

Persistence of suicidal ideation within acute phase treatment of major depressive disorder: analysis of clinical predictors

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Suicidal ideation (SI) is common in major depressive disorder (MDD), and it is a risk factor for suicidal behaviour. Antidepressants are effective in reducing SI, but in some subjects, SI may persist for weeks. This study aimed to disentangle the contribution of baseline clinical characteristics in SI nonremission at week 6. Research involved 198 outpatients with MDD and SI collected within the Combining Medications to Enhance Depression Outcomes trial and treated with different antidepressant combinations. Although SI decreased from baseline to week 6 ($P < 0.0001$), 78 patients (39%) failed to achieve SI remission. Insomnia [OR, 0.72; 95% confidence interval (CI), 0.52–0.99], reduced need for sleep (OR, 0.75; 95% CI, 0.58–0.99), self-confidence (OR, 0.52; 95% CI, 0.32–0.82), cheerfulness (OR, 0.57; 95% CI, 0.33–0.98), and comorbid panic disorder (OR, 0.93; 95% CI, 0.87–0.99) at baseline were associated with lack of SI remission after controlling for baseline depression and SI scores. The combination of baseline SI and insomnia was moderately effective

Introduction

Suicide is a global phenomenon that accounts for 1.4% of premature deaths worldwide (Bachmann, 2018). In mood disorders lifetime risk for suicide is estimated to range from 2 to 8% (Blair-West *et al.*, 1999; Bostwick and Pankratz, 2000; Nordentoft *et al.*, 2011) and mortality from suicide is more than 20 times higher than in the general population (Osby *et al.*, 2001). Among depressive symptoms, suicidal ideation (SI), which has been reported in up to 60% of depressive outpatients (Sokero *et al.*, 2003; Trivedi *et al.*, 2013), is known to substantially increase suicidal risk: a meta-analysis has estimated that suicide was 2.3 times more likely in mood disorder patients who had previously expressed SI than in their counterpart who had not (Hubers *et al.*, 2018). Based on this evidence, treating SI becomes a priority. Although antidepressant medications (ADs) have been debated about self-harm and SI in children and adolescent (Scahill *et al.*, 2005; Hammad *et al.*, 2006; Högberg *et al.*, 2015), in adults they have univocally shown superiority to placebo in reducing SI (Gibbons *et al.*, 2012; Näslund *et al.*, 2018). Despite this, at least one in five patients who take ADs are not likely to obtain a complete SI remission (Zisook *et al.*, 2011). We argue that, if these subjects could be identified as

in predicting the lack of SI remission, with a specificity of 80% (95% CI, 72–87%) and an NPV of 68% (95% CI, 63–72%). In individuals with MDD and SI, the presence of insomnia and bipolar features should prompt a search for more effective treatment solutions in order to favour SI remission and prevent suicidal behaviour. *Int Clin Psychopharmacol* 37: 193–200 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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earlier as possible and their treatments enhanced or modified to improve their effectiveness, this strategy would allow to minimise suicidal risk. Prior research indicates several factors that are associated with the occurrence of SI in depressive episodes such as depression severity, age at onset and course of depressive disorder (Zisook *et al.*, 2011), abuse and violence in childhood (Chou, 2012; Zisook *et al.*, 2022) and mental disorder comorbidities (Hardt *et al.*, 2015; Wiebenga *et al.*, 2021). Moreover, SI has been related to depression psychopathology, in particular hopelessness (Wolfe *et al.*, 2017; Ribeiro *et al.*, 2018; Wiebenga *et al.*, 2021) and self-blame (Olgiati *et al.*, 2006), irritability (Jha *et al.*, 2019), insomnia (Pigeon *et al.*, 2012; Wang *et al.*, 2019) and bipolar features (Akiskal *et al.*, 2005; Weinstock *et al.*, 2016; Rihmer and Rihmer, 2019). Little is known about the role of these clinical variables in predicting SI response during antidepressant treatment. To address this question, we analysed data from the Combining Medications to Enhance Depression Outcome (CO-MED) study (Rush *et al.*, 2011) in order to ascertain which characteristics of major depressive disorder (MDD) assessed at baseline were associated with a lack of SI remission after six treatment weeks.

Methods

Subjects

In CO-MED trial, eligible subjects were aged 18–75 years, with a primary DSM-IV diagnosis of nonpsychotic MDD

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and a HAM-D₁₇ score of at least 16 (Rush *et al.*, 2011). To be included in the current analysis, two additional criteria were required: (a) to endorse SI at baseline and (b) to have no missing visit during follow-up period until week 6.

Treatment and data collection

The CO-MED trial was characterised by a single-blind placebo-controlled design and three treatment arms: (a) escitalopram plus placebo; (b) bupropion SR plus escitalopram; (c) venlafaxine XR plus mirtazapine. The trial included a short-term (12 weeks) treatment followed by a continuation phase (weeks 12–28) (Rush *et al.*, 2011).

Research data were collected by a variety of assessment tools as reported in our previous publications (Olgati *et al.*, 2022; Olgati and Serretti, 2022; Serretti *et al.*, 2021): (a) a socio-demographic form including age, sex, ethnic group, education and monthly income; (b) the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998) for retrospective evaluation of depressive disorder (chronic or recurrent course of depression; number of depressive episodes and age at onset of first episode) and to ascertain the lifetime occurrence of subthreshold hypomanic episodes (see below); (c) a battery of scales for cross-sectional clinical assessment including the 30-item Inventory of Depressive Symptomatology-Clinician Rating (IDS-C₃₀) (Corruble *et al.*, 1999) and the 16-item Quick Inventory of Depressive Symptomatology (Rush *et al.*, 2003), the Concise Associated Symptoms Tracking (CAST) (Trivedi *et al.*, 2011b) for irritability, the Altman Self-Rating Mania Scale (ASRM) (Altman, 1998) and the Work and Social Adjustment Scale (WSAS) (Mundt *et al.*, 2002) to ascertain functional impairment; (d) the Psychiatric Diagnostic Screening Questionnaire (Zimmerman and Mattia, 1999) to investigate comorbid mental disorders including panic disorder, generalised anxiety, obsessive-compulsive disorder, social phobia, posttraumatic stress disorder, and alcohol and substance use disorders; and (e) two questionnaires that were specifically developed for CO-MED project to investigate lifetime suicidal behaviour and experiences of neglect and abuse during childhood (Serretti *et al.*, 2021; Olgati and Serretti, 2022).

Suicidal ideation

SI was assessed by means of the Concise Health Risk Tracking-Self Report (CHRT) (Trivedi *et al.*, 2011a). This version was composed of 12 items (overall score: 0–48), of which nine explored a generic suicidal propensity. Our analysis was based on the last three, which specifically investigated SI and plans over the last 24 h: scoring more than 1 at baseline was used as an inclusion criterion (see paragraph ‘subjects’) whereas a threshold less than 2 was selected to define SI remission at week 6.

Clinical variables

A number of clinical variables were compared between patients with and without SI remission: (a) chronic

depression: depressive episode lasting for at least 6 months; (b) baseline depression severity (IDS-C₃₀ total score) and symptom profile including negative self-outlook, negative outlook of future, loss of pleasure, irritability (CAST), anxious mood, interpersonal sensitivity; poor concentration, difficulty in falling asleep, middle nocturnal insomnia and early awakening. Subsequently, we achieved a combined variable by pooling baseline scores of SI and middle nocturnal insomnia together: subjects scoring more than 8 were classified as ‘SI plus insomnia’ group and compared with the rest of the sample (see below); (c) bipolar spectrum variables, including: (i) age of onset (Benazzi, 2009); (ii) mood disorder recurrence (number of episodes/illness years) (Mazzarini *et al.*, 2018); (iii) hypomanic symptoms occurring within major depressive episode (ASRM items): cheerfulness; self-confidence; reduced need for sleep; talkativeness; and goal-oriented hyperactivity; (iv) mixed depression, defined as a major depressive episode with three or more concurrent hypomanic symptoms (Akiskal *et al.*, 2005); (v) lifetime subthreshold hypomania: a period of elated or irritable mood with at least two concurrent hypomanic symptoms (MINI interview), which did not fulfil DSM criteria for hypomanic/manic episode (Angst *et al.*, 2003; Serretti *et al.*, 2021); (d) lifetime most severe suicidal behaviour, rated via a 0 (no suicidal tendency) to 7 (suicide attempt with definite intent to die) scale; (e) comorbid mental disorders; and (f) experiences of neglect and abuse during childhood.

Statistical analyses

A preliminary power analysis was conducted to estimate minimum detectable differences between SI remitter and nonremitter groups, considering a type I error (alpha level) of 0.05 and a type II error (1-power) of 0.20. Univariate analyses were performed using Student’s *t*-test and Chi-square test for continuous and categorical variables respectively. Significance threshold was set at alpha = 0.05, without a formal correction for multiple testing given the exploratory nature of our analysis (Amrhein *et al.*, 2019). Multiple logistic regression analysis was used to test the association of each factor with SI remission by controlling for confounding variables (see Tables 1–3 for details). Statistical software was OpenStat version 8 December 2014 (<https://openstat.info/OpenStatMain.htm>). Power analysis was carried out via G*Power 3 program that was developed by a Düsseldorf University team (Germany) (Faul *et al.*, 2007). Finally, to analyse the performance of ‘SI plus insomnia’ variable in predicting the lack of SI remission, a diagnostic test evaluation was conducted by means of Med-Calc free statistical calculator (<https://www.medcalc.org/>).

Results

Out of 665 participants in the CO-MED trial, our analysis involved 198 outpatients who endorsed SI and attended all scheduled visits until week 6. Their mean age was

Table 1 Patients with and without suicidal ideation remission (week 6), demographic variables and depressive symptomatology (baseline)

Features	SI remission (N = 120)	Lack of remission (N = 78)	P
Age	44.33 ± 11.56	43.96 ± 11.55	0.8252
Sex (M; %)	33 (0.27)	28 (0.36)	0.2110
Ethnic group (Caucasian; %)	89 (0.74)	51 (0.65)	0.1850
Education (years)	13.79 ± 3.22	13.59 ± 2.92	0.6613
Chronic depression (>6 months)	62 (0.51)	45 (0.57)	0.4060
IDS-C ₃₀			
Total score	39.77 ± 9.10	41.50 ± 9.14	0.1925
Negative self-outlook	2.09 ± 0.84	1.90 ± 0.91	0.1249
Negative outlook of future	1.71 ± 0.86	1.76 ± 0.87	0.7033
Loss of pleasure	1.61 ± 0.87	1.69 ± 0.92	0.5172
Anxious mood	1.90 ± 0.80	1.79 ± 0.74	0.3558
Psychomotor agitation	0.65 ± 0.64	0.64 ± 0.58	0.9208
Slowing	0.78 ± 0.64	0.63 ± 0.61	0.0895
Interpersonal sensitivity	1.50 ± 1.04	1.62 ± 1.11	0.4574
Difficulty in falling asleep	1.80 ± 1.25	1.95 ± 1.29	0.4194
Middle nocturnal insomnia	1.91 ± 1.12	2.31 ± 1.01	0.0114*
Early awakening	1.35 ± 1.25	1.44 ± 1.32	0.6447
Poor concentration	1.78 ± 0.69	1.72 ± 0.68	0.5129
Irritability (CAST)	0.78 ± 0.41	0.76 ± 0.43	0.6606
Suicidality (CHRT)			
Propensity	19.94 ± 6.78	21.42 ± 6.48	0.1280
Ideation/planning	3.66 ± 2.41	4.77 ± 2.08	0.0010*

Multiple logistic regression: dependent variable: SI remission; Chi-square = 22.23; df = 5; P = 0.0005

Predictors	OR (95% CI)
Negative self-outlook	1.41 (0.98–2.03)
Slowing	1.49 (0.92–2.42)
Middle nocturnal insomnia	0.71 (0.53–0.95)*
Suicide propensity	0.98 (0.94–1.04)
Suicidal ideation/planning	0.82 (0.71–0.96)*

Only variables with P < 0.15 were included in MLR model

MLR: dependent variable: SI remission; confounding factor; overall depression Chi-square = 7.23; df = 2; P = 0.0269

Predictors	OR (95% CI)
Overall depression score	0.96 (0.92–0.99)
Negative self-outlook	1.56 (1.07–2.27)

CAST, Concise Associated Symptoms Tracking; CHRT, Concise Health Risk Tracking-Self Report; CI, confidence interval; MLR, multiple logistic regression; OR, odds ratio; SI, suicidal ideation.

*P < 0.05.

44.19 ± 11.53 years; 61 patients (31%) were male and 140 (71%) were of Caucasian origin. Overall depression score (IDS-C₃₀) was 40.45 ± 9.13 at baseline and 22.65 ± 12.14 after 6 weeks of AD use ($t = 18.72$; $P < 0.0001$). SI score (CHRT items 10–12), which was equal to 4.10 ± 2.34 at baseline, decreased to 1.78 ± 2.25 at week 6 ($t = 10.05$; $P < 0.0001$), although 78 patients (39%) failed to achieve SI remission. Power analysis suggested that this sample might have an adequate power (0.8) to detect a small-medium effect size ($d = 0.45$) or differences of at least 10.5% between comparison groups.

Role of demographic characteristics and depression severity

Patients in whom SI remitted were similar to their counterparts without remission as regard demographic features. Conversely, at clinical level, no remission group was characterised by higher baseline scores of SI ($t = 3.34$; $P = 0.0010$) and middle nocturnal insomnia ($t = 2.55$; $P = 0.0114$). These inverse correlations with SI remission were confirmed by multivariate analysis [SI: odds ratio (OR), 0.82; 95% CI, 0.71–0.96; middle

nocturnal insomnia: OR, 0.71; 95% CI, 0.53–0.95] along with a direct correlation between lack of SI remission and lower levels of negative self-outlook (OR, 1.56; 95% CI, 1.07–2.27) after controlling for overall depression score (Table 1).

Comorbidities, childhood traumas and lifetime suicidal behaviour

Further characteristics of no remission group included more comorbid anxiety disorders (panic disorder: $t = 2.990$; $P = 0.0031$; social phobia: $t = 2.323$; $P = 0.0212$), more traumatic experiences during childhood ($t = 1.980$; $P = 0.0491$) and increased lifetime suicidality ($t = 2.196$; $P = 0.029$). After controlling for baseline depression score and SI, only panic disorder (OR, 0.93; 95% CI, 0.87–0.99) confirmed its negative association with SI remission (Table 2).

Bipolar spectrum variables

The distributions of hypomanic symptoms and bipolar spectrum markers are displayed in Table 3. Patients who failed to achieve SI remission endorsed higher levels of

Table 2 Patients with and without suicidal ideation remission

Features	With SI remission (N = 120)	Without SI remission (N = 78)	P
Work/social impairment	27.58 ± 8.52	29.86 ± 7.24	0.0531
Comorbidities			
Panic disorder	3.85 ± 4.57	5.99 ± 5.40	0.0031*
GAD	6.85 ± 2.82	7.35 ± 2.53	0.2095
PTSD	3.29 ± 4.09	4.12 ± 3.99	0.1640
Social phobia	4.91 ± 5.10	6.62 ± 4.97	0.0212*
Alcohol	0.56 ± 1.28	0.62 ± 1.83	0.2080
Substance	0.22 ± 0.81	0.38 ± 1.16	0.2333
Lifetime suicidal behaviour	2.33 ± 2.36	3.11 ± 2.41	0.0293*
Childhood traumas (total N°)	1.32 ± 1.41	1.73 ± 1.47	0.0491*
Neglect	51 (0.42)	40 (0.51)	0.2268
Emotional abuse	53 (0.44)	45 (0.58)	0.0636
Physical abuse	27 (0.22)	24 (0.31)	0.1947
Sexual abuse	27 (0.22)	26 (0.33)	0.0933
Multiple logistic regression analysis			
Predictors	OR (95% CI)		
Work/social impairment	0.97 0.93–1.01		
Panic disorder	0.93 0.87–0.99*		
Social phobia	0.95 0.89–1.01		
Lifetime suicidal behaviour	0.92 0.81–1.04		
Number of childhood traumas	0.88 0.71–1.08		
Emotional abuse	0.69 0.34–1.25		
Sexual abuse	0.69 0.35–1.34		

Comorbidities, lifetime suicidal behaviour and experiences of abuse and neglect during childhood.

MLR was performed to test all variables with $P < 0.15$ separately. Each MLR model included the following parameters: dependent variable: SI remission; covariates: baseline SI and overall depression scores.

CI, confidence interval; MLR, multiple logistic regression; OR, odds ratio; PTSD, post traumatic stress disorder; SI, suicidal ideation.

* $P < 0.05$.

self-confidence ($t = 2.528$; $P = 0.0123$) and reduced need for sleep ($t = 2.430$; $P = 0.0165$) during depressive episode in comparison with remission group. The negative association between hypomanic symptoms and SI remission was confirmed after controlling for confounding effects exerted by depression severity and baseline SI (self-confidence: OR, 0.52; 95% CI, 0.32–0.82; reduced need for sleep: OR, 0.75; 95% CI, 0.58–0.99; cheerfulness: OR, 0.57; 95% CI, 0.33–0.98).

Suicidal ideation plus insomnia

Fifty-six patients (28%) had baseline SI plus insomnia; in comparison with the rest of the sample, this group was younger at illness onset ($P = 0.0069$) and associated with higher levels of overall depression ($P = 0.0007$), comorbid generalised anxiety ($P = 0.0079$) and post traumatic stress disorder ($P = 0.0006$), traumatic experiences during childhood ($P = 0.0009$) and worse suicidal behaviours (0.0004). In addition, these patients were less likely to experience SI remission at week 6 ($P = 0.0014$) (Table 4). The combination of baseline SI and insomnia predicted the lack of SI remission with a specificity of 80% (95% CI, 72–87%) and a negative predictive value of 68% (95% CI, 63–72%).

Discussion

CO-MED data had already been used to analyse the prevalence and clinical correlates of SI (Zisook *et al.*, 2011; Jha *et al.*, 2020) as well as its prognostic impact along with other markers of depression severity (Zisook

et al., 2011; Sung *et al.*, 2013). Here, we focussed on baseline variables that could predict the persistence of SI during acute phase treatment. The severity of SI within the baseline assessment was strongly related to its lack of remission after 6 weeks. This was consistent with a large amount of literature displaying a negative correlation between the initial severity of depressive symptoms and the likelihood of remitting during treatment (Riedel *et al.*, 2011; Zisook *et al.*, 2019). Hence, it is arguable that depressed patients who report severe SI at baseline, similarly to those with higher levels of overall depression, may need augmentation or combination strategies to enhance antidepressant treatment response (Henssler *et al.*, 2022). A somehow unexpected result of our study was to find a positive correlation between higher levels of negative self-outlook and SI remission after controlling for depression severity. At first glance, this finding seems to be in contrast with the large body of evidence supporting the connection between negative self-appraisal and suicidality (Madsen and Harris, 2021). Nonetheless, it becomes less difficult to understand thanks to the knowledge that some ADs (e.g. escitalopram and agomelatine) can quickly normalise self-referential processing in depressed patients, an effect which is thought to play an important role in their therapeutical activity (Delaveau *et al.*, 2016; Komulainen *et al.*, 2018). Thus, basically, we suggest that patients who exhibited higher levels of negative self-outlook might be more impaired in self-referential processing and, as such, more sensitive to antidepressant treatment.

Table 3 Bipolar spectrum validators and suicidal ideation remission

Features	SI remission (N = 120)	No remission (N = 78)	P
Age of depression onset	23.03 ± 13.84	14.01 ± 12.35	0.2967
N. episodes/illness years	0.44 ± 0.72	0.33 ± 1.16	0.4352
Mixed depression (MxD)	14 (0.11)	12 (0.15)	0.4523
Subthreshold hypomania (SH)	15 (0.12)	7 (0.09)	0.4410
Irritability (CAST)	0.78 ± 0.41	0.76 ± 0.45	0.6606
Cheerfulness (ASRM)	0.16 ± 0.47	0.31 ± 0.73	0.0807
Self-confidence (ASRM)	0.14 ± 0.44	0.37 ± 0.84	0.0130*
Increased talkativeness (ASRM)	0.42 ± 0.81	0.26 ± 0.57	0.1284
Reduced need for sleep (ASRM)	0.45 ± 0.93	0.83 ± 1.28	0.0165*
Increased activity (ASRM)	0.09 ± 0.43	0.24 ± 0.78	0.0798

Multiple logistic regression models were performed for each variable with $P < 0.15$; each model included SI remission as dependent variable and baseline SI and depression severity as covariates.

Predictors of SI remission	OR (95% CI)
Cheerfulness	0.57 (0.33–0.98)*
Self-confidence	0.55 (0.33–0.91)*
Reduced need for sleep	0.76 (0.56–0.99)*
Increased talkativeness	1.43 (0.91–1.25)
Increased activity	0.61 (0.35–1.06)

ASRM, Altman Self-Rating Mania Scale; CAST, Concise Associated Symptoms Tracking; CI, confidence interval; OR, odds ratio; SH, suicidal ideation.

* $P < 0.05$.

The most clear-cut result of our analysis was the association between insomnia and SI response. The combination of insomnia and severe SI before starting treatment, which involved more than one-quarter of our sample, had the strongest connection with SI persistence. As a predicting test, it was characterised by a good level of specificity and a small number (24/198) of false-positive results, at the expense of a lower sensitivity, and it was correlated with lifetime suicidal behaviour. The relationship between insomnia and suicidality has become a matter of extensive research in recent years (Pigeon *et al.*, 2012; Wang *et al.*, 2019). Despite considerable differences in study designs, samples and assessment techniques, there is converging evidence for insomnia as an empirical risk factor for suicidal behaviour (Bernert *et al.*, 2015; Lau *et al.*, 2020; Simmons *et al.*, 2021). On the other hand, it is possible to reduce SI by targeting insomnia with both pharmacological treatment (McCall *et al.*, 2019) as well as cognitive behavioural therapy (Jernelöv *et al.*, 2021). Although the association between insomnia and suicidality can be independent of depression (Simmons *et al.*, 2020), it appears to be stronger in depressed patients, among whom a direct correlation has been reported between higher levels of insomnia and the intensity of suicidal thinking (McCall *et al.*, 2010; Bryan *et al.*, 2015). This connection might not be limited to a short time horizon as in our study; in a longitudinal analysis of the NESDA study, for example, insomnia was associated with SI persistence for 6–9 years (Kivela *et al.*, 2019). Exact pathophysiological mechanisms are not known yet; it has been hypothesised that sleep loss could increase susceptibility to suicidal thoughts and behaviours via its association with executive function deficits (Fernandes *et al.*, 2021) and cognitive hyperarousal (Fernandes *et al.*, 2021; Grove *et al.*, 2021). The

negative role of panic disorder during SI treatment was also consistent with available literature. In fact, among depressed patients, comorbid panic disorder has emerged as a risk factor for suicidality (Katz *et al.*, 2011; Scheer *et al.*, 2020; Zhang *et al.*, 2022) as well as a poor prognostic factor (Buckman *et al.*, 2021). The contribution of bipolar symptoms to convey an additional risk for suicidal behaviours during depressive episode is yet unclear, with studies yielding mixed results. For example, two prospective analyses of the Finnish Jorvi Bipolar Study have shown higher estimates of suicide attempts with mixed symptoms relative to depressive ones (Valtonen *et al.*, 2008; Holma *et al.*, 2014). Conversely, in a series of works based on the National Network of Depression Centres Mood Outcomes Program, mixed depressive and manic symptoms were associated with no excess risk for SI or behaviour (Fiedorowicz *et al.*, 2021; Persons *et al.*, 2022). Notably, prior studies analysed patients with bipolar depression (Valtonen *et al.*, 2008; Persons *et al.*, 2022) or mixed bipolar and unipolar samples (Holma *et al.*, 2014; Fiedorowicz *et al.*, 2021), whereas we only included subjects with MDD.

The CO-MED trial was characterised by a well-implemented design and a thorough clinical assessment. Despite this, we must acknowledge some limitations of our post hoc analysis. First, the group of patients without SI remission was relatively small and, therefore, underpowered to detect less clearcut differences from remitting subjects which, however, should be included in reliable prediction models (Abraham and Russell, 2008). A set of caveats involved the assessment of suicidality. In fact, no information was available about the characteristics of suicide attempts (impulsive or based on plans; use of potentially lethal methods; presence

Table 4 Characteristics of suicidal ideation (SI) plus insomnia (In) group

Features	SI+In (n = 56)	Rest of the sample (n = 142)	P
Age of onset	18.20 ± 12.95	23.33 ± 13.11	0.0069*
Depression severity	43.93 ± 9.08	39.08 ± 8.81	0.0007*
Generalised anxiety	7.86 ± 2.53	6.73 ± 2.73	0.0079*
PTSD	5.18 ± 4.19	3.00 ± 3.86	0.0006*
Childhood traumas	2.02 ± 1.58	1.27 ± 1.34	0.0009*
Lifetime suicidal behaviour	3.62 ± 2.36	2.26 ± 2.32	0.0004*
SI remission (week 6)	24 (0.43)	96 (0.68)	0.0014*
Lack of SI remission		Parameter	Value
		Sensitivity	41.03%
		Specificity	80.00%
		Positive likelihood ratio	2.05
		Negative likelihood ratio	0.74
		Lack of SI remission prevalence	39.00%
		Positive predictive value	56.74%
		Negative predictive value	67.97%
		Accuracy	64.80%
			95% CI
			30.01–52.75%
			71.72–86.75%
			1.31–3.20
			0.60–0.91
Predicted (SI+In test)			
Observed	No	Yes	Total
No	96	24	120
Yes	46	32	78
Total	142	56	198

Baseline SI + middle nocturnal insomnia scores ≥ 8 .

CI, confidence interval; PTSD, post traumatic stress disorder; SI, suicidal ideation.

*P < 0.05.

of intent to die, etc.) and symptomatology before their occurrence (SI; hypomanic symptoms, etc.). Moreover, no scales were administered to explore psychological correlates of suicidal behaviour such as hopelessness (Sokero *et al.*, 2006; Ribeiro *et al.*, 2018), thwarted belongingness and burdensomeness (Chu *et al.*, 2017). As for bipolar markers, the ASRM scale does not assess hypomanic manifestations such as racing thoughts, distractibility, and excessive involvement in risky activities and behaviours, which are often observed in mixed depression (Perugi *et al.*, 2015; Brancati *et al.*, 2019). In addition, family history of bipolar illness, one of the most useful variables to distinguish bipolar II depression from MDD (Zimmerman *et al.*, 2013), was not available for our sample. Such a missing information could have hindered the identification of bipolar spectrum cases and the assessment of their impact on suicidality. A recent analysis based on the Sequenced Treatment Alternatives to Relieve Depression study has supported the prognostic role of anhedonia and anxiety, which were associated with negative and positive SI trajectories respectively (Bloomfield-Claggett *et al.*, 2022). These findings were not replicated in the current study but further research is warranted using larger samples and specific tools for the assessment of anhedonia and anxiety-related manifestations. Similarly, the lack of formal correction for multiple testing prompts for replication of the observed findings.

In conclusion, to investigate variables that can affect the course of SI during antidepressant treatment is a clinical need to stop its possible progression to attempted suicide. In this context, our analysis has emphasised the role of sleep disorders and bipolar features as outcome predictors, which might require more effective drug combinations without increasing risk for hypomanic switch or rapid cycling. The assessment of these clinical manifestations could help in planning the pharmacological treatment of SI and suicide prevention.

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Statement of ethics: the CO-MED trial was conducted according to the Principles of Helsinki Declaration and its protocol was approved by ethical committees at local recruitment sites. All subjects who met selection criteria were included in the CO-MED trial after obtaining their written informed consent. This research group certifies that data collected from the CO-MED trial were exclusively used for scientific investigation and, before obtaining access to them, the objectives of our investigation were clearly reported in request form (Olgiati and Serretti, 2022).

Conflicts of interest

There are no conflicts of interest.

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