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The ability of early changes in motivation to predict later antidepressant treatment response

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Introduction: Baseline values and early changes of emotional reactivity, cognitive speed, psychomotor function, motivation, and sensory perception have not been studied to any extent in unipolar depression, although they could help to characterize different dimensions of illness that are harder to capture by clinicians, give new insights on how patients improve, and offer new early clinical markers for later treatment response.

Methods: About 1,565 adult outpatients with major depressive disorder receiving agomelatine completed the clinician-rated 16-item quick inventory of depressive symptoms, Clinical Global Impression, and Multidimensional Assessment of Thymic States (MATHyS) rating scales at inclusion, Week 2 and Week 6. The MATHyS includes a 20-item self-rated visual analog scale (from inhibition [0] to activation [10], with [5] representing the usual state) leading to five a priori dimensions (emotional reactivity, cognitive speed, psychomotor function, motivation, and sensory perception).

Results: All MATHyS dimension scores increased from inclusion to Week 2 and from inclusion to Week 6 ($P < 0.001$). Improvement was around 2 points (out of 10) for motivation, 1.5 points for psychomotor function, and 0.5 points for other dimensions. Motivation showed a trend to being more severely impaired at inclusion in future nonresponders ($t = 1.25$, $df = 1,563$, $P = 0.10$). Its improvement at Week 2 was the most discriminating MATHyS dimension between future responders and nonresponders, and represents the best predictor of future response, with the highest area under the receptor operating characteristic curve (area under curve = 0.616, 95% confidence interval [0.588–0.643], $P < 0.001$). Finally, improvements in motivation correlated the most strongly with clinician-rated 16-item quick inventory of depressive symptoms improvement ($r = -0.491$, $df = 1,563$, $P < 0.001$).

Conclusion: Motivation had the most capacity for early improvement, the best predictive value for response, and the largest global margin of progress in depressed outpatients. Assessing the evolution of self-reported motivation over time in major depressive disorder could offer an interesting complementary approach to predict response.

Keywords: depression, agomelatine, dimension, motivation, treatment response

Introduction

Major depressive disorder (MDD) is a complex mental disorder, which presents with disturbances to many psychological functions other than mood, including vigilance, drive and motivation, self-esteem, concentration, and psychomotor function. Several of these different facets of MDD are captured in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) diagnostic criteria for the disorder.¹ Numerous behavioral and psychophysiological studies have provided evidence that depression is associated with motivation-related deficits. These are manifested by decreased responsivity to positive or rewarding stimuli and reduced approach-related behaviors.^{2,3} Recent functional imaging studies have also indicated that depression is associated with

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reduced activity in the mesolimbic brain structures involved in motivation-related behaviors.^{4,5} Taken together, such findings suggest that loss of motivational drive is frequent in patients with MDD and may be related to the anhedonia that is commonly observed in these patients.²

Antidepressant medication has been demonstrated to improve depressive symptoms in patients presenting with a major depressive episode (MDE), and these symptoms are generally the focus of the large Phase III randomized clinical trials performed in order to demonstrate the efficacy of these drugs. Nonetheless, it is recognized that it is also important to consider other functional domains when evaluating treatment of MDD. Indeed, treatment effects on facets of the MDE other than depressive symptoms may vary between different classes of antidepressant drugs. For example, there is some evidence that mixed serotonin–noradrenaline reuptake inhibitors may improve psychomotor retardation more than selective serotonin reuptake inhibitors.^{6–8} Another study has suggested that agomelatine may have a more beneficial effect on anhedonia than venlafaxine.⁹

With regard to motivation, few data are available on the effects of antidepressants. The Multidimensional Assessment of Thymic States (MATHyS) scale is a useful patient-reported outcome measure with which to assess motivation in patients with depression in the clinical setting. The MATHyS scale was developed and validated to define mood states dimensionally.^{10,11} It was originally designed to assess levels of activation or inhibition in different mood states in bipolar disorder with a single tool and to determine whether a clinical description in terms of activation/inhibition can improve definition of mixed bipolar states associating both manic and depressive symptoms.¹⁰ This scale provides a measure of the degree of inhibition or activation on five a priori dimensions representing cognitive speed, motivation, emotional reactivity, psychomotor function, and sensory perception. This scale has been used in a range of mood states, essentially in patients with bipolar disorder.^{10–17} To date, the MATHyS has not been studied extensively in patients with unipolar depression, although we recently detected that an early increase in positive emotions rated by the MATHyS could be more predictive of later treatment response than a decrease in negative emotions.¹⁸

We have recently performed a large prospective naturalistic study which enrolled outpatients starting treatment for an MDE with agomelatine.¹⁹ The primary objective of the study was to describe the effectiveness of agomelatine, after 6 weeks of treatment as a function of patient characteristics at baseline and previous treatment history. The MATHyS

was administered as a secondary outcome measure. In this analysis, we aimed at first describing the dimension score distribution of the MATHyS rating scale in a large population of patients with a diagnosis of unipolar depression and then assessing the relationship between MATHyS dimension scores over the course of the study and antidepressant treatment response.

Methods

This was a multicentre, observational Phase IV study of the effectiveness and tolerability of agomelatine conducted in a naturalistic treatment setting in 819 hospital and community psychiatry centers in France between April 2009 and April 2010. The study design and methods have been presented in detail elsewhere.¹⁹

Patients

The study included adult outpatients with a diagnosis of MDD who fulfilled DSM-IV diagnostic criteria for an MDE.²⁰ The MDE was required to be moderate to severe and had to require the initiation or a change of antidepressant treatment. All patients received agomelatine (25–50 mg) once daily at bedtime.

Treatment, follow up, and data collection

Patients were evaluated at an inclusion visit (Week 0), when eligibility criteria were verified, data on demographic and clinical variables at baseline documented, and treatment with agomelatine 25 mg was initiated. Patients then returned for two follow-up visits at Week 2 and Week 6, when clinical response was evaluated with a number of rating scales completed by the physician and by the patient. At Week 2, the dose of agomelatine could be increased to 50 mg at the discretion of the investigator.

Outcome measures

At each study visit, depressive symptoms were rated with the clinician-rated 16-item quick inventory of depressive symptoms (QIDS-C₁₆),²¹ and overall clinical status was rated with the Clinical Global Impression scale.²² Levels of activation and inhibition were assessed using MATHyS.¹⁰ Other secondary outcome measures included the Patient Global Impression – Improvement Questionnaire,²² the Sheehan Disability Scale,²³ and the Leeds Sleep Evaluation Questionnaire;²⁴ these data have been discussed previously²⁰ and will not be presented in this article.

The MATHyS consists of a 20-item set of visual analog scales.^{10,11} Although the MATHyS is designed to be self-rated,

it is recommended that a clinician assists in order to explain how the scoring is performed. Each item is scored on a visual analog scale from 0 to 10, with 0 representing the most “inhibited” level and 10 representing the most “excited” level. A score of 5 is considered to represent the patient’s usual mood state. The items are each assigned to one of five dimensions, representing emotional reactivity, cognitive speed, psychomotor function, motivation, and sensory perception.^{11,17} For each dimension score, scores on the individual constitutive items are added together and normalized on a scale of 0–10. The total score is generally represented as the sum of all the individual item scores, providing a possible range of 0–200. However, to facilitate comparison with the individual dimension scores, in the present analysis, we have normalized the total score on a scale of 0–10 by dividing by the number of items for each dimension.

Statistical analysis

The analysis was performed on a subgroup of the intent-to-treat population of the overall study¹⁹ for whom exploitable QIDS-C₁₆ and MATHyS scores were available at baseline, Week 2, and Week 6. Missing data were not replaced. The analysis of MATHyS scores is principally descriptive, with changes in MATHyS scores between baseline and Weeks 2 and 6 being compared using analyses of variance. To compare Pearson’s correlation coefficients, all coefficients (*r*) were converted to the normally distributed variable *z'* ($z' = 0.5[\ln(1+r) - \ln(1-r)]$). Using its standard error ($SE = 1/\sqrt{N-3}$), confidence intervals were computed, with the endpoints being then converted back to *r* ($r = (\exp(2 \times z') - 1) / (\exp(2 \times z') + 1)$).

The ability of MATHyS dimension scores to predict clinical response at Week 6, defined as a reduction in the QIDS-C₁₆ score compared to baseline of at least 50%, was evaluated through construction of receiver operating characteristic (ROC) curves. Internal consistency of the MATHyS scale was evaluated using Cronbach’s α -coefficient.¹⁸ All data analyses were performed using IBM SPSS Statistics for Macintosh, Version 22.0 (IBM Corp, Armonk, NY, USA).

Ethics

The study was performed according to international and French regulatory guidelines and current codes of Good Clinical Practice. Each patient was informed about the aims and procedures of the study and provided written, informed consent. The study protocol was submitted to and approved by local independent ethics committees (C.P.P. Sud-Est 6 of Clermont-Ferrand and Comité Consultatif en Matière

de Recherche Biomédicale of Monaco) and A.F.S.Sa.P.S. (French Health Authority). With respect to confidentiality of patient records, data handling for the study was authorized by the Commission Nationale d’Informatique et de Libertés, the French agency which ensures that all medical information is kept confidential and anonymous.

Results

Patients

From the initial sample of 2,351 patients, the QIDS-C₁₆ and the MATHyS scores were available at each study assessment for 1,565 subjects (66.6% of the sample). These constituted the analysis population for this study. Given the relatively high numbers of patients for whom complete data was unavailable, the baseline characteristics of analysis population were compared with those of the patients evaluated in the primary analysis of the study (Table 1). The two populations were not significantly different ($P > 0.10$), with a marginally shorter disease duration, younger age, and lower number of women in the MATHyS analysis population.

Outcome

Over the course of the study, depressive symptoms as measured with the QIDS-C₁₆ scale improved significantly ($t = 66.1$, $df = 3,128$, $P < 0.001$), and mean symptom scores decreased by around 50% between baseline and Week 6 (Table 2). The proportion of responders at Week 6 was 58.0%. These observations were comparable ($P > 0.10$) to those observed in the total intent-to-treat population. Over the same period, mean MATHyS scores increased from 4.05 to 4.87 ($t = 20.2$, $df = 3,128$, $P < 0.001$).

At baseline, the mean MATHyS dimension scale scores were lower than the neutral value of 5 for motivation and

Table 1 Patient characteristics at baseline

Variable	Initial population (N=2,351)	Current analysis (N=1,565)
Age (years)	47.0±12.4	45.9±12.1
Sex (female, %)	1,851 (66.6%)	1,013 (64.7%)
Duration of MDD (years)	9.5±10.6	8.7±9.8
Duration of current MDE (months)	8.9±16.5	8.5±15.0
History of previous MDE (recurrent, %)	1,974 (71.0%)	1,094 (69.9%)
Number of previous MDEs	2.0±2.8	1.9±2.7
QIDS-C ₁₆ score at inclusion	18.8±2.4	18.8±2.3

Note: Data are presented as mean values ± SD for continuous variables and as frequency counts (%) for categorical variables.

Abbreviations: MDD, major depressive disorder; MDE, major depressive episode; SD, standard deviation; QIDS-C₁₆, 16-item quick inventory of depressive symptoms.

Table 2 Evolution of QIDS-C₁₆ and MATHyS scores over the course of the study

Timepoint	QIDS-C ₁₆ score	QIDS-C ₁₆ Response rate	MATHyS score
Baseline	18.8±2.3	NA	4.05±1.11
Week 2	12.7±4.7	NA	4.64±1.20
Week 6	9.3±5.2	908 (58.0%)	4.87±1.16

Notes: Data are presented as mean values ± SD for 1,565 patients in the current analysis.

Abbreviations: QIDS-C₁₆, 16-item quick inventory of depressive symptoms; MATHyS, Multidimensional Assessment of Thymic States; NA, not applicable; SD, standard deviation.

psychomotor retardation. The evolution of individual MATHyS dimension scales is presented in Figure 1. All dimensions of the scale improved significantly ($P<0.001$) from inclusion to Week 2 and from inclusion to Week 6 ($P<0.001$). The two dimension scores that changed the most over the course of the study were motivation and psychomotor function. The other three dimension scores, whose baseline values were close to the neutral value of 5, changed to a lesser degree. The internal consistency of the dimension scores of the MATHyS was acceptable, with a Cronbach's α coefficient of 0.69.

Relationship between MATHyS and QIDS-C₁₆ scores

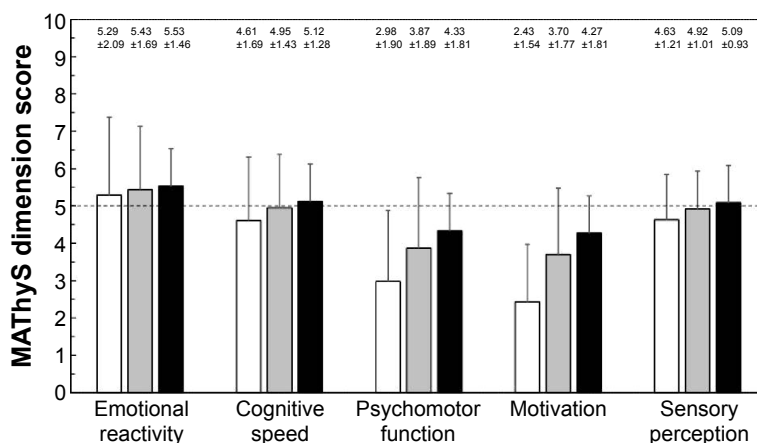
For all MATHyS dimension scores, the extent of improvement between baseline and Week 6 was positively correlated with the improvement in depressive symptoms measured with the QIDS-C₁₆ over the same period. The strongest correlation was observed for the motivation dimension of the MATHyS compared to all other dimensions (Table 3). When the baseline value of the QIDS-C₁₆ was controlled for in a partial correlation

analysis, the correlation between QIDS-C₁₆ and MATHyS changes was still larger for motivation, once again with no overlap with other correlation coefficients (Table 3).

In the next step, we evaluated the capacity of the change in MATHyS motivation score between baseline and Week 2 to predict treatment response (reduction from baseline in QIDS-C₁₆ score $\geq 50\%$) at Week 6 using ROC analysis. The ROC curve is illustrated in Figure 2. The area under the ROC curve was the highest for the change in motivation score at Week 2 (Figure 2 and Table 4). The latter also performed well as a predictor of clinical remission at Week 6, defined as a QIDS-C₁₆ score < 6 (area under the curve: 0.623; [95% confidence interval: 0.591–0.655]; $P=0.016$) and functional remission at Week 6, defined as a Sheehan Disability Scale score ≤ 2 (area under the curve: 0.606 [95% confidence interval: 0.567–0.644]; $P=0.020$) (Table 4). Finally, motivation showed a trend to being more severely impaired at inclusion in future QIDS-C₁₆ nonresponders ($t=1.25$, $df=1,563$, $P=0.10$).

Discussion

The goal of this analysis was to evaluate facets of MDE other than depressive symptoms using the MATHyS scale, and in particular, the motivation dimension. To the best of our knowledge, this study has provided the first opportunity to assess the performance of the MATHyS dimensions in measuring impairment in a large population of patients with a diagnosis of MDD who experience an active MDE. The mean total normalized MATHyS score in our patients was 4.05, corresponding to a crude score of 81.0. The motivation dimension score (mean: 2.36) was the lowest individual dimension score at baseline, indicating a high degree of

**Figure 1** Evolution of MATHyS dimension scale scores over the course of the study.

Notes: Numerical values (mean ± SD) are presented above each column. Open columns: baseline; gray columns: Week 2; black columns: Week 6. The dashed horizontal line indicates the reference value of 5.

Abbreviation: MATHyS, Multidimensional Assessment of Thymic States.

Table 3 Correlation between change in MATHyS dimension scores and change in QIDS-C₁₆ scores between baseline and Week 6 before and after adjustment for baseline QIDS-C₁₆ score

MATHyS dimension	Unadjusted		Adjusted	
	r	P-value	r	P-value
Emotional reactivity	-0.083 [-0.033; 0.132]	0.001	-0.064 [-0.113; -0.014]	0.011
Cognitive speed	-0.227 [-0.179; -0.274]	<0.001	-0.211 [-0.258; -0.160]	<0.001
Psychomotor function	-0.361 [-0.317; -0.404]	<0.001	-0.348 [-0.391; -0.290]	<0.001
Motivation	-0.491 [-0.452; -0.528]	<0.001	-0.478 [-0.515; -0.404]	<0.001
Sensory perception	-0.268 [-0.221; -0.314]	<0.001	-0.25 [0.296; -0.198]	<0.001

Note: Pearson correlation coefficients are presented with their 95% confidence intervals.

Abbreviations: MATHyS, Multidimensional Assessment of Thymic States; QIDS-C₁₆, 16-item quick inventory of depressive symptoms.

impairment on this dimension of depression. Significant inhibition was also observed for the psychomotor retardation dimension.

The finding that motivation is the most impaired dimension of the MATHyS scale is significant, since many studies have suggested depression to be related to motivation-related impairments.²⁵ In particular, patients with depression appear to be less responsive to rewarding stimuli

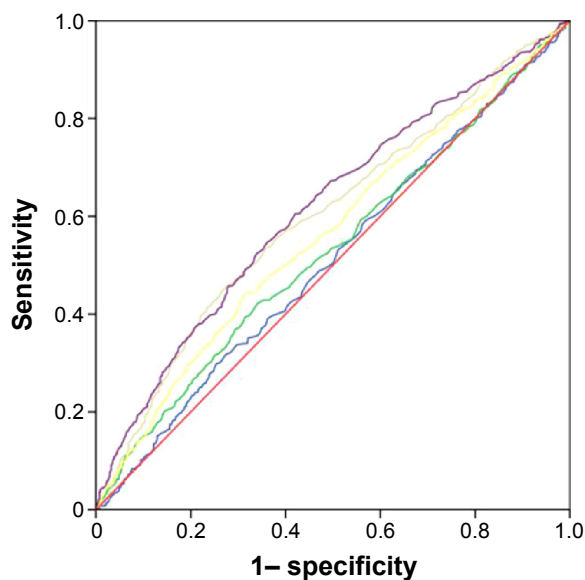


Figure 2 Receiver operating characteristics curve for the ability of changes in MATHyS dimension scores at Week 2 to predict QIDS-C₁₆ treatment response at Week 6.

Notes: Red line: reference line (no predictive value); blue curve: emotional reactivity; green curve: cognitive speed score; beige curve: psychomotor function score; purple curve: motivation score; yellow curve: sensory perception score.

Abbreviations: MATHyS, Multidimensional Assessment of Thymic States; QIDS-C₁₆, 16-item quick inventory of depressive symptoms.

but more responsive to negative cues and punishment.²⁶ In this context, it has been suggested by Kringelbach and Berridge²⁷ that anhedonia, which is considered a cardinal symptom of MDD, may be secondary to motivational deficits, and a number of studies have indicated that anhedonia is specifically associated with decreased willingness to expend effort for rewards.^{28–30} Motivation is one of the functional domains of mental health that have been highlighted for further research in the Research Domain Criteria of the National Institute of Mental Health,³¹ and it is anticipated that this will lead to a better understanding of the relationship between motivational deficits and mood disorders.

Our findings can be compared with data obtained with the MATHyS scale in patients with bipolar disorder experiencing an MDE. Two such samples have been described previously. The mean total score was 54.4 in the first sample^{10,11} and 75.3 in the second.¹² There are several possible explanations for the apparently lower scores in the bipolar patients. One such explanation is that the bipolar patients in the first sample may have been more severely ill, since they were recruited exclusively in a hospital department offering tertiary care for patients with bipolar disorder, whereas in our study, the patients were recruited from a mix of community care and hospital psychiatry centers. Alternatively, the difference may relate to the way the items are scored in the MATHyS on a visual analog scale between two extremes, for example, Item 17 “I am making decisions faster than usual”/“I am finding it harder than usual to make decisions”. This may permit differences in the frame of reference between different patient groups with respect, in this example, to what the patients consider as “usual”.

With respect to the individual dimension scores, our observations in patients with unipolar depression are also to some extent consistent with what has been reported in patients with bipolar depression.¹¹ Notably, the motivation and psychomotor dimensions were the most impaired in both patient groups. However, in bipolar depression, marked impairment was also observed for the cognitive speed, emotional reactivity, and sensory perception dimensions, which was not the case in our sample. Again, this may reflect a difference in the frame of reference, with bipolar patients experiencing a wider range of, for example, perceptions of intensity of emotions or speed of thought processing compared to unipolar patients.

Over the course of the study, the total MATHyS score increased toward the normative value of 5. This observation is consistent with that observed in patients with bipolar depression following initiation of treatment with an atypical

Table 4 Ability of changes in MATHyS dimension scores at Week 2 to predict QIDS-C₁₆ clinical response, QIDS-C₁₆ clinical remission, and SDS functional remission at Week 6

MATHyS dimension	Clinical response (QIDS-C ₁₆) at Week 6		Clinical remission (QIDS-C ₁₆) at Week 6		Functional remission (SDS) at Week 6	
	AUC	P-value	AUC	P-value	AUC	P-value
Emotional reactivity	0.511 [0.482–0.540]	0.015	0.527 [0.494–0.560]	0.017	0.512 [0.472–0.552]	0.021
Cognitive speed	0.531 [0.502–0.559]	0.015	0.530 [0.497–0.564]	0.017	0.525 [0.485–0.565]	0.021
Psychomotor function	0.599 [0.571–0.627]	0.014	0.599 [0.566–0.631]	0.017	0.592 [0.553–0.632]	0.020
Motivation	0.616 [0.588–0.643]	0.014	0.623 [0.591–0.655]	0.016	0.606 [0.567–0.644]	0.020
Sensory perception	0.565 [0.536–0.593]	0.015	0.552 [0.519–0.584]	0.017	0.554 [0.514–0.594]	0.020

Note: Data are presented as AUC of the corresponding receiver operating characteristics curves, together with their 95% confidence intervals.

Abbreviations: MATHyS, Multidimensional Assessment of Thymic States; QIDS-C₁₆, 16-item quick inventory of depressive symptoms; AUC, areas under the curve; SDS, Sheehan Disability Scale.

antipsychotic.¹² In our sample, the psychomotor function and motivation dimension scores also increased toward the normative value and were both over 4 at Week 6. The motivation dimension was the most sensitive to change, the most impaired at baseline, and had the greatest margin for improvement. The other three dimension scores, which were close to the normative value at baseline, improved by <0.5 points.

We observed an association between the increase in MATHyS motivation scores during the first 2 weeks of treatment and antidepressant response and remission measured with the QIDS-C₁₆ at Week 6, indicating that patients who became more motivated early in the treatment course were more likely to respond. Compared to other potential predictors of response and remission evaluated in the same study,¹⁹ this association was less strong than the association between QIDS-C₁₆ score at Week 2 and remission, but of similar size to that of mood quality rated with a visual analog scale. However, this difference is not entirely unexpected, since motivation represents a different psychological construct to mood state. An association between autonomous motivation and treatment response has been demonstrated previously in a study of interpersonal therapy for depression.³² In studies such as ours, it is not possible to address the nature of the association between motivation and treatment response. However, it may be anticipated, for example, that more motivated patients may be more adherent to their medication or may be more prone to develop more positive social interactions.³³ It is possible that motivation is also associated with more rapid spontaneous recovery from depressive episodes in the absence of treatment but, again, this cannot be addressed in studies such as ours.

The findings of this study indicate that assessing motivation, for example with the MATHyS scale, may be a useful adjunct to measuring the evolution of depressive symptoms

in patients starting antidepressant treatment for an MDE. In addition, our study raises the important question of whether behavioral therapies aimed at building motivation, if offered at the time antidepressant medication is initiated, may facilitate a favorable treatment outcome.

This study only evaluated patients treated with agomelatine and there was no comparator group. For this reason, it is not possible to draw any conclusions as to the specificity of this effect. Nonetheless, agomelatine does facilitate dopaminergic activity in mesolimbic and mesocortical pathways,^{34–36} which are believed to be involved with the regulation of motivation.³⁷ In this context it is also relevant to note that agomelatine has also been shown to have a beneficial effect on anhedonia,^{9,38,39} which may also be related to hypoactivity in these same dopaminergic circuits.^{40,41}

The study has a number of strengths and weaknesses. Among the strengths are the large number of patients included and the naturalistic treatment setting. The principal limitations of the study have been described previously¹⁹ and include those inherent to observational studies in general and the possibility of residual effects of previous antidepressant therapy. In addition, the lack of a specific diagnostic workup for the purposes of the study may have led to the inclusion of some patients with bipolar depression, since misdiagnosis of bipolar disorder as MDD is frequent.^{42,43} However, the absence of major departures from the usual state in the emotional reactivity dimension of the MATHyS may argue against this. Finally, there was no active or placebo comparator group in the study, so the specificity of the association between motivation and antidepressant response cannot be addressed.

In conclusion, this study demonstrates the ability of the MATHyS scale to assess impairment in patients experiencing an MDE. Notably, motivation was the dimension the most impaired in depressed patients, but was also the dimension that responded best to treatment and showed the

best predictive value for antidepressant treatment response. Assessing self-reported motivation in addition to depressive symptoms in MDD could offer an interesting approach to monitoring response.

Disclosure

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PG received research grants from Eli Lilly and Servier; honoraria for presentations in congresses from AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, and Servier; participated on advisory board of AstraZeneca, Janssen, Roche, and Servier; has a paid position at University of Paris-Descartes and Sainte-Anne Hospital, and no shares. FJB has received consulting fees within the last 4 years from Servier, Lundbeck, Eli Lilly, Bristol-Myers Squibb, and Janssen. GV received research grants from AstraZeneca; honoraria for presentations in congresses from AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Eli Lilly, and Servier; participated on advisory board of Janssen, Lundbeck, and Servier; has a paid position at University of Lille 2 and Lille University Hospital, and no shares. PC received research grants from Eli Lilly and Servier; honoraria for presentations in congresses from AstraZeneca, Bristol-Myers Squibb, Lundbeck, and Servier; has a paid position at University of Montpellier and CHU Montpellier, and no shares. EC has received consulting fees within the last 4 years from Servier, Lundbeck, Sanofi, Bristol-Myers Squibb, and Eisai. PML has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Euthérapie, Lundbeck, and Sanofi. The authors report no other conflicts of interest in this work.

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