Trajectories of Suicidal Ideation During 12 Weeks of Escitalopram or Nortriptyline Antidepressant Treatment Among 811 Patients With Major Depressive Disorder

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ABSTRACT

Background: Suicidal ideation is a frequent and difficult-to-treat clinical challenge among patients with major depressive disorder (MDD). However, little is known regarding the differential development during antidepressant treatment and whether some patients may suffer from persistent suicidal ideation.

Methods: Among 811 patients with Schedules for Clinical Assessment in Neuropsychiatry (SCAN)–verified MDD from 2004–2007 assessed weekly for 12 weeks of escitalopram or nortriptyline antidepressant treatment, we applied item response theory to integrate a suicidality score based on 3 rating scales. We performed latent growth mixture modeling analysis to empirically identify trajectories. Multinomial logistic regression analyses estimated associations with potential predictors.

Results: We identified 5 distinct classes of suicidal ideation. The *Persistent-low* class (53.7%) showed no suicidal ideation whereas the *Persistent-high* class (9.8%) had high suicidal ideation throughout 12 weeks. Two classes showed a fluctuating course: the *Fluctuating* class (5.2%) ended at a low level of suicidal ideation, whereas the *Slow-response-relapse* class (4.8%) initially responded slowly but then experienced a large increase to a high level of suicidal ideation after 12 weeks. The *Fast-response* class (26.5%) had a high baseline severity similar to the *Persistent-high* class but responded quickly within a few weeks and remained at a low level. Previous suicide attempts and higher mood symptom severity were associated with worse suicidal ideation trajectories, whereas living with a partner showed a trend toward better response.

Conclusion: Approximately 1 of 5 patients with MDD showed high or fluctuating suicidal ideation despite antidepressant treatment. Studies should investigate whether suicidal ideation may persist for longer periods and more targeted treatment possibilities.

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Suicide is a major health care problem with approximately 800,000 suicides each year worldwide,[1] and suicide is often preceded by depression.[2] Suicidal thoughts are an important risk factor for suicidal behavior and represent a frequent, dangerous, and difficult-to-treat challenge in patients with major depressive disorder (MDD).[3–5] Nevertheless, little is known regarding the development and persistence of suicidal thoughts among patients with MDD, including clinically relevant predictors for different trajectories of suicidal ideation and whether different treatment approaches may have better effects.

The method of latent growth mixture modeling has been increasingly used in psychiatric research to model heterogeneity in the course of symptoms over time.[6–13] This approach can identify subgroups sharing similar symptom trajectories instead of yielding 1 mean for the entire group of patients. Several studies among patients with MDD have identified different trajectories for depressive symptoms,[6,7,9] showing clinically important results such as subgroups with late response to antidepressant medication.[7]

However, previous trajectory studies focused on overall depressive symptomatology and did not specifically explore suicidal thoughts.[6,7] One study[10] found that 6.3% of 468 patients with MDD had high and

Clinical Points

- Suicidal ideation is a frequent and difficult-to-treat symptom in depression, but little is known regarding its development and response during antidepressant treatment.
- Among 811 individuals with moderate to severe depression treated with antidepressants for 12 weeks, 1 of 5 patients experienced a course with high or fluctuating suicidal ideation.
- Clinicians should place specific focus on individuals with previous suicide attempts and higher severity of mood symptoms to monitor those patients for less response on suicidal ideation.

persistent suicidal ideation during 16 weeks of antidepressant treatment; however, this study only included individuals aged 60 years or older who were treated with venlafaxine, thus investigating a selected study population while yielding no possibility to compare different treatments. It is important to investigate whether patterns with high or fluctuating suicidal thoughts despite treatment also exist in younger depressed patients in order to better be able to identify and treat these individuals. The finding by Kasckow et al[10] is in line with studies in psychosis[11] and bipolar disorder[13] showing that 7%–14% of patients suffer from persistent suicidal ideation despite relevant treatment. However, the few studies[10,11,13] that explored the trajectories of suicidal thoughts had rather small study populations. The importance of large study populations to identify small but still clinically relevant trajectory groups has been emphasized.[6,7] Furthermore, prior studies[10,11,13] had few assessments over time and used a single question from 1 scale, which gave little opportunity to perform very detailed and advanced trajectory analyses yielding limitations since no scale alone has been proven sufficient to measure suicidal ideation.[14]

Our primary aim was to identify trajectories of suicidal ideation among 811 patients with MDD who were monitored weekly during 12 weeks of treatment with the selective serotonin reuptake inhibitor (SSRI) escitalopram or the tricyclic antidepressant (TCA) nortriptyline. Furthermore, we aimed to explore whether specific baseline variables (including treatment arm) predicted membership of the different trajectory classes.

METHODS

Setting

The present study reports secondary analyses from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study, a European multicenter, open-label randomized clinical trial conducted from 2004–2007,[14] comparing escitalopram and nortriptyline treatment for 12 weeks. The study was approved by the research ethics boards of all 9 participating countries, and participants provided informed consent. The study was registered at http://www.isrctn.com (Identifier: ISRCTN03693000).

Participants

The GENDEP study recruited 811 adults with an MDD diagnosis, established with the semistructured Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview.[15] Patients had to be at least moderately depressed and were diagnosed in an in- or outpatient setting.[16] GENDEP had broad inclusion and minimal exclusion criteria. Exclusion criteria were a family history of bipolar affective disorder or schizophrenia in first-degree relatives and a personal psychiatric history of bipolar affective disorder, schizophrenia, mood incongruent psychotic symptoms, primary substance misuse, or a primary organic disease. All individuals initiated treatment with either escitalopram or nortriptyline. Of the 811 individuals, a total of 468 were randomly allocated to either escitalopram or nortriptyline (a detailed description and the flowchart are shown in Uher et al[16]). The remaining 343 individuals had contraindications to either escitalopram or nortriptyline and were therefore nonrandomly treated with the other study drug, resulting in a total of 458 individuals treated with escitalopram and 353 treated with nortriptyline. No other psychotropic treatment, except for occasional use of hypnotics, was allowed.

Suicidal Ideation

Participants were assessed at baseline and 12 weekly follow-up visits with the Montgomery-Åsberg Depression Rating Scale (MADRS),[17] the 17-item Hamilton Depression Rating Scale (HDRS),[18] and the self-reported Beck Depression Inventory (BDI).[19] The ratings were performed by trained psychiatrists and psychologists with high interrater reliability,[14] and weekly data were 92.9% complete.[16] The possible answers on the suicidal ideation items from the 3 rating scales are shown in Supplementary Table 1.

In a prior study[14] on the GENDEP sample, we have shown that there is imperfect correspondence in the content and number of response options between the 3 rating scales, and no single scale is optimal to measure suicidal ideation. Therefore, we applied the item response theory (IRT) graded response model to derive the best estimate of suicidal ideation from the suicide items of the 3 scales. The advantage of IRT is the integration of all available data and a less biased estimate despite missing values. In a previous study,[20] we have in detail presented the IRT approach for suicidal ideation on the GENDEP data. Briefly, the IRT-derived standardized composite score (θ) of suicidal ideation (ranging from −0.425 to 3.241) correlated 0.97, 0.92, and 0.77 with MADRS, HDRS, and BDI suicidal items, respectively. A score of 0 on all 3 scales corresponded to −0.425 on the standardized IRT θ scale, and we defined significant suicidal ideation as an IRT score of at least 1 standard deviation (SD) above 0, meaning an IRT score ≥0.575 was considered as significant suicidal ideation. On the basis of this definition, 473 participants reported significant suicidal ideation at baseline with the majority (67%) reporting suicidal ideation on all 3 measures.

Covariates

On the basis of prior studies,[10–13] we included the following baseline sociodemographic and clinical covariates: sex, age (continuous), age at first depressive episode (continuous), duration of current depressive episode (weeks, continuous), severity of mood symptoms (based on the IRT approach, which included the mood symptoms from the MADRS, HDRS, and BDI, as described previously[14]), marital status (living with a partner vs living without a partner), educational level (years, continuous), occupational status (employed vs not employed), number of depressive episodes (0 vs 1+), previous suicide attempts (0 vs 1+), whether patients were randomized to treatment or nonrandomly assigned (the latter being due to a history of nonresponse, side effects, or contraindications to 1 of the study medications), and treatment group (escitalopram vs nortriptyline).

Statistical Analysis

We used Mplus Editor (version 7.4; www.statmodel.com) to perform growth mixture modeling (GMM).[21] Information on suicidal ideation collected at up to 13 assessments was applied in GMM analyses to identify trajectories of suicidal thoughts and to establish whether subgroups existed within the population. GMM is a data-driven approach where trajectories are customized and possible subgroups are identified based on prototypical patterns in slope and intercepts. We applied GMM models with linear, quadratic, and cubic terms. Due to nonconvergence, we kept the within-group variance fixed for the quadratic and cubic terms. We then compared the different class models in terms of fit estimates (Bayesian information criterion [BIC], adjusted BIC, and Akaike information criterion [AIC]), where a lower value indicates a better fit of the data. Additionally, in our assessment of best model, we took into account class sizes, entropy, and clinical utility and estimated the bootstrap likelihood ratio test (BLRT), the Lo-Mendell-Rubin likelihood ratio test, and the Vuong-Lo-Mendell-Rubin likelihood ratio test, which all test whether the model with n number of classes fits the data better than a model with $n-1$ classes.[21]

After selecting the model with the best fit, we investigated predictors of class membership including all baseline covariates. When testing whether predictors were associated with class membership, covariates (ie, possible predictors) were treated as auxiliary variables and did not affect the formation of classes, but their association with the latent classes was tested on the basis of the probabilistic nature of class assignments.[22] We performed univariable multinomial logistic regression analyses and estimated associations between each predictor variable and latent class membership. Subsequently, we performed multivariable multinomial regression analyses including all of the significant ($P<.05$) covariates from the univariable analyses. Results from the logistic regression analyses are reported as odds ratios (OR) including 95% confidence intervals (95% CI).

Finally, to show the development of depressive symptoms, we calculated the mean MADRS scores before and after treatment, including the percentage of patients who achieved response (≥ 50% reduction in MADRS score) and remission (MADRS score ≤ 7).

Table 1. Baseline Characteristics for the GENDEP Study Population (N = 811)

Characteristic	Frequency
Female, n (%)	514 (63.4)
Age, y, mean (SD)	
Age	42.5 (11.8)
Age at first depressive episode	32.1 (10.7)
Marital status, n (%)	
Living without a partner	343 (42.3)
Living with a partner	468 (57.7)
Education, y, mean (SD)	12.2 (3.1)
Occupation, n (%)	
Unemployed	335 (41.3)
Employed	476 (58.7)
Number of depressive episodes, n (%)	
1	325 (40.1)
2+	486 (59.9)
Mean (SD)	1.73 (0.68)
Duration of current episode, wk, mean (SD)	21.5 (17.2)
Previous suicide attempts, n (%)	146 (18.0)
Treatment arm, n (%)	
Escitalopram	457 (56.3)
Nortriptyline	354 (43.7)
Severity, mean (SD)	
HDRS	21.7 (5.3)
MADRS	28.7 (6.8)
BDI	28.0 (9.7)
Mean (SD) IRT score suicidal ideation	0.80 (0.77)

Abbreviations: BDI = Beck Depression Inventory, GENDEP = Genome-Based Therapeutic Drugs for Depression study, HDRS = 17-item Hamilton Depression Rating Scale, IRT = item response theory, MADRS = Montgomery-Åsberg Depression Rating Scale.

RESULTS

Table 1 shows the baseline characteristics of the study population, and Table 2 shows the goodness-of-fit statistics from the GMM analyses.

We chose the model that included a cubic term because its fit estimates were better than those of the models including only linear or quadratic terms. We calculated cubic GMM models from 1 to 6 classes, keeping the variance around the quadratic and cubic terms fixed, and decided that the 5-class model represented the best fit of our data. All fit estimates showed large drops when adding 1 to 5 additional classes into the model. All P values were significant, and the 5-class model showed the highest entropy (0.74). In addition, even when increasing the number of random starts, the best log-likelihood was not replicated in the 6-class model due to local maxima problems.

Trajectories of Suicidal Ideation

The 5 distinct classes of suicidal ideation during the 12-week treatment period are illustrated in Figure 1, and the estimated means and observed individual values by class are shown in Supplementary Figure 1.

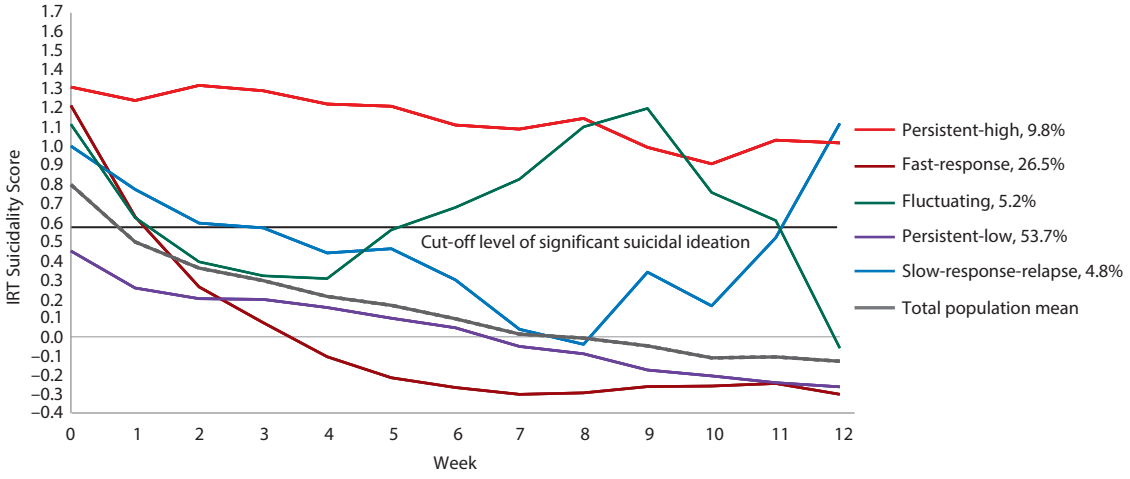
The *Persistent-low* class (53.7%) was the only class showing no significant mean suicidal ideation at baseline (ie, below a mean IRT score of 0.575) and improved further during the entire study period. The *Persistent-high* class (9.8%)

Table 2. Goodness-of-Fit Statistics for 1 to 5 Classes for the Cubic Growth Mixture Modeling Analyses[a]

No. of Classes	Fit Estimates[b]			Classification Quality			BLRT[f]	Vuong-Lo-Mendell-Rubin	Lo-Mendell-Rubin
	AIC	BIC	Adj BIC	Entropy[c]	Class Accuracy[d]	Class Size[e] (%)			
1	10,453	10,547	10,484	…	…	100.0	…		
2	10,210	10,328	10,248	0.58	84/89	32/68	**<.0001**	**<.0001**	**.0001**
3	9,970	10,111	10,016	0.68	85/87/81	14/58/28	**<.0001**	.1835	.1901
4	9,838	10,001	9,891	0.73	86/84/86/82	4/12/56/28	**<.0001**	.2175	.2250
5	9,722	9,910	9,783	0.74	83/85/85/81/96	10/54/5/26/5	**<.0001**	**.0448**	**.0479**
6	Not converging—best log-likelihood not replicated								

[a]Boldface type indicates statistical significance.
[b]A significant *P* value indicates that the model with *n* number of classes is a better fit of the data compared to a model with *n* – 1 number of classes.
[c]Entropy is estimated based on the average posterior probability and ranges from 0 to 1, where higher estimates represent greater classification accuracy for the overall model.
[d]Expresses the average accuracy of membership classification in each class. As the entropy measure it ranges from 0 to 1, where higher estimates represent greater classification accuracy.
[e]Distribution of total sample into identified classes based on the posterior probability. Percentages presented in integers.
[f]Statistical information criteria. A lower value indicates a better fit.
Abbreviations: Adj BIC = sample-size–adjusted BIC, AIC = Akaike information criteria, BIC = Bayesian information criteria, BLRT = bootstrap likelihood ratio test. Symbol: … = not applicable.

Figure 1. The Identified 5-Class GMM Trajectory Model Displaying the Status of Suicidal Ideation Among 811 Patients With MDD Throughout 12 Weeks of Antidepressant Treatment (IRT score > 0.575 represents significant suicidal ideation)[a]



[a]The IRT suicidality score was based on the suicidal ideation items from 3 rating scales (see Supplementary Table 1). The percentage in the legend represents mean percent of the score.
Abbreviations: GMM = growth mixture modeling, IRT = item response theory, MDD = major depressive disorder.

had the highest mean baseline value and was characterized by constant, high suicidal ideation during the 12 weeks of antidepressant treatment. The remaining 3 classes, the *Fluctuating* (5.2%), *Slow-response-relapse* (4.8%), and *Fast-response* (26.5%) classes, had high mean baseline levels of suicidal ideation a bit lower than the *Persistent-high* class, but all showed very different developments. The *Fluctuating* class responded within 2 weeks to no significant suicidal ideation but experienced an increase from week 4 to week 9 to a level higher than the *Persistent-high* class. However, it decreased again to a low level during the last 3 weeks. The *Slow-response-relapse* class responded slowly during the first 8 weeks to a level similar to the *Persistent-low* class but experienced a subsequent steep increase to the same level as the *Persistent-high* class. Finally, the *Fast-response* class responded quickly within the first few weeks and remained at a very low level.

In addition, we found that the *Persistent-high, Fluctuating,* and *Slow-response-relapse* classes responded worse to antidepressant treatment in general, as indicated by higher MADRS scores at the end of treatment and lower remission and response rates (Supplementary Table 2).

Predictors of Class Membership

In the univariate analyses, we found the following covariates to be significantly associated with class membership: increasing age, being employed, higher mood symptom severity, living without a partner, drug allocation, and previous suicide attempts (all $P < .05$).

These covariates were included in the multivariate analyses. First, we used the *Persistent-low* class as the reference class (Table 3). We found that previous suicide attempts and higher mood symptom severity were significantly associated with membership in all the other classes. In addition, living

Table 3. Multivariate Analyses Showing Associations Between Potential Predictors and Trajectory Class Membership Using the *Persistent-low* Class as the Reference[a]

	Fast-response Class		*Slow-response-relapse* Class		*Persistent-high* Class		*Fluctuating* Class	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age at baseline	0.97 (0.95–1.00)	.037	1.01 (0.97–1.06)	.59	0.99 (0.95–1.02)	0.43	1.02 (0.98–1.05)	.34
Marital status								
Living without a partner	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Living with a partner	0.87 (0.50–1.51)	.63	1.03 (0.44–2.43)	.93	**0.42 (0.20–0.91)**	**0.03**	0.58 (0.24–1.39)	.22
Occupation								
Unemployed	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Employed	0.83 (0.49–1.42)	.50	0.88 (0.37–2.09)	.77	0.49 (0.23–1.03)	0.06	0.70 (0.26–1.87)	.47
Treatment arm								
Nortriptyline	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Escitalopram	1.23 (0.74–2.04)	.41	1.08 (0.43–2.70)	.88	0.68 (0.33–1.37)	0.28	0.93 (0.38–2.32)	.88
Previous suicide attempts								
No	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	**3.09 (1.42–6.70)**	**.004**	**6.39 (2.20–18.53)**	**.001**	**6.45 (2.42–17.18)**	**<.001**	**11.98 (4.46–32.16)**	**<.001**
Mood symptom severity	**2.01 (1.25–3.24)**	**.004**	1.48 (0.57–3.82)	.42	**7.05 (3.30–15.08)**	**<.001**	**1.97 (1.04–3.72)**	**.04**

[a]Boldface type indicates statistical significance.
Abbreviation: OR = odds ratio.

Table 4. Multivariate Analyses Showing Associations Between Potential Predictors and Trajectory Class Membership Using the *Persistent-high* Class as the Reference[a]

	Fast-response Class		*Slow-response-relapse* Class		*Fluctuating* Class	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age at baseline	0.99 (0.95–1.02)	.47	1.03 (0.97–1.08)	.34	1.03 (0.99–1.08)	.16
Marital status						
Living without a partner	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Living with a partner	2.04 (0.96–4.35)	.06	2.43 (0.85–7.14)	.10	1.35 (0.48–3.85)	.56
Occupation						
Unemployed	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Employed	1.70 (0.81–3.55)	.16	1.79 (0.64–5.04)	.27	1.42 (0.47–4.32)	.54
Treatment arm						
Nortriptyline	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Escitalopram	1.82 (0.91–3.70)	.09	1.59 (0.53–4.76)	.41	1.39 (0.48–4.00)	.55
Previous suicide attempts						
No	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	0.48 (0.21–1.09)	.08	0.99 (0.29–3.35)	.99	1.86 (0.62–5.55)	.27
Mood symptom severity	**0.29 (0.15–0.56)**	**<.001**	**0.21 (0.06–0.68)**	**.009**	**0.28 (0.13–0.61)**	**.001**

[a]The *Persistent-low* class is not shown here because it is shown in Table 3. Boldface type indicates statistical significance.
Abbreviation: OR = odds ratio.

with a partner was associated with lower odds of being in the *Persistent-high* class.

Second, we were interested in identifying factors differing between the 4 classes with high baseline suicidal ideation but different developments. For this analysis, we used the *Persistent-high* class as the reference (Table 4). We found that higher mood symptom severity was associated with lower odds of being in all other classes. Living with a partner showed a trend toward lower odds of being in the *Fast-response* ($P = .06$) and *Slow-response-relapse* ($P = .10$) classes. Previous suicide attempts ($P = .08$) showed a trend toward lower odds, and treatment with escitalopram a trend toward better odds ($P = .09$) of being in the *Fast-response* class.

DISCUSSION

Among 811 patients with MDD treated with escitalopram or nortriptyline for up to 12 weeks, we identified 5 distinct trajectory classes of suicidal ideation, which indicates a very heterogeneous course of this clinically important symptom despite relevant pharmacologic treatment. A total of 9.8% experienced high and persistent suicidal ideation, whereas 10.0%, which divided into 2 different trajectories (*Fluctuating* and *Slow-response-relapse*), showed very fluctuating courses. Worse response on suicidal ideation was associated with poorer antidepressant treatment response in general. Previous suicide attempts predicted high baseline suicidal ideation and trajectories with high or fluctuating suicidal ideation. Individuals living with a partner and treatment with escitalopram showed a trend toward better response.

Differential Development of Suicidal Ideation

Trajectories of depressive symptoms have been investigated by several studies[6,7,9,23] revealing clinically important findings. Suicidal ideation represents a frequent, potentially dangerous, and difficult-to-treat symptom in patients with mental disorders. Nevertheless, few studies have explored the differential development of suicidal ideation. Our findings support prior data-driven trajectory studies showing that 6%–14% of patients with psychosis,[11] major depressive disorder,[10] or bipolar disorder[13] suffer from persistent high suicidal ideation despite relevant

pharmacologic treatment. Our results indicate slightly higher suicidal ideation than in the study by Kasckow and colleagues.[10] In that study, 6.3% of 468 patients with MDD had high and persistent suicidal ideation during 16 weeks of antidepressant treatment. However, that study only included individuals aged 60 years or older, all treated with venlafaxine. Thus, the present study is the first comparing 2 different antidepressants and including a large study population representing patients frequently seen in everyday clinical practice (mean age of 42.5 years, 63.4% female, mean HDRS score of 21.7). Our findings indicate that a large proportion of patients with MDD experience high or fluctuating suicidal ideation despite antidepressant treatment.

Predictors for Better Treatment Response

The identified predictors may lead to trials aiming at better characterization of those patients with high suicidal ideation not responding to standard antidepressant treatment.

First, clinicians should be aware of patients' history of suicide attempts and perform a thorough assessment of suicidal ideation at treatment initiation.[24] Past suicide attempts were strongly associated with poor reduction of suicidal ideation during antidepressant treatment, supporting previous findings.[25] In addition, the poor reduction in suicidal ideation in our study was related to worse antidepressant treatment response in general, indicating that worse response on suicidal ideation might represent a more general treatment-resistant depression. This finding is in line with a recent trial[26] showing that high baseline suicidal ideation was associated with worse antidepressant treatment response and remission after 6 weeks.

Second, familial support seems important as patients living with a partner had a trend toward reduced response on suicidal ideation.

Third, we found a trend that patients treated with the SSRI escitalopram showed reduced response on suicidal ideation. In contrast, a study[27] among 565 patients with moderate to severe depression and significant suicidal ideation found that patients treated with SSRIs had a higher risk for persistent suicidal ideation. However, that study did not apply trajectory analyses nor were patients randomized to treatment, making comparisons between treatment arms more difficult. Most importantly, our results do not show that subgroups experience emerging suicidal ideation after initiation of antidepressant treatment. The 20% of patients with high or fluctuating suicidal ideation already had a high level of suicidal ideation at baseline. Indeed, the vast majority of patients improved in suicidal ideation during the 12 weeks of antidepressant treatment, which is in line with previous clinical findings[20,26,28] and a recent meta-analysis[29] indicating that the association between SSRIs and suicidal ideation during treatment is present only in children and adolescents (odds ratio of 2.39) but not in adults (odds ratio of 0.81). Hence, our results suggest that SSRIs such as escitalopram may be well suited for adults with MDD and high baseline suicidal ideation.

Strengths and Limitations

Strengths of our study include the large population size (approximately twice as large as previous studies exploring heterogeneity of suicidal ideations[10,12,13]) and the close monitoring with weekly ratings, which is much more frequent than that of prior studies.[8,10–13] In addition, the IRT method integrated the suicide items from 3 standard rating scales to calculate a less biased and more comprehensive estimate of suicidal ideation for each patient.[20] The frequent assessments and the detailed IRT approach allowed us to perform very detailed trajectory models including both quadratic and cubic terms, whereas prior studies could apply only quadratic term models.[10,11,30] Furthermore, we were able to identify 5 trajectory classes and hence give a more detailed picture of the differential development of suicidal ideation compared with prior studies,[10,11,31] a difference which may be due to the large study population and IRT approach yielding more power to detect distinct trajectories. Finally, the broad inclusion criteria of GENDEP result in a study setting very close to real-world clinical settings where patients have comorbidities, use other medication, and suffer from suicidal ideation. These factors often represent exclusion criteria in clinical trials.

Limitations include that the GENDEP trial was not designed to specifically monitor and treat suicidal ideation, ie, the applied measure for suicidal ideation is based on 3 different depression scales but not on a specific suicidal ideation scale. Second, suicidal thoughts may persist for several years.[11,31] Hence, future trials designed to intervene on suicidal ideation should investigate whether suicidal thoughts may persist for longer periods and whether targeted interventions may improve the development of suicidal ideation. Third, 2 classes were rather small with approximately 5% in each class. But owing to the large study population, these groups are still clinically relevant. Fourth, we could not include biomarkers in prediction models. For example, only 241 of the 811 patients had baseline measurements of C-reactive protein.[32] Fifth, the broad inclusion criteria may have resulted in some selection bias regarding suicidal ideation, since individuals could have experienced previous suicide attempts and previous depressive episodes (mean 10.4 years between first depressive episode and inclusion in GENDEP). Sixth, we have previously found that men treated with nortriptyline had higher risks for treatment-emergent and treatment-worsening suicidal ideation compared with men treated with escitalopram,[20] which may have influenced the trajectories of suicidal ideation. However, our analyses only indicated a trend toward differences between nortriptyline and escitalopram regarding class membership. Finally, we could not perform analyses on the association with suicidal behavior after treatment initiation since only 1 individual reported a suicide attempt during the GENDEP trial.

Conclusion and Perspectives

Among 811 patients with MDD treated 12 weeks with standard antidepressants, we identified 5 different classes of suicidal ideation, which indicates a very heterogeneous course of this clinically challenging symptom. Our data-driven

approach showed that the *Persistent-low* class (53.7%) on a group mean level had no significant suicidal ideation at any time point and that 26.5% with high suicidal ideation at baseline responded quickly to treatment. One class (9.8%) showed high and persistent suicidal ideation, and 2 classes comprising 10.0% showed very fluctuating courses. The classes with high or fluctuating suicidal ideation experienced worse antidepressant response. Previous suicide attempts and higher mood symptom severity predicted trajectories with high suicidal ideation. Future large-scale trials need to (1) explore whether suicidal ideation may persist for longer periods and (2) identify predictors enabling clinicians to early identify the patients at risk for persistent suicidal ideation. On the basis of those findings, trials should (3) investigate whether specific treatment approaches, both pharmacologic and nonpharmacologic, may help high-risk patients with depression and persistent suicidal ideation, thereby potentially reducing the rate of suicide attempts and, hence, suicides.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Trajectories of Suicidal Ideation During 12 Weeks of Escitalopram or Nortriptyline Treatment Among 811 Patients With Major Depressive Disorder

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List of Supplementary Material for the article

1. **Table 1** Range of Response Options for Suicide Items on the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI)

2. **Figure 1** The Individual-Level Developments in Suicidal Ideation Within the Distinct Trajectory Classes

3. **Table 2** Depression Scores Before and After Treatment Including Percentage of Patients Who Responded or Achieved Remission Within the Five Trajectory Classes

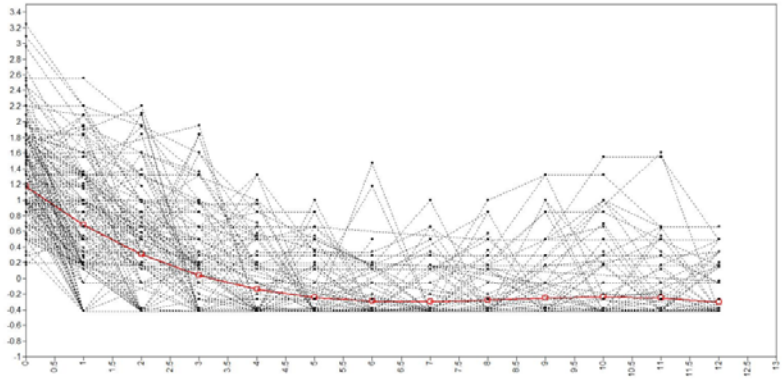
Disclaimer

Supplementary Table 1: Range of response options for suicide items on the Hamilton Depression rating scale (HAM-D), the Montgomery Aasberg Depression rating scale (MADRS) and the Beck Depression Inventory (BDI).

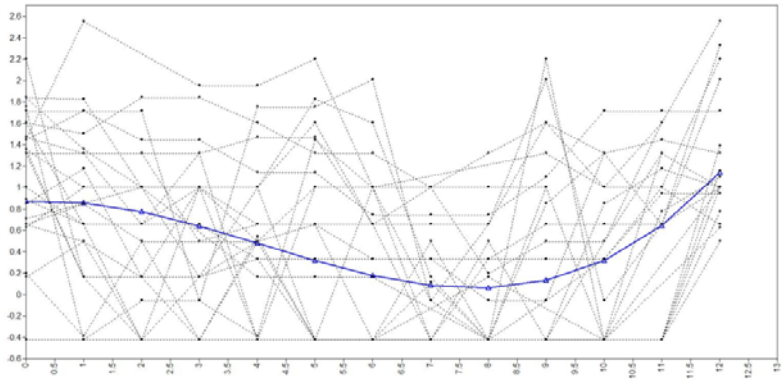
Scale	Score	Meaning
HAM-D	0	Absent
	1	Feels life is not worth living
	2	Wishes he/she were dead, or any thought of possible death to self
	3	Suicide ideas or half-heartened attempt
	4	Attempts suicide
MADRS	0 to 1	Enjoys life or take it as it comes
	2 to 3	Weary of life. Only fleeting suicidal thoughts
	4 to 5	Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intentions.
	6	Explicit plans for suicide when there is an opportunity. Active preparations for suicide.
BDI	0	Absent
	1	Thought of killing myself
	2	I would like to kill myself
	3	I would like to kill myself if I had a chance

<u>Supplementary Figure 1:</u> The individual-level developments in suicidal ideation within the distinct trajectory classes.

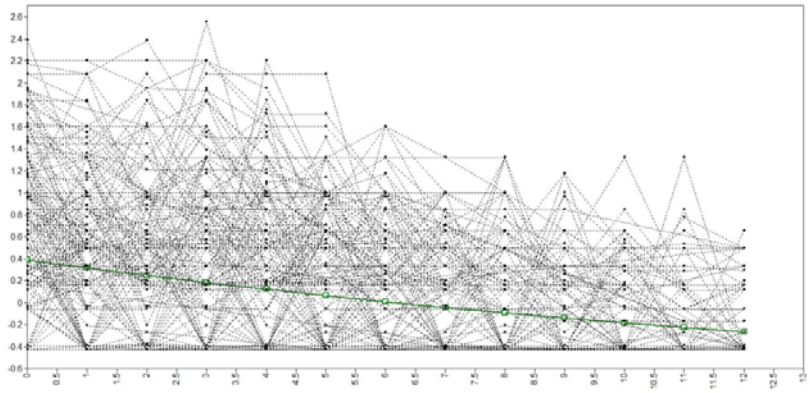
Class 1 – Fast-Response



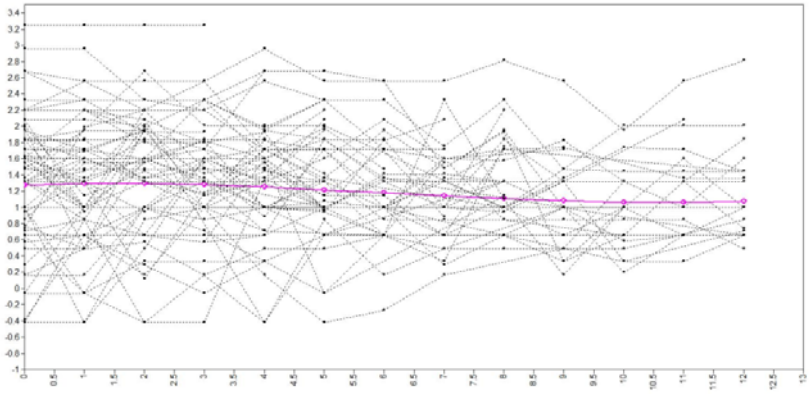
Class 2 – Slow-Response-Relapse



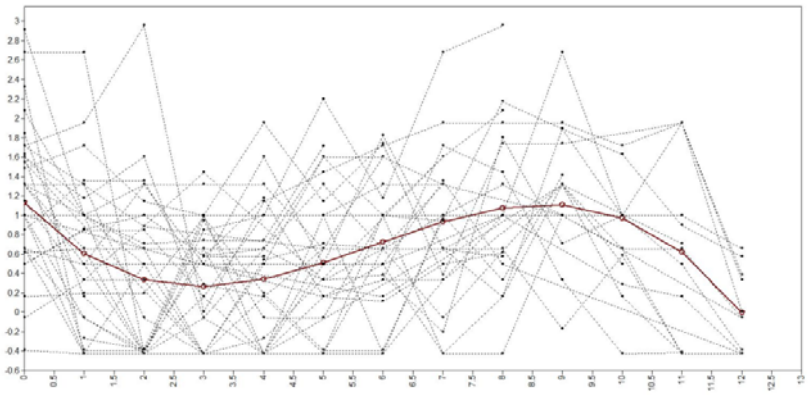
Class 3 – Persistent-Low



Class 4 – Persistent-High



Class 5 – Fluctuating



Supplementary Table 2: Depression scores before and after treatment including percentage of patients who responded or achieved remission within the five trajectory classes.

	Mean (SE) MADRS before treatment	Mean (SE) MADRS after treatment	Response (MADRS reduction≥50%))	Remission (MADRS≤7)
Persistent-low (53.7%)	26.39 (0.39)	8.85 (0.40)	59%	47%
Fast-response (26.5%)	30.70 (0.51)	7.46 (0.44)	83.8%	61.3%
Persistent-high (9.8%)	34.65 (1.03)	22.46 (0.92)	1%	0%
Slow-response-relapse (4.8%)	28.04 (1.62)	21.37 (1.60)	3.1%	2.1%
Fluctuating (5.2%)	31.33 (1.28)	20.06 (2.11)	6.3%	5.3%