, suggesting that it may depend on antidepressant classes. We assessed the impact of Val66Met polymorphism on antidepressant response and remission depending on antidepressant classes.

**Methods:** In a 6-month prospective, real-world setting, treatment study, 345 Caucasian depressed patients requiring a new or different drug treatment with a selective serotonin reuptake inhibitor (SSRI), a serotonin and noradrenalin reuptake inhibitor (SNRI) or a tricyclic antidepressant (TCA), were genotyped and assessed for response and remission.

**Results:** 231 (67%) patients were homozygous for the Val66 allele (Val/Val) and 114 (33%) were carriers of Met allele (Met). 152 (44.1%) patients were treated with SSRI, the others with SNRI/TCA. Both response and remission were explained by interactions between the Val66Met polymorphism and antidepressant drug classes (multivariate models adjusted for propensity-scores:  $p=0.02$  and  $p=0.03$  respectively). With SSRI, Val/Val patients had a higher response rate 3 months post-treatment than Met patients (68.1% versus 44%; adjusted-OR: 3.04, IC95% [1.05; 9.37],  $p=0.04$ ). With SNRI/TCA, Val/Val patients had a lower remission rate 6 months post-treatment than Met patients (33.3% versus 60.9%, adjusted-OR: 0.27, IC95% [0.09; 0.76],  $p=0.02$ ).

**Limitations:** Limited sample size.

**Conclusions:** This study argues for a personalized prescription of antidepressants in Caucasian patients with major depressive disorder, based on the BDNF Val66Met polymorphism: SSRI should be preferred for Val/Val patients and SNRI/TCA for Met patients. Further studies are required to confirm these data.

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<http://dx.doi.org/10.1016/j.jad.2015.01.013>

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## 1. Introduction

The Brain Derived Neurotrophic Factor (BDNF) Val66Met polymorphism (rs 6265) can affect BDNF secretion, neuronal survival, plasticity, neurogenesis, synaptic connectivity and is responsible for

disruption of cellular processing, trafficking, the Met allele being associated with a decreased dendritic trafficking (Egan et al., 2003).

Although antidepressant drugs may act by normalizing the levels of BDNF (Sen et al., 2008), the impact of the Val66Met polymorphism on response and remission under antidepressant drug treatment in major depression is still under debate. This question is relevant for public health since antidepressant response and remission are still difficult to predict in depressed patients.

Some studies suggest an association between the Val66Met polymorphism and response or remission with antidepressant drugs, either in Asian (Choi et al., 2006; Xu et al., 2012; Yoshida et al., 2007; Zou et al., 2010) or in Caucasian (Alexopoulos et al., 2010; El-Hage et al., 2015; Lanctôt et al., 2010) patients. However, several studies failed to replicate this association, both in Asian (Ji et al., 2013; Kang et al., 2010; Katsuki et al., 2012; Tsai et al., 2003) and in Caucasian (Brunoni et al., 2013; Domschke et al., 2010; Kocabas et al., 2011; Licinio et al., 2009; Musil et al., 2013; Taylor et al., 2011; Wilkie et al., 2007) patients, especially two 6-month studies (Bukh et al., 2010; Taylor et al., 2011) and the powerful study comprising the STAR-D results (Domschke et al., 2010).

Meta-analyses evidenced either a higher response rate in Met patients that may be specific to Asian patients (Kato and Serretti, 2010; Yan et al., 2014; Zou et al., 2010) or no difference in response and remission rates between Met and Val/Val Caucasian patients (meta-analysis of Niitsu et al., 2013 including 10 studies (8 of Asian patients (Chi et al., 2010; Choi et al., 2006; Kang et al., 2010; Su et al., 2011; Tsai et al., 2003; Yoshida et al., 2007; Yoshimura et al., 2011; Zou et al., 2010), one study of Caucasian patients (Wilkie et al., 2007) and data from STAR-D).

Several factors may explain the few reported association between the Val66Met polymorphism and efficacy of antidepressant drugs. First, the majority of studies are based on small and heterogeneous samples of patients. Second, available data suggest different results in Asian and Caucasian patients. Since the frequency of the Met66 allele is lower in Caucasian (16.7–19.5%) than in Asian (34.4–63.3%) populations (PubMed SNP: [http://www.ncbi.nlm.nih.gov/projects/SNP/snp\\_ref.cgi?rs=6265](http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6265)), additional studies in Caucasian patients are needed. Third, the majority of studies are short-term ones (4 to 8 weeks). However, as suggested by Yan et al. (2014), this point should be focused on, since functional effects of BDNF related to neurogenesis may require longer time to be observed. Fourth, despite differences between antidepressant drug classes in terms of mechanism of action and efficacy (Anderson, 1998; DUAG, 1990), and changes in BDNF serum levels (Matriciano et al., 2009; Molendijk et al., 2011), no clinical study aimed at assessing the association between the effects of antidepressant classes and the BDNF Val66Met polymorphism on antidepressant efficacy.

Yet no study has tested the impact of the BDNF Val66Met polymorphism on antidepressant efficacy, comparing different antidepressant drugs, with a sufficient study duration in Caucasian depressed patients. Here, we hypothesized that the impact of the BDNF Val66Met polymorphism could vary depending on a given antidepressant class. And we investigated in Caucasian patients whether 6-month antidepressant drug response and remission were influenced by the Val66Met polymorphism and antidepressant classes.

## 2. Materials and methods

### 2.1. Design

In a 6-month prospective, real-world setting treatment study, patients with a current major depressive episode (MDE) were assessed at the beginning of antidepressant treatment, 3 and 6 months later. This

study was registered by the French National Agency for Medicine and Health Products Safety (ANSM) and the Commission Nationale de l'Informatique et des Libertés (CNIL), was approved by the Ethics Committee of Paris-Boulogne, France, and conformed to international ethical standards.

### 2.2. Patients

Caucasian in- or out-patients, aged 18–65 years, with a current MDE diagnosis in a context of major depressive disorder (MDD) (DSM-IVTR) based on the Mini International Neuropsychiatric Interview (MINI), with a minimum depression score of 18 on the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960) and requiring a first or different antidepressant treatment were included. Patients with DSM-IVTR bipolar disorders, psychotic disorders, current substance abuse or dependence, pregnancy, breast feeding, organic brain syndromes or unstable medical conditions were excluded. Patients provided written informed consent for study participation and for genetic analyses. Clinical assessments were performed blind to genotyping results.

### 2.3. Genotype

Genomic DNA was extracted from circulating blood leukocytes by using Genra Puregene Blood Kits according to the manufacturer's protocol (Qiagen) and was stored at  $-20^{\circ}\text{C}$ . The BDNF Val66Met polymorphism (rs 6265) was genotyped using TaqMan allelic discrimination (Coulbault et al., 2006), with the ABI Prism<sup>®</sup> 7900HT Sequence Detection System (Life Technologies). The sequence of interest was amplified using the following primers:

5'-CTGCTTGTGTTTCTGCTTCTCCCT-3' and reverse primer

5'-ACCCTCATGGACATGTTTGCA-3. Wild type allele (Val) was

detected using a

5'-CTTTCGAACACGTGATAG-3' VIC-fluorescent probe. Mutant

allele (Met) was detected using 5'-ACTTTCGAACACATGATAGA-3' FAM-fluorescent probe. For both genes RT-PCR was performed on a TaqMan ABI PRISM<sup>®</sup> 7000 sequence detection system (Applied Biosystems) for allelic discrimination.

Participants were classified into two groups: Val/Val and Met (Met/Met and Met/Val genotypes), on account of the dominant nature of the Met allele (Frodl et al., 2007).

### 2.4. Antidepressants

Antidepressant drugs that were studied were the 3 most commonly prescribed classes of antidepressants: SSRI, SNRI and tricyclic antidepressants (TCA). A monotherapy of antidepressants was required. The drug and its dose were chosen by the prescribing psychiatrist in naturalistic conditions, using "real world" treatment options.

Antidepressant drugs were studied in two groups, SSRI versus SNRI/TCA, based first on the mechanism of action and the nature of the monoaminergic transporter blocked by the drugs (serotonin for SSRI or serotonin and noradrenalin for SNRI/TCA), and second on efficacy, which is higher for SNRI/TCA than for SSRI (Anderson, 1998; DUAG, 1990; Molendijk et al., 2011).

### 2.5. Concomitant treatments

Patients were not permitted to be taking other antidepressants, antipsychotics, or mood stabilizers. Benzodiazepines were allowed at the minimum effective dose and for the minimum duration to treat symptoms like anxiety or insomnia.

## 2.6. Antidepressant efficacy

The HAMD and Clinical Global Impressions scales were rated by trained clinicians at baseline, 1 month, 3 months and 6 months after the beginning of antidepressant treatment.

The HAMD was the primary outcome criterion. The percentage of responders 3 months post-treatment was defined a-priori as the main outcome measure. Responders were defined by a decrease in the HAMD score of at least 50% from baseline to follow-up. The percentage of remitters was assessed 6 months post-treatment. Remitters were defined by a HAMD score of 7 or less at follow-up.

The Clinical Global Impression Severity (CGI-S), Improvement (CGI-I) scales (Guy, 1976) were the secondary outcome criteria.

## 2.7. Antidepressant side effects

Since antidepressant treatment failure may be related to tolerability, side effects were assessed on a 4-item scale derived from the CGI (Guy, 1976) (None=0; Do not significantly interfere with patient's functioning=1; significantly interferes with patient's functioning=2; outweighs therapeutic effect=3).

## 2.8. Statistical analysis

The primary analysis was a series of logistic regressions performed to disentangle the respective role of antidepressant classes and genotypes on response and remission in the whole sample: interactions between genotype and antidepressant class were calculated. Sensitivity analyses were performed using a propensity score matching method. Indeed, propensity scores (including age, gender, living alone, educational level, recurrent MDE, number of previous MDE, previous antidepressant treatments, first line antidepressant treatment, and baseline HAMD scores) were used to correct biases in this non-randomized “real world” study (D'Agostino and D'Agostino, 2007). Logistic regressions were also performed within the genotype groups (Val/Val and Met) and within antidepressant class groups (SSRI and SNRI/TCA). Unadjusted and adjusted odds-ratios (adjusted for age and previous antidepressant treatments) and their statistical significance were computed. A-posteriori power calculations (alpha risk=0.05) were also performed within the Val/Val and the Met groups.

Linear regression analyses were performed to disentangle the respective role of antidepressant drug classes and genotypes on CGI scores. Unadjusted and adjusted hazard-ratios (adjusted for age and previous antidepressant treatments) and their statistical significance were computed.

If there were significant statistical differences in the outcome between groups, number needed to treat (NNT) were calculated with the formulae of Kraemer and Kupfer.

All statistical analyses were performed with R 2.15.3, except the power calculation performed with the G\*power 3.1.7 software. All tests were two-tailed. A *P* value of 0.05 was considered significant.

## 3. Results

### 3.1. Sample characteristics

The demographic and clinical features of the 345 patients are shown in Table 1.

152 (44.1%) patients were treated with SSRI (escitalopram, *n*=52, 13.3 ± 7.3 mg/d; citalopram, *n*=33, 33.6 ± 51.1 mg/d; paroxetine, *n*=33, 23.6 ± 8 mg/d; fluoxetine, *n*=21, 19.1 ± 3 mg/d; sertraline, *n*=9, 100.0 ± 57 mg/d; fluvoxamine, *n*=3, 150.0 ± 71 mg/d). 193 (55.9%) patients were treated with SNRI/TCA (SNRI (*n*=156) (45.2%): venlafaxine, *n*=140, 152.1 ± 77 mg/d; duloxetine, *n*=15,

60.0 ± 15 mg/d; minalcipran, *n*=1, 100 mg/d); TCA (*n*=37) (10.7%): clomipramine, *n*=32, amitriptyline, *n*=3, imipramine, *n*=2, 110.5 ± 80 mg/d). Patients treated with SSRI did not differ from those treated with SNRI/TCA, except for age and previous antidepressant drug treatments: they were younger and were more often antidepressant naïve (Table 1). Thus, further analyses have been adjusted for these variables.

The Val/Val group comprised 231 (67.0%) patients. The Met group comprised 114 (33%) patients (Val/Met: 28.1%; Met/Met: 4.9%). No significant deviation from Hardy-Weinberg equilibrium was reported. Genotyping distribution did not differ regarding patient characteristics, attrition rates, antidepressant classes, drug side effects, response and remission rates (Table 1).

Patients who prematurely dropped out from the study (48.7% after 3 months and 63.9% after 6 months) did not significantly differ from completers. The dropout reasons were: stop of the antidepressant medication studied (27.1%), prescription of unauthorized drugs (10.1%), change of diagnosis not compatible with the study (6%), investigator's decision (5%), patient's decision (6%), lost to follow up (39.7%), and other (6.1%).

Fig. 1 shows HAMD scores at baseline, after 1 month, 3 months and 6 months of antidepressant treatment.

### 3.2. Interactions between genotypes and antidepressant classes

The percentage of HAMD responders 3 months post-treatment was explained by a significant interaction between the Val66Met polymorphism and antidepressant classes (OR:0.23, IC95% [0.06; 0.81], *p*=0.02) (Fig. 2). In a multivariate model adjusted for propensity-score deciles, the interaction was still significant (OR: 0.22, IC95% [0.05; 0.82], *p*=0.03). Accordingly, the CGI-I score 3 months post-treatment was explained by an interaction between the BDNF Val66Met polymorphism and antidepressant classes (HR:2.56, IC95% [1.23; 5.25], *p*=0.01). In a multivariate model adjusted for propensity-score deciles, this interaction was still significant (HR: 2.70, IC95% [1.28; 5.68], *p*=0.009). Regarding the percentage of HAMD remitters 3 months post-treatment, there was a coherent trend toward an interaction between the Val66Met polymorphism and antidepressant classes (OR:0.29, IC95% [0.07; 1.24], *p*=0.10). The percentage of HAMD remitters 6 months post-treatment was also explained by a significant interaction between the Val66Met polymorphism and antidepressant drugs (OR:0.14, IC95% [0.03; 0.70], *p*=0.02) (Fig. 3). In a multivariate model adjusted for propensity-score deciles, the interaction was still significant (OR: 0.12, IC95% [0.02; 0.69], *p*=0.02). Of note, these interactions were still significant first using a “Last Observation Carried Forward” (LOCF) imputation method for prematurely withdrawn patients, second when adjusting for side effects, and third in the subgroup of patients receiving a first-line antidepressant drug treatment for the current MDE. No interaction between the Val66Met polymorphism and antidepressant classes was shown for antidepressant side effects 3 and 6 months post-treatment.

### 3.3. Val/Val patients

Val/Val patients had a higher HAMD response rate 3 months post-treatment with SSRI than with SNRI/TCA antidepressants (Table 2, Fig. 2) (68.1% versus 42.3%; unadjusted-OR: 2.91, IC95% [1.36; 6.44], *p*=0.006; adjusted-OR: 2.60, IC95% [1.14; 6.11], *p*=0.02). Accordingly, trends toward higher remission rates 6 months post-treatment were shown for Val/Val patients treated with SSRI as compared to SNRI/TCA (52.8% versus 33.3%; unadjusted-OR: 2.24, IC95% [0.95; 5.38], *p*=0.07; adjusted-OR: 2.34, IC95% [0.93; 6.11], *p*=0.07). The NNT were equal to 4 for response and 5 for remission. In addition, Val/Val patients treated with SSRI

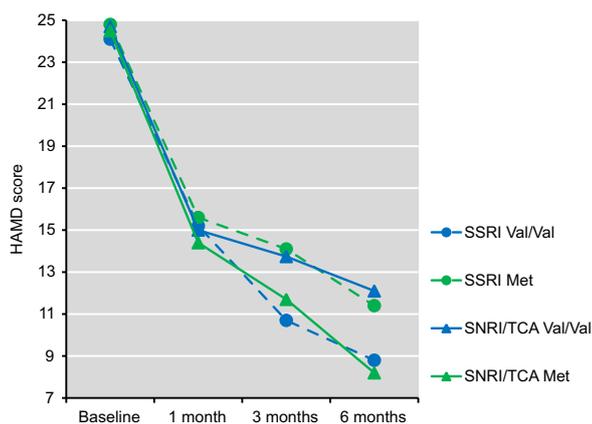
**Table 1**  
Demographic, clinical characteristics and antidepressant effects, depending on antidepressant treatment classes and BDNF Val66Met polymorphism.

	SSRI (n=152)	SNRI/TCA (n=193)	P <sup>a</sup>	Val/Val (n=231)	Met (n=114)	P <sup>b</sup>
<b>Baseline</b>						
Age (years)(m(sd))	42.7 (13.8)	47.2 (11.7)	< 0.01	45.5 (12.9)	44.7 (12.8)	ns
Women (%)	67.1	66.3	ns	68.8	62.3	ns
Living alone (%)	57.2	49.2	ns	52.5	55.3	ns
Recurrent MDD (%)	74.3	76.6	ns	77.0	72.8	ns
HAMD (m (sd))	24.3 (4.9)	24.7 (4.9)	ns	24.5 (4.8)	24.7 (5.1)	ns
CGI-S (m (sd))	4.8 (0.8)	4.9 (0.6)	ns	4.8 (0.7)	4.9 (0.7)	ns
Antidepressant naïve (%)	32.5	10.9	< 10 <sup>-4</sup>	20.0	21.2	ns
First line antidepressant for the current episode (%)	75.7	71.5	ns	74.5	71.1	ns
Antidepressant (%)						ns
SSRI				42.9	46.5	
SNRI	-	-	-	44.6	46.5	
TCA				12.6	7.0	
<b>1 month post-treatment</b>						
HAMD % score decrease (m (sd))	35.8 (28.7)	40.6 (26.1)	ns	38.7 (27.1)	38.4 (27.6)	ns
HAMD Responders (% (n))	33.6	39.6	ns	37.6	36.2	ns
HAMD Remitters (% (n))	17.7	15.1	ns	17.4	13.8	ns
CGI-S (m (sd))	3.7 (1.3)	3.8 (1.2)	ns	3.7 (1.3)	2.3 (1.3)	ns
CGI-I (m (sd))	2.7 (1.0)	2.5 (0.9)	ns	2.6 (0.9)	2.6 (1.0)	ns
CGI-Side effects (m (sd))	0.8 (0.5)	0.9 (0.5)	ns	0.8 (0.5)	0.8 (0.6)	ns
<b>3 months post-treatment</b>						
HAMD % score decrease (m (sd))	49.1 (31.5)	47.0 (28.2)	ns	48.2 (29.2)	47.4 (30.6)	ns
HAMD Responders (%)	59.7	46.2	ns	52.5	50.0	ns
HAMD Remitters (%)	30.6	22.6	ns	24.6	28.3	ns
CGI-S (m (sd))	3.0 (1.5)	3.2 (1.4)	ns	3.1 (1.4)	3.2 (1.5)	ns
CGI-I (m (sd))	2.3 (1.2)	2.3 (1.1)	ns	2.3 (1.2)	2.3 (1.2)	ns
CGI-Side effects (m (sd))	0.6 (0.5)	0.9 (0.9)	< 0.01	0.8 (0.5)	0.7 (0.5)	ns
<b>6 months post-treatment</b>						
HAMD % score decrease (m (sd))	58.4 (31.2)	54.7 (29.9)	ns	55.1 (29.6)	58.7 (32.4)	ns
HAMD Responders (%)	68.6	64.9	ns	65.6	68.4	ns
HAMD Remitters (%)	47.1	41.6	ns	41.1	50.0	ns
CGI-S (m (sd))	2.3 (1.4)	2.7 (1.5)	ns	2.6 (1.5)	2.5 (1.6)	ns
CGI-I (m (sd))	1.9 (1.1)	2.0 (1.3)	ns	2.0 (1.3)	1.8 (1.1)	ns
CGI-Side Effects (m (sd))	0.6 (0.5)	0.8 (0.4)	< 0.01	0.7 (0.5)	0.7 (0.5)	ns

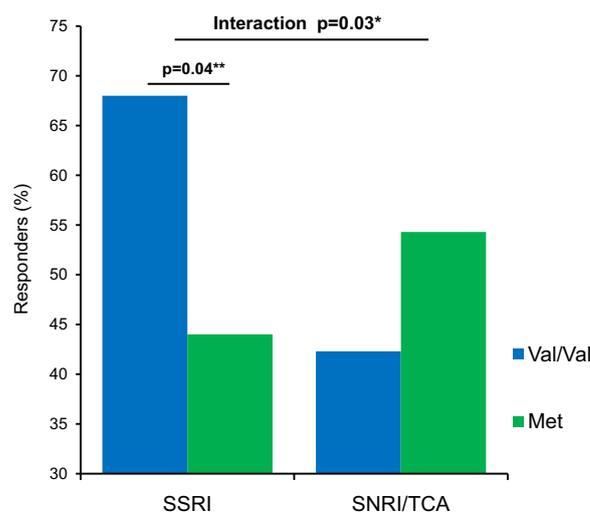
SSRI: Serotonin Selective Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; TCA: tricyclic antidepressants; MDD: major depressive disorder; HAMD: Hamilton Depression Rating Scale 17 items; CGI-S: Clinic Global Impression Severity; CGI-I: Clinic Global Impression Improvement. ns: non-significant.

<sup>a</sup> P values are for comparison between SSRI and SNRI/TCA.

<sup>b</sup> P values are for comparison between Val/Val and Met. All statistical tests shown in this table are non-adjusted tests. P values are shown when < 0.10. ns: non-significant.



**Fig. 1.** Efficacy of antidepressant classes depending on the Val66Met polymorphism. Met: Met/Met and Met/Val; HAMD: Hamilton Depression Rating Scale (17 items); SSRI: Serotonin Selective Reuptake Inhibitor; SNRI/TCA: Serotonin and Norepinephrine Reuptake Inhibitor and Tricyclic antidepressants.

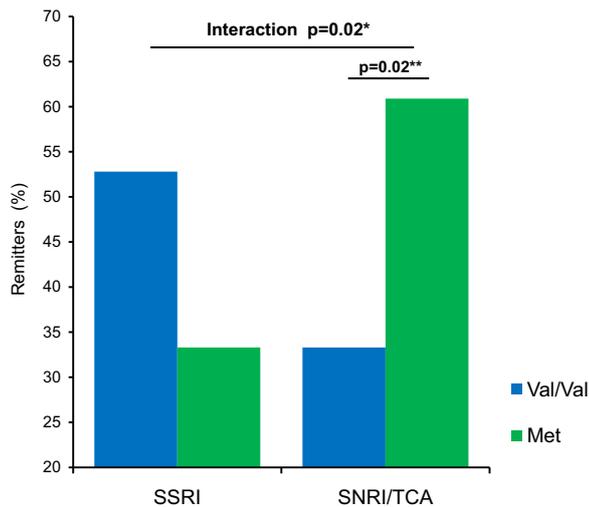


**Fig. 2.** Interaction of Val66Met BDNF polymorphism and antidepressant classes on responder rates 3 months post-treatment. Met: Met/Met and Met/Val, Responders: Hamilton depression rating scale score decrease at least 50% from baseline to 3 months; SSRI: Serotonin Selective Reuptake Inhibitor; SNRI/TCA: Serotonin and Norepinephrine Reuptake Inhibitor and tricyclic antidepressants; \*: multivariate model adjusted for propensity-score deciles; \*\*: multivariate model adjusted for age and previous antidepressant treatments.

had lower CGI-S scores 6 months post-treatment than those treated with SNRI/TCA (unadjusted-HR: 0.45, IC95%[0.25; 0.83],  $p=0.01$ ; adjusted-HR: 0.51, IC95% [0.27; 0.92],  $p=0.03$ ).

3.4. Met patients

Conversely, Met patients had higher remission rates 6 months post-treatment with SNRI/TCA than with SSRI (Table 2, Fig. 3) (60.9% versus 33.3%, unadjusted-OR: 2.11, IC95% [0.82; 12.9],  $p=0.09$ ; adjusted-OR: 6.4, IC95% [1.25; 50.7],  $p=0.04$ ). The corresponding NNT was equal to 4.



**Fig. 3.** Interaction of Val66Met BDNF polymorphism and antidepressant classes on remitter rates 6 months post-treatment. Met: Met/Met and Met/Val; Remitters: Hamilton Depression Rating Scale score of 7 or less after 6 months of treatment; SSRI: Serotonin Selective Reuptake Inhibitor; SNRI/TCA: Serotonin and Norepinephrine Reuptake Inhibitor and tricyclic antidepressants; \*: multivariate model adjusted for propensity-score deciles; \*\*: multivariate model adjusted for age and previous antidepressant treatments.

3.5. SSRI drugs

With SSRI, Val/Val patients had a higher response rate 3 months post-treatment than Met patients (Table 2, Fig. 2) (68.1% versus 44%, unadjusted-OR: 2.71, IC95% [1.01; 7.55],  $p < 0.05$ ; adjusted-OR: 3.04, IC95% [1.05; 9.37],  $p=0.04$ ). The corresponding NNT was equal to 4. Almost significant convergent results were shown with the CGI-I 3 months post-treatment (Table 2).

3.6. SNRI/TCA drugs

With SNRI/TCA, Val/Val patients had a lower remission rate 6 months post-treatment than Met patients (Table 2, Fig. 3) (33.3% versus 60.9%, unadjusted-OR: 0.32, IC95% [0.11; 0.87],  $p=0.02$ ; adjusted-OR: 0.27, IC95% [0.09; 0.76],  $p=0.02$ ). The corresponding NNT was 4. Convergent results were shown with the CGI-I 3 months post-treatment (Table 2) (unadjusted-HR: 1.43, IC95% [0.93; 2.25],  $p=0.10$ ; adjusted-HR:1.57, IC95% [1.01; 2.44],  $p < 0.05$ ).

4. Discussion

This study shows that the BDNF Val66Met polymorphism influences antidepressant response and remission in Caucasian patients, in a different manner for SSRI and SNRI/TCA. Val/Val patients have a higher probability of 3-month response to SSRI as compared to SNRI/TCA. And carriers of the Met allele have a higher probability of 6-month remission rate with SNRI/TCA as compared to SSRI. This effect is not related to antidepressant side effects. Thus, our results argue for a personalized approach of antidepressants prescription based on the BDNF Val66Met polymorphism and suggest that SSRI should be recommended for Val/Val patients and that, conversely, SNRI/TCA should be recommended for Met patients.

Our results with SSRI are in agreement with those of a previous clinical 6-week study (Lancôt et al., 2010) of 90 MDE patients

**Table 2**  
Efficacy of antidepressant classes in Val/Val and Met patients.

	Val/Val			Met		
	SSRI (n=99)	SNRI/TCA (n=132)	p	SSRI (n=53)	SNRI/TCA (n=61)	p
<b>Baseline</b>						
Age (m (sd))	43.2 (13.5)	47.3 (12.1)	0.03	41.9 (14.3)	47.1 (10.7)	0.03
Women (%)	65.7	71.2	ns	69.8	55.7	ns
Living alone (%)	53.5	50.0	ns	64.2 (34)	47.5	0.08
Recurrent MDD (%)	74.7	78.6	ns	73.6	72.1	ns
HAMD-17 baseline (m (sd))	24.1 (4.8)	24.7 (4.8)	ns	24.8 (5.1)	24.5 (5.1)	ns
CGI-S (m (sd))	4.8 (0.7)	4.9 (0.6)	ns	4.9 (0.6)	4.8 (0.8)	ns
Antidepressant naïve (%)	33.3	9.9	$< 10^{-4}$	30.8	13.1	0.02
First line antidepressant for the current episode (%)	77.8	72.0	ns	71.7 (38)	70.5	ns
<b>3 months post-treatment</b>						
HAMD % score decrease (m (sd))	54.1 (29.2)	44.3 (28.7)	0.07	39.8 (34.2)	52.8 (26.8)	ns
HAMD Responders (%)	68.1	42.3	0.006	44.0	54.3	ns
HAMD Remitters (%)	34.0	18.3)	0.05	24.0	31.4	ns
CGI-S (m(sd))	2.8 (1.4)	3.3 (1.4)	0.046	3.4 (1.6)	3.0 (1.5)	ns
CGI-I (m (sd))	2.1 (1.1)	2.4 (1.2)	ns	2.7 (1.5)	2.0 (0.9)	ns
<b>6 months post-treatment</b>						
HAMD % score decrease (m (sd))	62.0 (29.8)	50.6 (28.0)	0.08	49.7 (33.8)	64.5 (30.9)	ns
HAMD Responders (%)	72.2	61.1	ns	60.0	73.9	ns
HAMD Remitters (%)	52.8	33.3	0.07	33.3	60.9	0.09
CGI-S (m (sd))	2.1 (1.3)	2.9 (1.5)	0.01	2.3 (1.5)	2.7 (1.7)	ns
CGI-I (m (sd))	1.8 (1.2)	2.1 (1.3)	ns	1.9 (0.8)	1.8 (1.3)	ns

SSRI: Serotonin Selective Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; TCA: tricyclic antidepressants; HAMD: Hamilton Depression Rating Scale (17 items); CGI-S: Clinic Global Impression Severity; CGI-I: Clinic Global Impression Improvement. All statistical tests shown in this table are non-adjusted tests. P values are for comparison between SSRI and SNRI/TCA. P values are shown when  $< 0.10$ . ns: non-significant.

treated with an SSRI, showing higher response rates to SSRI in Val/Val patients. However, our results differ from those of several studies: the 12-week study on a small sample of 32 Caucasian geriatric depressed patients treated with escitalopram (Alexopoulos et al., 2010), the study of El-Hage et al. (2014), which focused on 3-week response in both bipolar and MDD patients, the negative 6-week study of Brunoni et al. (2013) in a small sample of 120 patients of heterogeneous ethnicity, and studies in Asian patients (Choi et al., 2006; Katsuki et al., 2012; Niitsu et al., 2013). Thus, these differences may be related to the study duration, since these studies were short-term ones, whereas our study is a 6-month study. These differences may also be due to ethnicity in studies of Asian patients, who have a different allelic repartition for the BDNF Val66Met polymorphism than Caucasians, or a genetic disequilibrium linkage with another polymorphism that could counteract the effect of the Met allele.

Several animal studies evidenced a lower response rates to SSRI in Met carriers. Indeed, our results are coherent with those showing that SSRI failed to increase both hippocampal BDNF protein levels in BDNF homozygote Met/Met mice (Bath et al., 2012). Since the BDNF Met polymorphism influences brain 5-HT transporter expression or the density of serotonergic neurons, the altered 5-HT transporter expression and function associated with the BDNF Met polymorphism might be involved in the blunted response to SSRI treatments in Met patients (Henningsson et al., 2009; Hensler et al., 2007; Yu et al., 2012).

Interestingly, the differential effects of the BDNF Val66Met polymorphism on response and remission rates depending on the class of the antidepressant observed here, are in line with results of preclinical studies showing that Met carrier mice responded to a TCA, but not to a SSRI treatment (Yu et al., 2012). Furthermore, a BDNF response in the frontal cortex was observed with SNRI but not with SSRI treatment (Calabrese et al., 2007; Cooke et al., 2009). Moreover, a chronic treatment with a SNRI, but not a SSRI, can reduce mature BDNF in the cytosol and increase its level in the crude synaptosomal fraction, suggesting that SNRI, but not SSRI, not only produce a marked upregulation of BDNF mRNA and protein, but may also affect the subcellular redistribution of the BDNF (Calabrese et al., 2007). Thus, it could be hypothesized that, in Met patients, who have a low BDNF functionality, SSRI would have a low antidepressant efficacy, whereas SNRI/TCA would be more efficient antidepressants. In Val/Val patients, who have a normal BDNF functionality, SSRI would be active and sufficient, whereas the more effective antidepressants SNRI/TCA may saturate the BDNF system, with a detrimental effect on mood. Altogether, our results, in line with those of Calabrese et al. (2007) in animals, suggest that BDNF can modulate antidepressant efficacy. This hypothesis is in line with results of animal studies obtained from a single genetically engineered mouse strain, showing that, although BDNF exerts an antidepressant effect, too high levels of BDNF, such as those of Val/Val patients receiving SNRI/TCA may have a detrimental effect on mood (Govindarajan et al., 2006). Our results are also in agreement with data showing that the saturation of the BDNF system with acute intra-hippocampal BDNF injections in healthy mice can induce an anxiogenic-like activity, that might be interpreted as a detrimental effect on mood). Our results are also in line with those suggesting that BDNF may have antidepressant-like effects in mice (Kalueff et al., 2006), but that BDNF inactivation may also lead to antidepressant effects (Berton et al., 2006). This suggests that a fine tuning of the BDNF signaling pathway is required to ensure an appropriate antidepressant effect. Altogether, our results may be explained by regulations of the brain serotonin and norepinephrine systems. Indeed, Yu et al. (2012) evidenced in Met carrier mice, a reduced serotonin transporter mRNA in the dorsal raphe nucleus and an increased norepinephrine transporter mRNA in the locus coeruleus.

This study has some limitations. First, we are probably measuring not only the effect of antidepressant classes, but also the fact that patients were different in terms of age and previous antidepressant drug treatment. However, propensity scores showed that the effect of antidepressant classes is maintained while adjusting for age and previous antidepressant drug treatments. In this context, whether a randomized predictive study in naive depressed patients may be discussed. But the drawbacks of such studies (non-representativity of patients treated in real world, costs, etc.) have to be balanced with the informations they could actually provide. Second, the attrition rate here is rather high (48.4% 3 months post-treatment) and due to treatment changes before the end of the study. However, it did not differ between groups and was very similar to the attrition rate of the STAR-D study, the main naturalistic study of antidepressant drugs performed in MDD patients, suggesting the generalizability of our results. Indeed, 58.2% of the STAR\*D patients had interrupted their antidepressant or dropped out from the study before 3 months post-treatment (Trivedi et al., 2006). Of note, the attrition rate of our study did not differ among genotypes or antidepressant classes. And the main interactions were still significant when imputing lacking data with a LOCF method. Third, side effects might have impacted our results by reducing treatment adherence. However, side effects did not differ between Val/Val and Met patients. In addition, in multivariate analyses controlling for side effects, the interactions between Val66Met and antidepressant classes remain unchanged, suggesting that the Val66Met polymorphism impact on antidepressant efficacy was not related to antidepressant side effects.

This study has some strengths. First, it is a naturalistic one, with “real world” treatment options rather than a randomized clinical trial design, in which patients are different from «real world» patients, thus not warranting the clinical applicability of study results. However, the disadvantage of a real-world design lies in the possibility of some uncontrolled biases related to the lack of randomization. However, in this study, the polymorphism frequencies did not differ between treatment groups and antidepressant drug efficacy was assessed blind from the polymorphisms, thus limiting these potential uncontrolled biases. Second, the reproducibility of our results is strengthened by the reasonable sample size of our sample and by a remission rate 3 months post-treatment quite similar to that in STAR\*D (25.8%) (Trivedi et al., 2006). Third, the duration of our study is longer than the duration of previous ones (4 to 8 weeks), which are brief regarding the recommended duration of antidepressant drug treatment. Indeed, only 4 published studies have a 3-month (Alexopoulos et al., 2010; Wilkie et al., 2007) or 6-month (Bukh et al., 2010; Taylor et al., 2011) duration. The 6-month duration of our study argues for the clinical relevance of its results. Moreover, Yan et al. (2014) assumed that neurogenesis, which is dependent from the BDNF functionality, could require significant durations of treatment to become effective in real world settings.

Finally, our results suggest that the BDNF Val66Met polymorphism could lead to a personalized prescription of antidepressants in MDD. These results may be relevant for public health since antidepressant response is still difficult to predict in depressed patients. If our results could be replicated, the current recommendations for clinical practice could be reconsidered. Indeed, currently, the recommended first-line treatments of MDD are SSRI. However, here we show that, for Met carriers, who represent one third of our sample, this strategy could be optimized in terms of efficacy, by choosing SNRI or TCA rather than an SSRI. Moreover, in patients with an inadequate response to a first line antidepressant, whereas SNRI are recommended, in this sample, SSRI are more effective than SNRI in Val/Val subjects, suggesting that Val/Val patients could benefit from a second SSRI. Of note, regarding cost-utility, genotyping costs are 5-fold lower than those of a one-day treatment in the hospital. Thus, this strategy could lead to significant reductions of treatment costs.

### Role of funding source

This study was funded by the Programme Hospitalier de Recherche Clinique from the French Ministry of Health (AOR10071) and the Assistance Publique – Hôpitaux de Paris (P060219).

### Conflict of interest

Romain Colle has no conflicts of interest. Florence Gressier has given talks for Servier, Lundbeck and received a grant from Servier. Celine Verstuyft has no conflicts of interest. Jean-Pierre Lepine has no conflicts of interest. Florian Ferreri has received consulting fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly company, Lundbeck, Otsuka and Servier. Patrick Hardy has no conflicts of interest. Anne-Cécile Petit has no conflicts of interest. Bruno Feve received consulting or conference fees from NovoNordisk, MSD, Sanofi-Aventis. Bruno Falissard has been consultant, expert or has given talks for E. Lilly, BMS, Servier, Sanofi, GlaxoSmithKline, HRA, Roche, Boeringer Ingelheim, Bayer, Ammiral, Allergan, Stallergene, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck. Laurent Becquemont received consulting fees from Sanofi, Pfizer, Servier and lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb and Merck Sharp and Dohme. Close family member working at Sanofi. Emmanuelle Corruble received consulting or conference fees from Astra-Zeneca, Bristol Myers Squibb, Eisai, Lundbeck, Otsuka, Sanofi-Aventis, Servier.

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