

Association Between the A118G Polymorphism of the *OPRM1* Gene and Suicidal Depression in a Large Cohort of Outpatients with Depression

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Background: Growing evidences suggest that depression with suicidal ideation (SI) could be a specific phenotype with its own characteristics. Moreover, opioid system deregulation might be implicated in suicidal behaviour (SB). The aim of this study was to determine whether the A118G polymorphism (rs1799971) in *OPRM1* (the gene encoding opioid receptor mu 1) is associated with suicidal depression (ie, moderate to severe depression with SI) in a large cohort of outpatients with depression.

Methods: GENESE is a large, prospective, naturalistic cohort of French adult outpatients with depression (DSM-IV criteria), treated and followed for 6 weeks. Depression severity was assessed with the Hospital Anxiety and Depression Scale (HADS), and SI with the suicidal item of the Montgomery–Åsberg Depression Rating Scale (MADRS-SI). From this cohort, patients with moderate or severe depression (HADS-D subscale score >11) were selected and classified as without SI (MADRS-SI < 2), or with SI (MADRS-SI ≥ 2).

Results: The AA/AG genotypes of the A118G polymorphism were significantly associated with suicidal depression in the non-adjusted (OR = 2.32, 95% CI = [1.28; 4.18]; *p*-value = 0.005) and in the adjusted models (OR = 2.54, 95% CI = [1.35; 4.78]; *p*-value = 0.004).

Conclusion: Outpatients with depression harbouring the A allele are at higher risk of SI (and possibly SB) than those carrying the G allele. More studies are needed to better understand the link between this polymorphism and SB.

Keywords: suicide, suicidal ideation, opioid system, A118G, *OPRM1*

Introduction

Suicide is a major public health problem. Most studies on suicidal behaviour (SB) have focused on suicide and suicide attempts (SA). Conversely, suicidal ideation (SI) too often escapes the attention of suicide prevention research and clinical treatments.¹ SI physiopathology may be different from that of SB² because subjects experiencing SI do not systematically attempt suicide and some suicide completers have no past history of SB.^{3,4} Yet, SI is the third most potent predictor of future death by suicide.⁵ One-third of patients with SI will attempt suicide, and among them 60% within the year following SI onset.^{3,6,7} It can be hypothesized that reducing SI may help to prevent SB.

SI is frequent in patients with major depressive episode (from 40 to 75%).⁸ Growing evidence suggests that suicidal depression (ie, depression with SI) could be a specific phenotype of depression. Compared with depressed patients without SI, suicidal depressed patients are characterized by more severe clinical features

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(eg, greater depressive symptom severity and number of depressive episodes, more frequent history of SA)^{9–11} and worse response to antidepressant treatment. They are also less likely to achieve remission.¹² Although SI and depression severity are associated, their progression is not overlapping. For instance, in a cohort of patients with severe depression, Khan et al¹³ found that SI reduction preceded depression improvement and that the magnitude of SI reduction was larger than that of depression reduction. These results suggest that contrary to current beliefs, SI decrease may not be a consequence of depression improvement. This hypothesis is sustained by a study demonstrating that SI reduction by ketamine administration is only partially linked to the reduction of depressive symptomatology.¹⁴ On the other hand, Seo et al¹⁵ showed that in 46% of patients with pre-existing SI during depression treatment, SI persisted despite the improvement of the depressive symptomatology. These findings suggest that the trajectories of SI and depression might be separated, while somehow related.¹⁶ Indeed, depressive symptomatology profiles are different in patients with and without SI.^{10,17,18}

The opioid system might be involved in SB physiopathology.¹⁹ It has been shown that consumption of opiate analgesics is higher in patients with suicidal depression than in those without suicidal depression and in healthy controls, independently of their health status.^{20,21} Furthermore, the density of mu-opioid receptors (MOR) in prefrontal cortex and nucleus caudate is higher in brain of suicide victims.^{22,23} Recent randomized controlled trials showed a significant reduction of SI in patients with depression on buprenorphine (a partial mu agonist and kappa antagonist) than in those on placebo, suggesting the usefulness of opioid drugs in suicide prevention.^{24,25} The A118G (rs1799971) variant in the first exon of *OPRM1* (opioid mu receptor gene) is a functional single nucleotide polymorphism (SNP) in the opioid system. The G allele (recessive) of this SNP results in an amino-acid change, resulting in a change of MOR expression and function.^{27,28} This SNP has been associated with pain regulation and sensitivity to social rejection, which are known to play a role in SB.^{29–32} For instance, G allele was associated with a greater sensitivity to social pain^{32–34} and with the occurrence of a depressive episode following a rejection event (but not other stressful life events).³⁵ Few studies are available concerning the association between this SNP and SB. One study found that AA genotype was associated with complete suicide.³⁶

Our group reported that this SNP was involved in treatment emergent SI (TESI) at antidepressant onset (AA genotype was significantly associated with TESI), independently of the depressive symptomatology course.³⁶ Genetics studies in SB are still scarce and even if some candidate genes have been found, these studies need to be replicated and more genes have to be explored.³⁷

We recently showed that suicidal depressed patients were different from non-suicidal patients in this cohort (eg, more severe clinical features, different course of depression and less response to treatment).¹⁰ Thus, we decided to assess whether the A118G SNP was associated with the phenotype of suicidal depression. Indeed, considering our precedent results, we hypothesized that patients with a AA genotype could be more prone to have a suicidal depression.

Methods

Participants

GENESE is a large, prospective, naturalistic cohort of 3566 French outpatients with a major depressive episode (diagnosis according to the DSM-IV criteria) treated with tianeptine. Tianeptine dose was chosen by their general practitioner (GP) or psychiatrist, and ranged between 12.5 and 37.5 mg/day, according to the prescription recommendations. The same physician (GP or psychiatrist) followed the patients for at least 6 weeks after treatment initiation. Demographic data, history of major depressive disorder and of lifetime SA were collected by the physician at the first visit (ie, treatment initiation). Non-inclusion criteria were: age <18 years, non-Caucasian ethnicity, alcohol and substance dependence, or any psychiatric pathology from axis I other than current major depressive episode.

The study was performed according to the French regulatory guidelines and the current codes of Good Clinical Practice. Each patient was informed about the aims and procedures of the study and provided a written, signed consent. The study protocol was submitted to and approved by local independent ethics committees (Comité de Protection des Personnes CPP Ile de France XI (CPPIDF11), Centre Hospitalier Intercommunal CHI Poissy Saint-Germain, Saint Germain en Laye, reference no. 08042).

Clinical Assessments

Hetero-evaluations were performed at the first visit and at the follow-up end. Auto-evaluations were performed at

the first visit, week 2 and week 4, and at the follow-up end. Our priority was to use self-reported evaluations of SI and depression because patients are more likely to disclose SI in self-reported measures than to a clinician. Moreover, self-report seems to be a good predictor of future SA.^{38–40} Depression severity was assessed with the validated French version of the Hospital Anxiety and Depression Scale (HADS). This scale has a good performance for assessing depression severity in both psychiatric and primary care patients and a good sensitivity to changes.⁴¹ Most factor analyses found a two-factor solution in accordance with the Anxiety (HADS-A) and Depression (HADS-D) subscales. This scale was chosen for its simplicity of use and understanding and for its good psychometric properties, which have been demonstrated also in outpatient groups.⁴² As no specific scale has been univocally proposed for clinical practice or for clinical research to assess SI, here SI was evaluated using the suicidal item of the self-rated Montgomery–Åsberg Depression Rating Scale (MADRS-SI) completed by patients. The ratings range from 0 to 6: 0 to 1) enjoys life or takes it as it comes; 2 to 3) weary of life, only fleeting suicidal thoughts; 4 to 5) probably better off dead, suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention; and 6) explicit plans for suicide when there is an opportunity, active preparations for suicide. It has been demonstrated that a single suicide item from a depression rating scale, either clinician-rated or self-reported, is a valid approach to assess SI, compared with Beck's scale.⁴³ This method was used in large clinical studies, such as the STAR*D,⁴⁴ and also in more recent studies.³⁶

Plutchik's Impulsivity Questionnaire⁴⁵ and the sleep item of the self-rated MADRS were used to assess impulsivity and sleep quality, respectively.

Single Nucleotide Polymorphism and Genotyping

The SNP A118G of *OPRM1* was chosen on the basis of two criteria: 1) SNP of the opioid system that was previously reported as associated with suicide and depression; 2) minor allele frequencies above 5%. The Hardy-Weinberg equilibrium was respected.

DNA was collected at baseline by buccal swab. Genotyping was performed with a 5' exonuclease assay (TaqMan, Life Technologies). Assay products were run on

an applied Biosystem 7900HT Fast Real-Time PCR System (Life Technologies).

The success rate of SNP genotyping in our population was 95%. In each 96-well plate, four DNA samples were assessed in replicate (duplicate) to measure the reproducibility rate. The plate was genotyped again When a discrepancy in one of these replicates was observed. Overall, the replication rate was 99.9% for all genotyping runs.

Definition of Suicidal Depression Phenotypes

Only the scores of self-administered questionnaires were used for the analyses. Among the 3566 patients of this cohort, A118G genotyping could be performed in 2801 (78.5%). Among the patients with genotyping data, patients with moderate to severe depression at baseline were selected (N = 2012, 71.8%) according to the French High Authority of Health definition (ie, HADS-D subscale score > 11). The MADRS-SI score was used to classify patients as having suicidal depression (MADRS-SI score ≥ 2) or non-suicidal depression (ie, MADRS-SI score < 2).

Statistical Analysis

Categorical variables were presented as percentages, and quantitative variables as means with standard deviation (SD). Demographic and clinical characteristics in patients with non-suicidal depression and with suicidal depression were compared using a univariate logistic regression model.

To study the association between genotype and then allele (separately) and depression phenotype, firstly a univariate logistic regression model was used to estimate the odds-ratios (OR) and their 95% confidence interval (95% CI) in crude association. Then, baseline sociodemographic and clinical variables associated with suicidal depression at $p < 0.10$ were included in the logistic regression models to estimate the adjusted OR and 95% CI. For these models, depression phenotype (suicidal depression vs non-suicidal depression) was defined as the outcome and genotypes were defined as "exposure". Genotypes were coded as follows: GG = 0; AG = 1 and AA = 2 and regrouped genotypes as: AG or GG = 1; AA = 2 on one hand and AA or AG = 1; GG = 2 on the other hand.

Sensitivity analyses in which patients with lifetime SA were removed were performed using the same models.

The significance level was set at $P < 0.05$. Analyses were performed using the SPSS statistical software

(version 26; IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp).

Results

Baseline Characteristics

The study sample included 2012 depressed patients with a mean age of 49 years; 799 (39.7%) were men. Comparison of the baseline characteristics of patients with non-suicidal depression ($n = 298$; 14.8%) and suicidal depression ($n = 1714$; 85.2%) (Table 1) showed that socio-demographic characteristics were comparable between groups, except for professional status (suicidal patients were less active, p -value = 0.0004). Compared with the non-suicidal depression group, the number of major depressive episodes (p -value = 0.01), and the percentage of patients with associated treatment (p -value < 0.001) and of patients who needed a change of antidepressant treatment (vs initiation of a new one) for the current episode (p -value = 0.01) were higher in the suicidal depression group. Moreover, the baseline clinical characteristics were more severe in patients with suicidal depression than in those with non-suicidal depression: higher percentage of patients with history of lifetime SA (p -value < 0.001), higher HADS total score and sub-scores (p -value < 0.001), higher impulsivity score (p -value < 0.001) and more sleep disturbances (p -value < 0.001).

Association Between the A118G SNP and Suicidal Depression

The AA and AG genotypes of the A118G SNP were significantly associated with suicidal depression (model 0: OR = 2.36, 95% CI = [1.30; 4.29], p -value = 0.02; OR = 2.19, 95% CI = [1.17; 4.11], p -value = 0.02, respectively; Table 2). This association remained significant after adjusting for potential confounders (professional activity, lifetime SA, HADS total score, impulsivity score, MADRS-sleep score, associated treatment and instauration/change of treatment) for both genotypes (model 1: OR = 2.51, 95% CI = [1.32; 4.74], p -value = 0.02; OR = 2.62, 95% CI = [1.34; 5.14], p -value = 0.02, respectively; Table 2). The multivariate logistic regression analysis did not include the number of depressive episodes because this was associated with both suicidal depression and SNP genotype.

After grouping genotypes (AA/AG versus GG) (Table 2), the AA/AG genotypes were significantly associated with suicidal depression in the non-adjusted model (OR = 2.32, 95% CI = [1.28; 4.18]; p -value = 0.005;

model 0) and also in the adjusted model (OR = 2.54, 95% CI = [1.35; 4.78]; p -value = 0.004; model 1).

Finally, comparison of the A and G allele frequency in the two patient groups (Table 3) showed that the A allele was associated with suicidal depression in the unadjusted model (OR = 1.27, 95% CI = [1.01; 1.59]; p -value = 0.04; model 0), but not in the adjusted model.

Association Between A118G and SA During the Follow-Up

During the follow-up, eight SA (0.4%) were reported. None of these patients harboured the GG genotype (data not shown).

Sensitivity Analysis

When removing patients with lifetime history of SA, the results did not change (Tables 4 and 5). The AG/AA genotypes remained significantly associated with suicidal depression (OR = 2.77, 95% CI = [1.49; 5.13]; p -value = 0.001; model 0), even after adjusting for potential confounders (OR = 2.88, 95% CI = [1.50; 5.51]; p -value = 0.001; model 1).

Discussion

This is the first study to assess the association between the SNP A118G in *OPRM1* and suicidal depression (ie, moderate to severe depression with SI) in a large cohort of depressed outpatients. We found that genotypes with the A allele (dominant) were significantly associated with suicidal depression, with a stronger relation after adjusting for potential confounders. These results did not change after removing from the analysis patients with lifetime SA (sensitivity analysis). In the same cohort, we previously reported that the A allele is associated with higher risk of treatment-emergent SI at antidepressant onset.³⁶ Previously, a post-mortem study reported that the AA genotype is associated with a 1.7-fold higher risk of completed suicide.³⁵ Therefore, we could hypothesize that the G allele (recessive) protects from SI and complete suicide.

Interestingly, the presence of the G allele leads to a change of MOR expression and function. However, more studies are needed to better understand the related biological and behavioural consequences of this change.²⁶ Some studies in healthy subjects found that the levels of pro-inflammatory cytokines are significantly lower in G allele carriers (correlated with higher score of health-related quality of life) and that cortisol levels in response

Table I Association Between Baseline Sociodemographic and Clinical Data and Suicidal Depression

	Suicidal Depression				
	No		Yes		
	N= 298		N= 1714		
Variables	n	%	n	%	P-value
Sex					0.86
Men	117	39.3	682	39.8	
Women	181	60.7	1032	60.2	
Age (years)	48.49 (14.92)		49.96 (14.67)		0.11
Marital Status					0.07
Single	53	17.8	314	18.4	
Married	190	64	971	56.8	
Divorced	36	12.1	296	17.3	
Widower	18	6.1	129	7.5	
Study level					0.06
Lower secondary school	113	38.6	775	45.5	
Upper secondary school	80	27.3	446	26.2	
University	100	34.1	484	28.4	
Professional activity					0.004
Working	184	62.6	881	51.8	
Unemployment	19	6.5	175	10.3	
Retired	58	19.7	372	21.9	
Other	33	11.2	272	16	
MDE duration					0.07
<2 months	114	39	550	32.8	
[2; 6] months	120	41.1	711	42.4	
>6 months	58	19.9	414	24.7	
First MDE					0.002
Yes	190	64	926	54.2	
No	107	36	784	45.8	
Number of MDE	2.26 (1.37)		2.88 (2.53)		0.01
Lifetime cumulated MDE duration (weeks)	30.68 (25.38)		34.99 (28.78)		0.16
Age at first MDE (years)	36.58 (14.79)		35.74 (13.70)		0.56
HADS-A	13.53 (3.35)		14.59 (3.41)		<0.001
HADS-D	14.71 (2.34)		15.80 (2.63)		<0.001
HADS total score	28.24 (4.69)		30.40 (4.92)		<0.001
Impulsivity score	35.93 (5.75)		37.41 (6.38)		<0.001
MADRS-sleep	3.15 (1.60)		3.88 (1.41)		<0.001
Lifetime suicide attempts					<0.001
Yes	9	3.1	219	13.1	
No	280	96.9	1447	86.9	
Associated treatment					<0.001
Yes	143	48	1013	59.1	
No	155	52	701	40.9	
Treatment instauration					0.01
Yes	255	85.9	1350	79.6	
No	42	14.1	346	20.4	

Note: Bold value represent significant results (p -value < 0.05).

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS-Anxiety; HADS-D, HADS-Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode.

Table 2 Association Between *ORPM/ A118G* SNP Genotype and Suicidal Depression

	Suicidal Depression				Model 0		Model 1	
	No N= 298		Yes N= 1714		OR [95% CI]	p-value	OR [95% CI]	p-value
	n	%	n	%				
A118G								
GG	16	5.4	41	2.4	I*	0.02	I*	0.02
AG	77	25.8	433	25.3	2.19 [1.17; 4.11]		2.62 [1.34; 5.14]	
AA	205	68.8	1240	72.3	2.36 [1.30; 4.29]		2.51 [1.32; 4.74]	
A118G								
AA/AG	282	94.6	1673	97.6	2.32 [1.28; 4.18]	0.005	2.54 [1.35; 4.78]	0.004
GG	16	5.4	41	2.4	I*		I*	

Notes: Model 0: crude association. Model 1: adjusted for professional activity, lifetime SA, baseline HADS total score, impulsivity score and MADRS-sleep, associated treatment and instauration/change of treatment. *Means that this genotype was taken as reference for binary logistic regression. Bold value represent significant results (p-value < 0.05).

Table 3 Association Between *ORPM/ A118G* SNP Allele and Suicidal Depression

	Suicidal Depression				Model 0		Model 1	
	No N= 298		Yes N= 1714		OR [95% CI]	p-value	OR [95% CI]	p-value
	n	%	n	%				
A118G								
G	109	18.3	515	15	I*	0.04		0.16
A	487	81.7	2913	85	1.27 [1.01; 1.59]			

Notes: Model 0: crude association. Model 1: adjusted for professional activity, lifetime SA, baseline HADS total score, impulsivity score and MADRS-sleep, associated treatment and instauration/change of treatment. *Means that this allele was taken as reference for binary logistic regression. Bold value represent significant results (p-value < 0.05).

to stress are lower in women harbouring the G allele.^{46,47} This finding is very interesting because cortisol stress response and inflammatory system are upregulated in SB.⁴⁸ Moreover, the G allele has been associated with greater sensibility to social rejection,^{31–33} higher risk of depressive episodes following social rejection (but not other type of negative event),³⁴ and greater social capacity (eg, higher pleasure and engagement in social interactions).^{29,49} On the basis of these findings, it could be hypothesized that carriers of the G allele are more sensitive to social interactions, whatever their valence (rejection or support). Consequently, they could be more prone to develop social support, a protective factor against SB.⁵⁰ Unfortunately, as we did not assess social support and recent social negative events in our cohort, we could not test this hypothesis.

Our study has some limitations. First, we assessed SI with a single item of a depression severity scale,

although this is considered a valid approach to assess SI.⁴³ Second, we did not assess childhood trauma, social support and recent social events. It could have been interesting to evaluate the link between the A118G SNP, suicidal depression and childhood trauma and/or social background. Finally, due to the low number of SA during the follow-up (N = 8), it was impossible to investigate the link between SA and genotype. Nevertheless, it is interesting that all SA were made by patients carrying the A allele. Our study has also strengths. Indeed, we used a large cohort of depressed outpatients (more than 2000 patients) who were recruited by GPs or psychiatrists throughout France. Therefore, they are representative of patients from “real life” situations. Then, we adjusted our analyses for a large number of potential confounders, and performed sensitivity analyses to strengthen the validity of our results. Finally, our study adds significant results in the genetic of SB.

Table 4 Baseline Sociodemographic and Clinical Data in Patients with and without Suicidal Depression After Removal of Patients with Lifetime SA

	Suicidal Depression				
	No		Yes		
	N= 280		N= 1447		
Variables	n	%	n	%	P-value
Sex					0.40
Men	108	38.6	597	41.3	
Women	172	61.4	850	58.7	
Age (years)	48.54 (14.97)		50.39 (14.94)		0.06
Marital Status					0.22
Single	47	16.8	254	17.6	
Married	181	64.9	849	58.8	
Divorced	34	12.2	224	15.5	
Widower	17	6.1	117	8.1	
Study level					0.21
Lower secondary school	104	37.8	625	43.4	
Upper secondary school	77	28	383	26.6	
University	94	34.2	433	30	
Professional activity					0.05
Working	173	62.7	773	53.8	
Unemployment	18	6.5	127	8.8	
Retired	56	20.3	335	23.3	
Other	29	10.5	201	14	
MDE duration					0.18
<2 months	108	39.3	478	33.8	
[2; 6] months	113	41.1	611	43.2	
>6 months	54	19.6	326	23	
First MDE					0.12
Yes	180	64.5	862	59.6	
No	99	35.5	585	40.4	
Number of MDE	2.27 (1.40)		2.49 (1.97)		0.27
Lifetime cumulated MDE duration (weeks)	28.73 (20.35)		32.31 (26.89)		0.23
Age at first MDE (years)	37.03 (15.05)		37.66 (14.06)		0.69
HADS-A	13.58 (3.34)		14.55 (3.40)		<0.001
HADS-D	14.76 (2.36)		15.79 (2.65)		<0.001
HADS total score	28.34 (4.68)		30.34 (4.91)		<0.001
Impulsivity score	35.97 (5.68)		37.22 (6.34)		0.002
MADRS-sleep	3.15 (1.61)		3.87 (1.37)		<0.001
Associated treatment					0.02
Yes	138	49.3	826	57.1	
No	142	50.7	621	42.9	
Treatment instauration					0.09
Yes	242	86.4	1181	82.3	
No	38	13.6	254	17.7	

Note: Bold value represent significant results (p -value < 0.05).

Table 5 Association Between *ORPM/ A118G* SNP Genotype and Suicidal Depression After Removal of Patients with Lifetime SA

	Suicidal Depression				Model 0		Model 1	
	No N= 280		Yes N= 1447		OR [95% CI]	p-value	OR [95% CI]	p-value
	n	%	n	%				
A118G								
GG	16	5.7	31	2.1	I*	0.005	I*	0.005
AG	68	24.3	372	25.7	2.82 [1.47; 5.44]		3.07 [1.54; 6.12]	
AA	196	70	1044	72.1	2.75 [1.47; 5.12]		2.81 [1.46; 5.41]	
A118G								
AA/AG	264	94.3	1416	97.9	2.77 [1.49; 5.13]	0.001	2.88 [1.50; 5.51]	0.001
GG	16	5.7	31	2.1	I*		I*	

Notes: Model 0: crude association. Model 1: adjusted for age, professional activity, baseline HADS total score, impulsivity score and MADRS-sleep, associated treatment and instauration/change of treatment. *Means that this genotype was taken as reference for binary logistic regression. Bold value represent significant results (p-value < 0.05).

Indeed, genetic studies on SB and especially on SI are still scarce (even more in the French population). Further studies are needed to better understand physiopathology of SB and propose specific therapeutics to suicidal patients.

In conclusion, we found that the AG/AA genotypes from the SNP A118G are associated with suicidal depression. It seems that the GG genotype might protect against suicidal depression. More studies are needed to better understand the link between this SNP and SB, by taking into account also the social background.

Data Sharing Statement

Due to ethical and legal restrictions, data involving clinical participants cannot be made publicly available.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have interests in relation with one or more organization that could be perceived as a possible conflict of interest in the context of the subject of this manuscript. The relationships are summarized as follows. Benedicte Nobile, Nicolas Ramoz, Emilie Olié and Jonathan Dubois report no financial relationships with commercial interests. Sebastien Guillaume received honoraria or research or educational conference grants from Bristol-Myers Squibb, Otsuka, Servier, Lundbeck, AstraZeneca and Janssen. Philip Gorwood reports no shares; has paid positions at University of Paris Descartes & Hospital Sainte-Anne; is on the advisory board at AstraZeneca, Janssen, Servier, and Wyeth; reports personal fees from GSK, Janssen, Lundbeck, Otsuka, and SAGE, outside the submitted work. Philippe Courtet reports no shares; has paid positions at University of Montpellier & CHU Montpellier; is on the advisory board at Servier; reports grants and/or personal fees from Janssen, Exeltis, Pfizer, Otsuka, and Lundbeck, outside the submitted work. The authors report no other conflicts of interest in this work.

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