Activation syndrome induced by the antidepressant tianeptine and suicidal ideation: Evidence from a large depressed outpatient sample

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Abstract

Objective: To determine the characteristics of the activation syndrome (AS) that predict the emergence or worsening of suicidal ideation (SI) in the first month of antidepressant treatment with tianeptine, as well as the temporal relationship between both conditions.

Method: A naturalistic sample of 2422 depressed outpatients starting a new antidepressant treatment with tianeptine was assessed at 2, 4 and 6 weeks of follow-up using validated questionnaires. Four main dimensions of AS were examined: impulsivity, sleep problems, anxiety and agitation.

Results: The emergence of an AS was more likely in long-lasting depressive episodes, but less likely if the patient responded to the antidepressant or benzodiazepines were added as an add-on treatment. Treatment-emergent SI was strongly associated to the presence of an AS, particularly in case of sleep problems (OR=8.42) or impulsivity upsurges (OR=3.89), even after adjustment for all relevant confounding factors.

Conclusions: Our findings suggest a dose-effect mechanism modulating the relationship between treatment-related SI and AS. AS symptoms may need to be monitored closely in the weeks that follow the introduction of an antidepressant treatment.

Index words: Suicidal behavior; jitteriness; anxiety; sleep;

Introduction:

Starting in 2004, agencies in several countries have issued regulatory warnings against the prescription of antidepressants in patients under 25 years of age. These warnings are generally based on retrospective analyses of suicidality (not suicide) in antidepressant clinical trials (Courtet and Lopez-Castroman, 2017). Surprisingly, although so-called activation syndrome (AS) has been repeatedly implicated (Amitai et al., 2015), few studies have tried to explore its association with antidepressant-related suicidality. Practicing psychiatrists are well-aware of the risks of behavioral activation when introducing a new antidepressant treatment, which usually appears in the first two weeks of treatment and depends on the dosage. The term AS is also used by scientific literature and health agencies alike (sometimes replaced by anxiety-jitteriness syndrome), but to date there is no operative definition or assessment measure for adults. The U.S. Food and Drug Administration (FDA) defined it using a list of 10 criteria in different dimensions (Harada et al., 2008), including anxiety, agitation, and aggressive-impulsive behavior. Knowledge gaps exist regarding its reported incidence (4-65%), duration (symptoms are usually greater in the first month), and effects on outcome such as early discontinuation or poor response (for review see (Sinclair et al., 2009)). Earlier studies have tried to examine the connection between AS and suicidal outcomes. Retrospective analyses of RCTs with antidepressants, designed to explore efficacity rather than adverse events, have reported that suicidality was associated with AS in children and adolescents (Sharma et al., 2016) but not in adults (Tollefson et al., 1994).

However, research on AS is limited and only a handful of papers have tried to improve its characterization, each of them using different criteria (Sinclair et al., 2009). In pediatric population, a treatment-emergent activation and suicidality assessment profile has been recently developed and validated in patients with obsessive-compulsive disorder (Bussing et al., 2013).

One prospective study examined AS specifically in 301 adult outpatients (Harada et al., 2014). They used FDA criteria to define at least one AS symptom in the 3 months that followed the introduction of an antidepressant treatment, independently of the diagnosis. Only records of major depression predicted AS after adjustment by age, sex, antidepressant type, anxiety disorder or benzodiazepine use. No suicidal behaviors were declared. A retrospective study by the same group (n=2521) found similar results (Harada et al., 2008).

Since clinical characteristics at baseline are poor predictors of subsequent treatment-emergent suicidal ideation (SI), determining the kinetics of AS (a clinical correlate of treatment-emergent SI) and its temporal association with suicidal outcomes could be useful to detect at-risk patients after the introduction of an antidepressant (Coughlin et al., 2016). With this aim, we report here the results of a naturalistic study with a large sample of outpatients that were assessed 15 and 30 days after the introduction of an antidepressant treatment by tianeptine.

Materials and methods:

Participants:

A total of 3771 outpatients with major depression were recruited in primary care settings and psychiatric practices across France in the GENESE study (Voegeli et al., 2016). General practitioners (GPs) and psychiatrists participating in the study were asked to include consecutive patients for whom a new prescription of tianeptine had to be made for a major depression episode (MDE). Tianeptine was at the time when this study took place one of the most prescribed antidepressants among French GPs (Hérique and Kahn, 2009).

Participants in this study were depressed adults of Caucasian ethnicity for genetic purposes, able to speak fluent French, and possessing a social security number. They also needed to fulfill diagnostic criteria for MDE and their symptoms could not be better explained by

substance use or bereavement. In order to ensure inclusion criteria, physicians filled during the first visit of the patient a checklist of DSM-IV criteria for MDE diagnosis (at least 5 out of 9 should be present), and the other inclusion criteria (age above 18 years and Caucasian ethnicity), as well as two questions exploring: 1) the existence of alcohol or substance use disorders, and 2) the experience of bereavement in the last two months associated to MDE diagnoses. Affirmative responses to any of these two questions determined exclusion from the study. The presence of a characterized psychiatric disorder other than MDE was also a criterion for exclusion from the study. Of note, patients with past suicide attempts, present SI, or suicidal risk were included if their clinicians approved outpatient treatment.

All concomitant treatments for current somatic problems or associated symptoms of depression (e.g., sleep and agitation) were permitted based on clinical judgment. For instance, physicians could prescribe or add during follow-up anxiolytics, antipsychotics and/or hypnotics as needed. Any change of antidepressant, an increase in dose or the addition of a benzodiazepine or mood stabilizer was recorded at the last visit. A French research ethics committee approved the study protocol (C.P.P., reference number: 08042). All patients were informed about the study before recruitment and provided a written consent to participate. The study was performed according to French regulatory guidelines and current codes of Good Clinical Practice.

From the initial sample of 3771 participants, 205 did not comply with all inclusion criteria or presented missing data about at least one relevant variable such as age or sex. From the resulting sample of 3566 patients, only those with complete data to calculate the score of AS or SI during the follow-up were included. The final sample was composed by 2422 patients with complete data. Excluded participants (N=1144) were slightly older, and more often female, with lower educational level, and unemployed. They reported a longer duration of MDE, more

previous suicide attempts and more MDEs but were less severely depressed. Among excluded patients with AS data, only one in five presented an AS ($p<0.05$ for all comparisons).

Assessments

At baseline, GPs collected socio-demographic information and psychiatric records, including number of suicide attempts and features of depressive episodes: duration of current MDE, age at onset of first MDE, and total number and duration of previous MDEs. At the last visit, the diagnosis of alcohol use disorder was made according to the judgment of the clinician, in this paper we have used the term "alcohol misuse" to reflect the lack of precision regarding this comorbidity.

The assessment prioritized the collection of self-reported and repeated measures of SI and depression longitudinally, as recommended in a consensus statement (Meyer et al., 2010). Depression and anxiety symptoms, sleep problems and SI were assessed using self-questionnaires at baseline, and then in standard time intervals at week 2, 4 and at a last visit (between day 42 and day 56). No specific scale has been univocally proposed for clinical practice and, as in prior research, we chose to assess SI by using the suicidal item of the self-rated Montgomery-Asberg Depression Rating Scale (MADRS), a valid approach to assess SI (Desseilles et al., 2011). *This item has shown high correlation ($r>0.80$) with the suicide item of the Hamilton Depression Rating Scale, and the first 5 items of the Scale for Suicide Ideation (Ballard et al., 2015).* The self-assessed item 10 of the MADRS-S (Svanborg and Åsberg, 1994) was therefore used as the core variable assessing SI according to the patient. Similarly, a single item of the MADRS was used to evaluate sleep reduction during follow-up. A single item assessment of sleep quality has shown good psychometric properties compared to longer instruments (Snyder et al., 2018). *To our knowledge, the validity of the MADRS item 4 has never been directly tested, but it has been*

frequently used as an outcome of reduced sleep along with specific instruments such as the Pittsburgh Sleep Quality Index (Trivedi et al., 2013). SI (MADRS item 10) and sleep reduction (MADRS item 4) were rated also by GPs at the first and last visit. No other items of the MADRS scale were used in the assessment.

The item on suicidal thoughts assesses the presence of ideas "representing the feeling that life is not worth living, that a natural death would be welcome", and is scored (0) "Enjoys life or takes it as it comes", (2) "Weary of life. Only fleeting suicidal thoughts", (4) "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". The item on sleep reduction assesses "the experience of reduced duration or depth of sleep" and scores (0) "Sleeps as usual", (2) "Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep", (4) "Sleep reduced or broken by at least two hours" and (6) "Less than two or three hours sleep". Intermediate scores (1), (3) and (5) are possible (Montgomery and Åsberg, 1979).

The emergence or worsening of SI was defined by any 1-point increase in the MADRS SI item score between baseline and the time of assessment, as proposed elsewhere (Bondolfi et al., 2010). Changes from 0 to 1 were considered neither as SI emergence nor as SI worsening. Of note, self-reported measures of depression might be better predictors of future suicidal risk than clinician-rated scales (Mann et al. 1999), and patients seem to be more likely to self-report SI rather than communicating them to a clinician (Meyer et al., 2010). For simplicity, treatment emergent and treatment worsening SI will be termed treatment-related SI hereon.

Depression and anxiety were assessed with a French version of the Hospital Anxiety and Depression Scale (HADS) (Friedman et al., 2001), filled by the patients at every time point and re-assessed by the GPs at the final visit. This scale shows good performance and good change-

sensitivity in assessing depression severity in both psychiatric and primary care patients (Friedman et al., 2001). Most factor analyses indicate a two-factor solution in accordance with the subscales for Anxiety (HADS-A) and Depression (HADS-D). This scale was chosen because of its simplicity and good psychometric properties, which have been demonstrated also in outpatient groups (McDowell, 2006). HADS improvement and HADS worsening during follow-up were calculated by a 20% decrease and a 20% increase in HADS score from baseline to the time of the assessment, respectively. The 20% cutoff was decided to establish clinically relevant changes in depression severity (Courtet et al., 2014).

Finally, we used Plutchik's Impulsivity Scale to assess impulsivity. This questionnaire comprises 15 Likert-type items scored from 0 to 3. The final value ranges from 0 to 45. Plutchik's Impulsivity Scale is a short easy-to-apply scale that provides a good measure of impulsivity traits related to suicide risk (Apter et al., 1993). This scale has demonstrated good psychometric properties, with high internal reliability and significant correlation with suicide and violent risk measures (Grosz et al., 1994). We used a validated version in French (Damy et al., 1999).

AS evaluation

Four symptom dimensions, corresponding to the 10 symptoms described by the FDA, were built using the assessments: i) anxiety (anxiety, panic attacks), ii) agitation (agitation, akathisia, hypomania), iii) sleep reduction and, iv) impulsivity (impulsivity, aggressiveness, irritability, hostility). AS was defined according to the following criteria: 1) HADS psychic anxiety score composed by items 3, 5, 9 and 13; 2) HADS agitation score composed by items 1, 7 and 11; 3) Plutchick impulsivity score; 4) sleep reduction score according to the sleep item of the MADRS. For each dimension, one point was assigned when scores increased over >10% from baseline to the time of the assessment. The 10% increase was chosen to maximize the sensitivity

to any change that had some clinical relevance, since it reflects any one-point increase in anxiety, agitation or sleep symptoms or a 4-point increase in Plutchik's score. Score changes in each dimension were calculated according to the following equation:

$$\boldsymbol{\delta} = \frac{\sum items_t - \sum items_{t-1}}{\sum items_{t-1}}$$

Resulting AS scores vary from 0 to 4, scores≥1 were considered positive.

Physicians assessed suicidal acts answering specific questions about the occurrence and the suicidal intent of any suicide attempt during follow-up. Suicide attempts registered in our sample conveyed at least a minimal intent to die in agreement with the definition accepted by the National Institute of Mental Health (Silverman et al., 2007).

Statistical analyses

Univariate logistic regression models were performed to analyze the associations between socio-demographic, clinical and treatment variables assessed at baseline with (1) the onset of SI and (2) the occurrence of an AS. Associations were quantified using odds ratios (OR) and their 95% confidence intervals (CI). For each outcome, multivariate logistic regression models were performed for all variables with p-values <0.15 in the univariate analysis as potential candidates. Significance level was set at $p<0.05$. Analyses were performed using SAS statistical software (version 9.4; SAS Inc, Cary, North Carolina).

Results:

Sample description:

There was a majority of females (n=1457, 60.2%) and mean age was 48.7±14.6 years. Less than half of the participants were in couple (n=1018, 42.2%), and working (n=1066, 44.4%)

at the time of the study. Regarding the maximum level of studies attained, primary studies were the most common (n=1029, 42.8%), followed by university studies (n=757, 31.5%).

In most cases, current MDE started in the 6 months preceding inclusion (2 to 6 months, n=995, 41.9%; less than 2 months, n=793, 33.4%). For half of the patients, the current MDE was the first episode (n=1362, 56.4%). Mean baseline HADS depression score was 14.2±3.7. About 12% of participants had made at least one suicide attempt in their lifetime (n=291).

Concerning tianeptine prescriptions, clinicians followed treatment recommendations. They prescribed a daily dose of 37.5 mg in most cases (n=2060, 85.4%). Some participants (n=288; 11.9%) received lower dosages and only 65 (2.7%) received higher dosages. Participants receiving low dosages were older (54.2±18.2 years; p <0.0001) than those receiving modal (48.0±13.9) or high dosages (49.5±12.6).

AS and SI screening:

One in three patients reported an AS during the first month (760/2422; 31.4%), frequently at the first assessment (n=634, 26.2%). Some participants fulfilled criteria for AS only at day 30 (n=126; 5.2%), and about twice as many at both time points (n=322; 13.3%).

Within those who endorsed an AS at day 15, most of them reported only symptoms in one dimension (n=469, 74.0%), particularly agitation (n=338, 53.3%), or anxiety (n=254, 40.1%). Only 43 participants had symptoms in 3 or more dimensions (6.8%). In total, 96 patients reported AS and SI simultaneously (15.1%) and 62 reported SI but not AS.

At day 30 only one in five participants reported AS symptoms (448/2422, 18.5%). Within those who endorsed an AS, most of them reported only symptoms in one dimension (n=325, 72.5%), particularly agitation (n=222, 49.5%) or anxiety (n=184, 41.1%). Only 30 participants had symptoms in 3 or more dimensions (6.7%). In total, 58 patients reported AS and SI simultaneously (12.9%), and 40 patients reported SI but not AS. To further verify if the

emergence of SI was linked to the presence of AS, we checked out if SI and AS disappeared at the same assessment time. 80.5% of the patients reporting an AS at day 15 but not at day 30 (33/41), saw their SI disappear as well.

At the end of follow-up (day 45), some patients presented a 'new' AS, absent in previous assessments (53/2422, 2.2%). Sixty-one patients reported SI but only 3 patients presented both 'new' AS and 'new' SI at that moment. A total of 285 patients reported the continuation of an AS already present in prior assessments (11.7%).

Factors associated to the emergence of AS after the introduction of tianeptine:

Detailed results can be found in Table 1. Only the significant findings in the univariate analyses are summarized. Several demographic factors, such as age, being in couple, or having a job, were associated with the emergence of an AS in the month following the initiation of an antidepressant treatment. Conversely, an educational level beyond primary school was associated with a protective effect.

AS was more likely when participants had experienced more than one MDE, the depressive disorder was present for more than 6 months or antidepressant treatment had been changed at inclusion. Participants receiving low dosages of tianeptine were more likely to have an AS than those with modal treatment. The use of benzodiazepines as a concomitant treatment showed a protective effect. Concerning baseline scores of depression severity according to the HADS, the higher the score at inclusion, the lower the risk of AS. When we examined the evolution of depression scores until AS emergence, HADS improvement showed a protective effect, while HADS worsening was associated with a higher risk of AS compared to no change. Individuals with a history of suicide attempts were also more likely to present an AS.

Multivariate analyses of factors associated to the emergence of AS:

After adjustment for potential confounders, three factors remained independently associated with an AS (Table 2). A long evolution of the current episode increased the risk of AS. Conversely, the use of benzodiazepines and an improvement in depressive symptomatology during follow-up were associated with a decreased risk of AS, particularly the latter ($p<0.0001$).

Factors associated to treatment-related SI:

Detailed results can be found in Table 3. No socio-demographic factors were associated with the emergence or worsening of SI. Three clinical features increased the risk of treatment-related SI: MDEs lasting for more than 6 months, the presence of an AS and records of prior suicide attempts. Inversely, high baseline scores of depression (HADS), improvement of depression scores during follow-up, and having experienced more than one MDE were associated with less risk of treatment-related SI.

Multivariate analyses of factors associated to the emergence of SI:

After adjustment for potential confounders, three factors remained independently associated with SI (Table 4). Patients experiencing a MDE of intermediate duration (from 2 to 6 months vs. less than 2 months) and especially those presenting an improvement in HADS scores were less likely to report emergent SI ($p<0.0001$). Patients experiencing an AS were more likely to report emergent SI ($p<0.0001$).

Association between features of the AS and treatment-related SI (Table 5, Figure 1)*:*

After adjustment for sex, duration of MDE, more than one MDE, previous suicide attempt, tianeptine dosage, and depression score at baseline (HADS), the presence of AS was still strongly associated with treatment-related SI ($p<0.0001$): i) only 15 days after treatment onset, and ii) both 15 and 30 days after treatment onset.

We also found that the higher the severity of the AS, according to the number of symptomatic dimensions concerned, the higher the risk of treatment-related SI. OR [95% CI]

ranged from 2.33 [1.61;3.37] for those having symptoms of activation in just one dimension, to 10.77 [5.89;19.7] for those having symptoms in 3 or 4 dimensions. Although all symptomatic dimensions were significantly associated with an increased risk for treatment-related SI ($p<0.0001$ in all comparisons), the level of risk varied between them. The highest risks were associated with sleep problems (OR=8.42 [5.78;12.30]) and impulsivity upsurges (OR=3.89 [2.57;5.80]).

To verify which symptomatic dimension was more strongly associated to treatment-related SI, we repeated the analyses adjusting also for any other symptomatic dimensions. The result was that sleep problems and impulsivity upsurges were still strongly associated with SI (OR=6.17 [4.16;9.16] and OR=2.70 [1.73;4.20], respectively, $p<0.0001$ in both cases), anxiety symptoms showed a weaker association (OR=1.61 [1.08;2.40], $p=0.02$) and agitation was no longer associated to SI (OR=1.28 [0.87;1.87], $p=0.22$).

Discussion:

In this naturalistic study we have demonstrated that AS is frequent among depressed individuals starting a new antidepressant treatment. Almost one in three patients presented an AS according to our criteria (760/2422). Harada et al (2014) surveyed a prospective sample after one month of antidepressant treatment using a similar cutoff, the presence of any symptom of AS according to the FDA, and reported an incidence of only 7% (Harada et al., 2014). This large difference could be explained by the use of self-reported measures and a closer follow-up in our study. Our incidence is a mid-range value according to the literature (4-65%), most studies estimate incidences over 20% (Sinclair et al, 2009). Besides, the peak of AS incidence seems to be placed around the second week and then decays rapidly according to most studies (including our own), and this fact probably introduces memory biases in longer follow-up.

Sociodemographic factors suggesting lower social support, as well as clinical factors related to a more severe depressive illness, such as records of suicidality, are associated to a higher likelihood of AS in univariate analyses. However, the regression models indicate that the most relevant factors associated to AS emergence are on one side the persistence of depressive symptoms, i.e. MDE duration beyond 6 months, and on the other side the response to treatment. Thus, clinical improvement and the use of benzodiazepines as an adjuvant treatment seemed to moderate the risk of AS in our sample. The effect of clinical improvement could be partly due to a ceiling effect, severely depressed patients being less likely to see a worsening of symptoms. However, our results show also that a better response leads to less frequent treatment-related SI, and that benzodiazepines treatment, probably prescribed for anxiety or sleep problems, was associated with a reduced likelihood of AS. Might a short-term benzodiazepine prescription at the beginning of the antidepressant treatment attenuate AS symptoms? *The answer is far from clear.* Co-prescription is a common clinical practice, concerning around one-tenth of antidepressant initiators in the US, but the risks associated to benzodiazepine introduction include long-term use, addiction, accidents and poisoning (Bushnell et al., 2017). A recent Cochrane review found that co-prescription was more effective in improving antidepressant response in the early phase only (Ogawa et al., 2019). Besides, there is evidence of an overall increase in the risk of attempting suicide or dying by suicide in persons treated with benzodiazepines, supposedly in part because of an upsurge in impulsive-aggression that facilitates suicidal acts (Dodds, 2017). Future studies are therefore needed to verify this finding and to explore the risk-benefit balance.

Treatment-related SI is associated with similar clinical factors than AS (features of the MDE and previous suicidality), suggesting parallel pathophysiological mechanisms. Indeed, AS is the strongest predictor of treatment-related SI, especially when presenting an early onset (day 15) and persisting along the follow-up (at both assessments). Confirming this view, there seems

to exist a dose-effect mechanism modulating the relationship between treatment-related SI and AS (Figure 2). Increasing severity of AS is associated with similarly increasing risks of treatment-related SI. It should be highlighted that these results are independent of the most relevant factors associated to SI emergence such as treatment response and records of prior suicidal behavior. Indeed, according to the results of the multivariate analysis, treatment-related SI appears to be determined better by the presence of an AS than by prior records of suicidal behavior. Finally, not all symptoms of activation seem to convey the same risk of treatment-related SI. Impulsivity and sleep problems may need to be especially monitored when introducing a new antidepressant since they showed the highest odds of treatment-related SI when all other variables were controlled for.

This is a naturalistic study in a large sample of depressed outpatients. We used broad inclusion criteria to be as close as possible to real clinical practice. However, several limitations should be considered. In the first place, all patients started a tianeptine treatment and therefore our conclusions cannot be generalized to other antidepressants, although there is no evidence of differences in AS depending on antidepressant type (Sinclair et al., 2009). The bulk of the existing literature concerning the association between AS and antidepressant-emergent SI have studied SSRIs or TCAs. Tianeptine is a selective serotonin reuptake promoter structurally similar to tricyclic antidepressants but with very different pharmacological properties. Indeed, contrary to tricyclic antidepressants and SSRIs, tianeptine produces no serotonin recapture (Uzbay, 2008). Tianeptine's antidepressant and anxiolytic effects seem to derive from the modulation of dopamine transmission, a normalization of glutamatergic neurotransmission, and an opioid agonism that produces analgesic activity (Invernizzi et al., 1992). Tianeptine also seems to have memory-protective effect and anti-stress properties on the brain by facilitating neuroplasticity processes (Uzbay, 2008; Zoladz et al., 2008). In an independent sample of depressed outpatients,

we have recently shown preliminary evidence of a reduced risk of treatment-emergent SI with tianeptine compared to other antidepressants, which could be related to its analgesic activity (Nobile et al., 2017). In the present study, an effect dose-response was not observed after adjustment for other factors. Larger doses of tianeptine were not associated with more frequent suicidal ideas or AS.

A second limitation of our study is the creation of an *ad hoc* definition of AS. There is no currently valid definition of AS and there is very little agreement about the constituent symptoms of AS in the literature (Sinclair et al., 2009), so we grounded our definition on the criteria proposed by the FDA. We were able to calculate a severity score for each of four main dimensions of the AS but some FDA's criteria, such as (hypo)manic symptoms and irritability/hostility, are only partially reflected by these dimensions. Of note, only the FDA included (hypo)manic symptoms among the constituent symptoms of AS. For simplicity we also discuss our results assuming that AS produces SI. This might not be completely true since SI (or overall worsening) may cause sleeplessness or anxiety.

The exclusion of patients with missing data on AS or SI (32%) may have partially biased our results. These patients had lower socio-economic position and a longer history of depression (longer duration of MDE, more lifetime suicide attempts and more MDEs), which could imply a greater risk for AS and decrease the generalizability of the results. However, AS was less frequent among excluded patients for whom it was possible to calculate this outcome than among included patients. Since the data seemed not to be missing at random, we avoided the use of multiple imputation methods.

We decided to focus our study on a reduced time-frame of one month based on the evidence that AS appears during this period, sometimes within hours (Nakamura et al., 2017), and rapidly decreases afterwards (Sinclair et al., 2009). In our sample, although 285 patients

(11.7%) maintained criteria for AS at the last assessment, day 45, for a large majority of them AS onset happened during the first month of treatment (97.8%). In most studies, the peak of treatment-related SI falls also within the 4 first weeks (Courtet et al., 2014; Perlis et al., 2007), and this lapse corresponds to the time needed to confirm a positive response after the introduction of a new antidepressant treatment. We could not study the association of AS with suicide attempts since only 10 patients (0.4%) reported a suicide attempt during the follow-up (of whom 50% endorsed an AS).

Although many authors and clinicians consider that AS is a risk factor for treatment-related SI and suicide attempts, very little research has been specifically focused on their association. Our results suggest that the precocity, length and severity of AS symptoms are strongly associated with more frequent SI. This seems to be particularly the case for sleep problems, and to a lesser degree for increased impulsivity, symptoms that may need to be monitored closely in the weeks that follow the introduction of an antidepressant treatment. Alternative therapies to antidepressants should also be considered more widely, even by GPs.

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Jorge Lopez-Castroman reports no financial relationships with commercial interests.
Isabelle Jaussent reports no financial relationships with commercial interests.

Philip Gorwood:
Interest Name of Organisation

Grant	Eli Lilly, Servier.
Honoraria	AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Servier.
Advisory board	AstraZeneca, Janssen, Servier, Wyeth

Philippe Courtet:

Interest	Name of Organisation
Grant	Eli Lilly, Servier.
Honoraria	AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Servier.
Advisory board	Servier

Contributors

Jorge Lopez-Castroman, Isabelle Jaussent, and Philippe Courtet conceived and designed the study. Jorge Lopez-Castroman drafted the manuscript and managed the literature searches and analyses. Isabelle Jaussent performed the statistical analysis and analyzed and interpreted the data. Phillip Gorwood and Philippe Courtet helped to draft the manuscript and to analyze and interpret the data. All authors revised the article critically. All authors read and approved the final manuscript. There is no one else who fulfils the criteria but has not been included as an author.

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Figure 1. Evolution of activation syndrome, treatment-related suicidal ideation and HADS score (with confidence interval) along the follow-up.

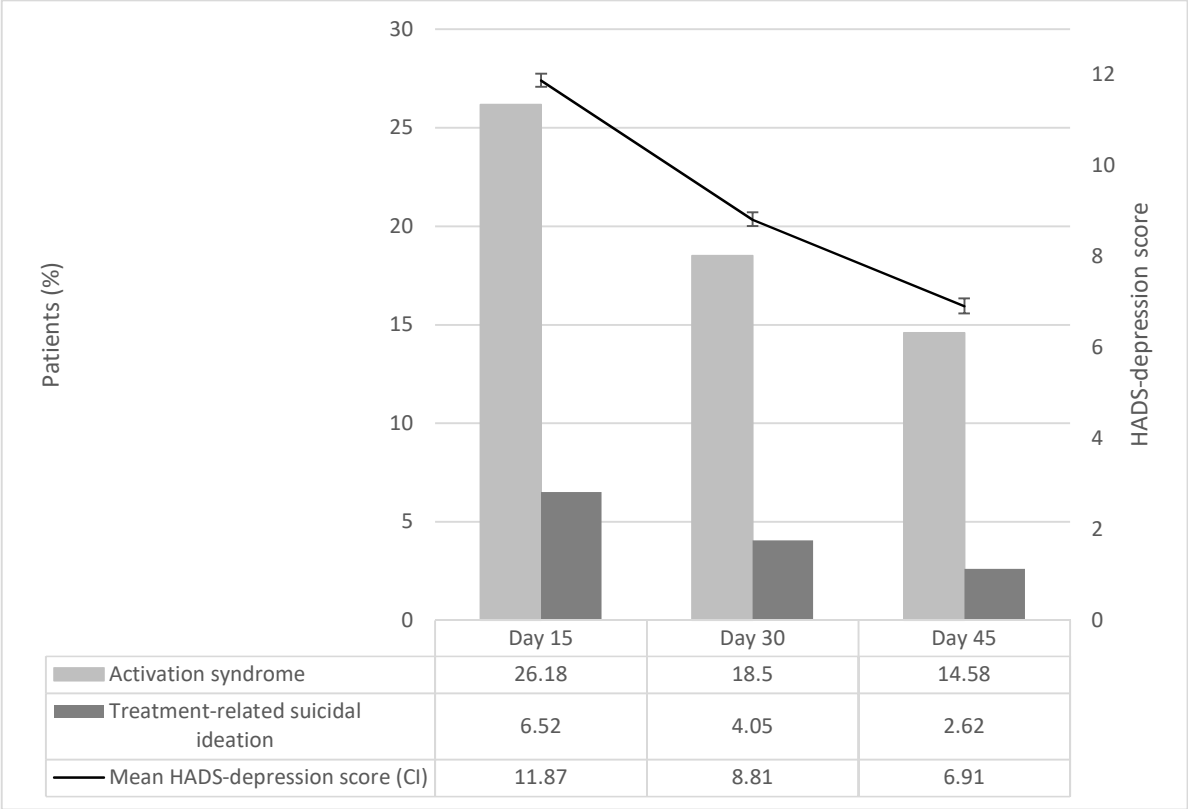

Figure 2. Association of treatment-related suicidal ideation during follow-up with the number of symptoms and the type of clinical dimension in activation syndrome (Odds Ratios and 95% Confidence Intervals). The horizontal line indicates the reference group, composed by participants without activation syndrome.

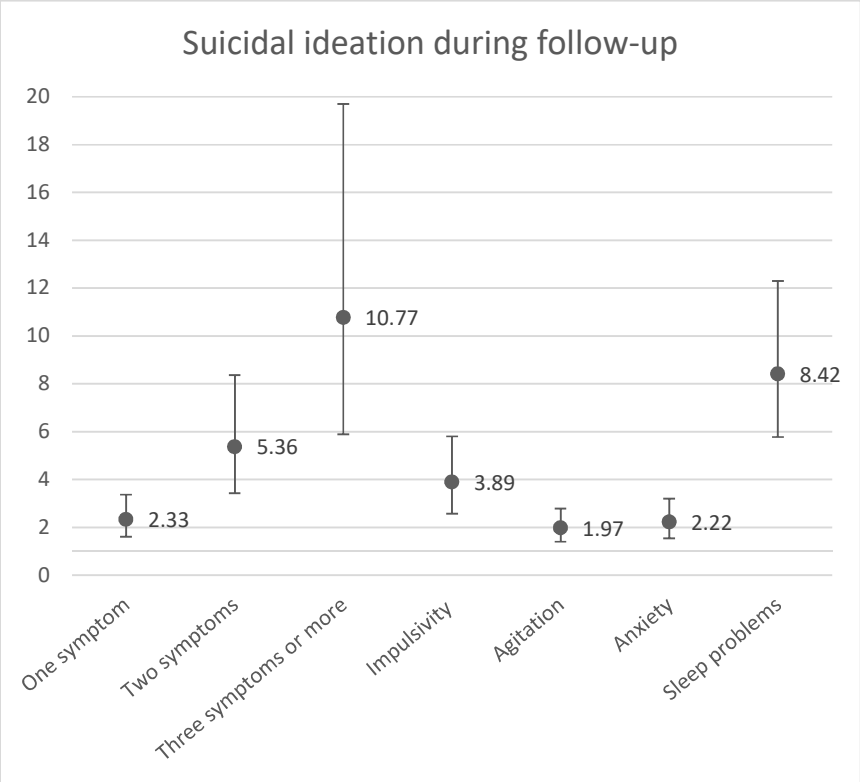

Table 1. Factors associated with the emergence of an activation syndrome 15 and/or 30 days after the initiation of an antidepressant treatment.

	Activation syndrome in the first month of treatment					
	No N=1662		*Yes N=760*		*OR [95% CI]*	*P-value*
Variable	*n*	*%*	*n*	*%*		
Female gender	984	59.21	473	62.24	1.14 [0.95;1.35]	0.16
Age (years), *mean (SD)*	48.34 (14.42)		49.73 (14.87)		1.07 [1.01;1.13] (1)	**0.03**
In couple	676	40.77	342	45.06	1.19 [1.00;1.42]	**0.05**
Study level						
Primary school	673	40.76	356	47.09	1	**0.01**
Secondary school	444	26.89	177	23.41	0.75 [0.61;0.94]	
University studies	534	32.34	223	29.50	0.79 [0.64;0.97]	
Working currently	700	42.53	366	48.41	1.27 [1.07;1.51]	**0.007**
Onset of MDE						
Less than 2 months	565	34.60	228	30.65	1	**<0.0001**
2-6 months	718	43.97	277	37.23	0.96 [0.78;1.18]	
More than 6 months	350	21.43	239	32.12	1.69 [1.35;2.12]	
More than one MDE	687	41.46	366	48.28	1.32 [1.11;1.57]	**0.002**
Change of treatment	273	16.58	174	23.08	1.51 [1.22;1.87]	**0.0002**
Daily tianeptine intake levels, mg						
<37.5	178	10.74	110	14.55	1.42 [1.10 ;1.83]	**0.03**
37.5	1435	86.60	625	82.67	1	
>37.5	44	2.66	21	2.78	1.10 [0.65;1.86]	
Treatment associated						
No	710	42.72	357	46.97	1	**0.05**
Yes, mood stabilizer	28	1.68	21	2.76	1.49 [0.84;2.66]	
Yes, benzodiazepines	877	52.77	361	47.50	0.82 [0.69;0.98]	
Yes, both	47	2.83	21	2.76	0.89 [0.52;1.51]	
Baseline score of depression (HAD)	14.66 (3.56)		13.38 (4.02)		0.91 [0.89;0.93]	**<0.0001**
Previous suicide attempt	176	10.60	115	15.13	1.50 [1.17;1.94]	**0.002**
Change in depression score (HADS) from baseline to emergence of AS						
Improvement	1543	92.84	474	62.37	0.18 [0.13;0.25]	**<0.0001**
No change	67	4.03	114	15.00	1	

	Activation syndrome in the first month of treatment					
	No N=1662		*Yes N=760*		*OR [95% CI]*	*P-value*
Variable	*n*	*%*	*n*	*%*		
Worsening	52	3.13	172	22.63	1.94 [1.26;3.00]	

[(1)] OR for 10-year increase
BZD : Benzodiazepine; MDE: Major Depression Episode; HADS: Hospital Anxiety and Depression scale.

Table 2. Multivariate analysis on 705 patients presenting an activation syndrome vs. 1541 without activation syndrome.

Variable	*OR [95% CI]*	*P-value*
Age (years)	1.03 [0.96;1.11][(1)]	0.41
In couple	1.13 [0.92;1.38]	0.25
Study level		
Primary school	1	0.55
Secondary school	0.87 [0.68;1.12]	
University studies	0.94 [0.74;1.20]	
Working currently	1.04 [0.84;1.30]	0.71
Onset of MDE		
Less than 2 months	1	**0.003**
2-6 months	0.82 [0.65;1.03]	
More than 6 months	1.26 [0.97;1.64]	
More than one MDE	1.10 [0.88;1.36]	0.41
Change of treatment	1.25 [0.96;1.63]	0.10
Daily tianeptine intake levels, mg		
<37.5	1.34 [0.99;1.80]	0.15
37.5	1	
>37.5	1.09 [0.61;1.95]	
Treatment associated		
No	1	**0.04**
Yes, mood stabilizer	1.45 [0.76;2.78]	
Yes, benzodiazepines	0.80 [0.65;0.97]	
Yes, both	0.68 [0.36;1.27]	
Previous suicide attempt	1.12 [0.82;1.54]	0.48
Change in depression score (HADS) from baseline to emergence of AS		
Improvement	0.19 [0.13;0.26]	**<0.0001**
No change	1	
Worsening	1.97 [1.25;3.09]	

[(1)] OR for a 10-year increase
MDE: Major Depression Episode.
HADS: Hospital Anxiety and Depression scale.

Table 3. Factors associated with the emergence or worsening of suicidal ideation (SI) in the month after the initiation of tianeptine treatment.

	Treatment-related SI in the first month					
	No *N=2233*		*Yes* *N=189*		*Unadjusted model*	
Variable	*n*	*%*	*n*	*%*	*OR [95% CI]*	*P-value*
Female gender	1332	59.65	125	66.14	1.32 [0.97;1.81]	0.08
Age (years), *mean (SD)*	48.73 (14.59)		49.37 (14.41)		1.03 [0.93;1.14] (1)	0.56
In couple	929	41.70	89	47.09	1.24 [0.92;1.68]	0.15
Study level						
Primary	940	42.34	89	47.59	1	0.37
Secondary	578	26.04	43	22.99	0.79 [0.54;1.15]	
University studies	702	31.62	55	29.41	0.83 [0.58;1.17]	
Working currently	975	44.06	91	48.15	1.18 [0.88;1.59]	0.28
Onset of MDE						
Less than 2 months	730	33.35	63	33.51	1	**0.0005**
2-6 months	937	42.80	58	30.85	0.72 [0.50;1.04]	
More than 6 months	522	23.85	67	35.64	1.49 [1.04;2.14]	
More than one MDE	949	42.59	104	55.61	1.69 [1.25;2.28]	**0.0006**
Change of treatment	408	18.44	39	20.74	1.16 [0.80;1.67]	0.44
Daily tianeptine intake levels, mg						
<37.5	257	11.55	31	16.49	1.53 [1.01;2.29]	0.12
37.5	1909	85.80	151	80.32	1	
>37.5	59	2.65	6	3.19	1.29 [0.55;3.03]	
Treatment associated						
No	981	43.93	86	45.50	1	0.54
Yes, mood stabilizer	45	2.02	4	2.12	1.01 [0.36;2.89]	
Yes, benzodiazepines	1141	51.10	97	51.32	0.97 [0.72;1.31]	
Yes, both	66	2.96	2	1.06	0.35 [0.08;1.44]	
Previous suicide attempt	256	11.47	35	18.52	1.75 [1.19;2.59]	**0.005**
Baseline score of depression (HADS)	14.32 (3.73)		13.44 (3.91)		0.94 [0.91;0.98]	**0.002**
Change in depression score (HADS) from baseline to emergence of SI						
Improvement	2000	89.57	99	52.38	0.15 [0.10;0.24]	**<0.0001**
No change	112	5.02	36	19.05	1	

Worsening	121	5.42	54	28.57	1.39 [0.85;2.28]	
Activation syndrome at SI onset	636	28.48	115	60.85	3.90 [2.87;5.30]	**<0.0001**

(1) OR for a 10-year increase
MDE: Major Depression Episode.
HADS: Hospital Anxiety and Depression scale.
SI: Suicidal ideation

Table 4. Multivariate analysis on 180 patients presenting an emergence or worsening of suicidal ideation (SI) in the month after the initiation of tianeptine treatment vs. 2114 without.

	Adjusted model	
Variable	*OR [95% CI]*	*P-value*
Female gender	1.25 [0.89;1.75]	0.20
Onset of MDE		
Less than 2 months	1	**0.04**
2-6 months	0.64 [0.43;0.95]	
More than 6 months	1.01 [0.68;1.50]	
More than one MDE	1.39 [0.98;1.96]	0.06
Previous suicide attempt	1.20 [0.76;1.88]	0.44
Daily tianeptine intake levels, mg		
<37.5	1.28 [0.82;2.01]	0.53
37.5	1	
>37.5	1.19 [0.48;2.95]	
Change in depression score (HADS) from baseline to emergence of SI		
Improvement	0.19 [0.12;0.30]	**<0.0001**
No change	1	
Worsening	1.18 [0.70;1.99]	
Activation syndrome at SI onset	2.45 [1.76;3.42]	**<0.0001**

(1) OR for a 10-year increase
MDE: Major Depression Episode.
HADS: Hospital Anxiety and Depression scale.

Table 5. Association between activation syndrome (AS) and the emergence or worsening of suicidal ideation (SI) in the month after the initiation of tianeptine treatment.

	Treatment-related SI in the first month							
	No N=2233		*Yes N=189*		*Unadjusted model*		*Adjusted model*	
Variable	*n*	*%*	*n*	*%*	*OR [95% CI]*	*P-value*	*OR [95% CI]*	*P-value*
Activation syndrome	636	28.48	115	60.85	3.90 [2.87;5.30]	**<0.0001**	3.43 [2.50;4.70]	**<0.0001**
Activation syndrome								
Never present	1597	71.52	74	39.15	1	**<0.0001**	1	**<0.0001**
Only at day 15	264	11.82	41	21.69	3.35 [2.24;5.02]		3.17 [2.10;4.78]	
Only at day 30	115	5.15	9	4.76	1.69 [0.82;3.46]		1.50 [0.73;3.08]	
At both assessments	257	11.51	65	34.39	5.46 [3.81;7.81]		4.60 [3.16;6.69]	
Severity of activation syndrome								
0	1597	71.52	74	39.15	1	**<0.0001**	1	**<0.0001**
1	468	20.96	55	29.10	2.54 [1.76;3.65]		2.33 [1.61;3.37]	
2	129	5.78	38	20.11	6.36 [4.13;9.78]		5.36 [3.43;8.37]	
3-4	39	1.75	22	11.64	12.17 [6.87;21.6]		10.77 [5.89;19.7]	
Dimensions of activation syndrome								
Impulsivity	135	6.05	40	21.16	4.17 [2.82;6.16]	**<0.0001**	3.89 [2.57;5.80]	**<0.0001**
Agitation	360	16.12	58	30.69	2.30 [1.66;3.20]	**<0.0001**	1.97 [1.40;2.78]	**<0.0001**
Anxiety	279	12.49	51	26.98	2.59 [1.83;3.65]	**<0.0001**	2.22 [1.54;3.20]	**<0.0001**
Sleep problems	103	4.61	59	31.22	9.39 [6.51;13.5]	**<0.0001**	8.42 [5.78;12.30]	**<0.0001**

Adjusted model: adjustment for sex, duration of Major Depression Episode (MDE), more than one MDE, previous suicide attempt, depression score at baseline according to the HADS (Hospital Anxiety and Depression scale) and daily tianeptine intake levels.