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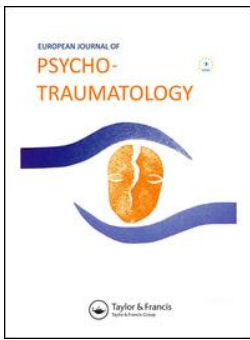
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## Childhood maltreatment and risk for suicide attempts in major depression: a sex-specific approach

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### ABSTRACT

**Background:** Childhood maltreatment increases the risk of suicide attempts in the general population, possibly having similar effects among patients with major depressive disorder (MDD). The few studies that have addressed this association have been restricted to specific populations (e.g. treatment-resistant depression, personality disorders) and have rarely taken sex into account.

**Objective:** To examine the impact of childhood maltreatment on suicide attempts among MDD patients above and beyond other risk factors and potential confounders, while considering potential sex-specific effects.

**Methods:** The study assessed 165 patients with a principal diagnosis of MDD. Neurological alterations, psychiatric comorbidities, and drug abuse were reasons for exclusion. Logistic regressions using the whole sample, and divided by sex, were run to test the association between childhood maltreatment and history of suicide attempts, controlling for symptom severity, comorbidities, and treatment-resistant depression.

**Results:** There was a significant and clinically relevant association between childhood maltreatment and history of suicide attempts in the total sample. Patients with childhood maltreatment were 3.01 times more likely to present a history of suicide attempts than patients without childhood maltreatment. A family history of psychiatric disorders also contributed to the variance of attempted suicide, but its interaction with childhood maltreatment was not statistically significant. When testing the model separately, the effect of childhood maltreatment on suicide attempts remained for females, whereas for males, age of MDD onset and Childhood Trauma Questionnaire minimization-denial scale were predictive variables.

**Conclusions:** Childhood maltreatment is a clear predictor of suicidal behaviour among MDD patients, and this effect remains significant after controlling for potential confounders. Also, the sex of patients emerges as a relevant factor that may model the mechanisms underlying the prediction of suicide attempts. Since suicide is the main cause of premature death among MDD patients, interventions targeting childhood maltreatment should be included in preventive and clinical strategies.

### Maltrato infantil y riesgo de intentos de suicidio en la depresión mayor: un enfoque específico del sexo

**Planteamiento:** el maltrato infantil aumenta el riesgo de intentos de suicidio en la población general, y podría tener efectos similares en pacientes con trastorno depresivo mayor (TDM). Los escasos estudios que han abordado este tema se han restringido a poblaciones específicas (p.ej. depresión resistente al tratamiento, trastornos de personalidad) y rara vez tienen en cuenta el sexo.

**Objetivo:** evaluar el impacto del maltrato infantil en las tentativas de suicidio en pacientes con TDM, considerando potenciales factores de riesgo y de confusión, al tiempo que se estudian los posibles efectos del sexo.

**Método:** se evaluó una muestra de 165 pacientes con diagnóstico principal de TDM. Las alteraciones neurológicas, las comorbilidades psiquiátricas y el abuso de drogas fueron motivos de exclusión. Para explorar la asociación entre el maltrato infantil y el historial de intentos de suicidio (controlando por la gravedad de los síntomas, la comorbilidad y la resistencia al tratamiento), se realizaron regresiones logísticas con la muestra completa, así como en hombres y mujeres por separado.

**Resultados:** existe una asociación significativa y clínicamente relevante entre el maltrato infantil y la historia de intentos de suicidio en el total de la muestra. Las personas con maltrato infantil tenían 3,01 veces más probabilidades de presentar historia de tentativas de

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### PALABRAS CLAVE

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### 关键词

童年虐待; 抑郁; 自杀企图; 风险因素; 性别差异

### HIGHLIGHTS

- Childhood maltreatment significantly increases the risk of suicide attempts in MDD patients, above and beyond previously proposed factors.
- This association is particularly evident among female MDD patients.
- The underlying mechanisms in male patients may be dependent on further biopsychological factors.
- MDD patients should be screened for childhood maltreatment as a strategy to prevent suicide attempts in adulthood.

suicidio que aquellas sin maltrato infantil. Los antecedentes familiares de trastorno psiquiátrico también contribuyeron a la varianza de los intentos de suicidio, pero su interacción con el maltrato infantil no resultó estadísticamente significativa. Al analizar el modelo por separado, el efecto del maltrato infantil en las tentativas suicidas se mantuvo en las pacientes mujeres, mientras que en los pacientes hombres la edad de inicio del TDM y la escala de minimización-negación del CTQ fueron las variables explicativas.

**Conclusiones:** el maltrato infantil predice el comportamiento suicida en pacientes con TDM, persistiendo este efecto después de controlar posibles factores de confusión. Además, el sexo de las personas modelaría los mecanismos subyacentes en cuanto a predecir las tentativas de suicidio. Dado que el suicidio es la principal causa de muerte prematura entre pacientes con TDM, las intervenciones dirigidas al maltrato infantil deberían incluirse dentro de las estrategias tanto preventivas como terapéuticas.

### 重度抑郁症中童年虐待和自杀企图的风险：对性别进行区分

**背景:** 在一般人群中，童年虐待会增加自杀的风险。在患有严重抑郁症（MDD）的病人群体中可能有相似的关联。少数研究讨论这种关联的研究仅限于特定人群（即治疗抵抗性抑郁症，人格障碍），并且很少考虑到性别。

**目的:** 在其他风险因素和潜在混淆因素之外，研究儿童虐待对MDD患者自杀企图的影响，同时考虑性别的潜在影响。

**方法:** 对165例诊断为MDD的患者进行评估，排除神经系统改变、精神病合并症和药物滥用。对整个样本进行逻辑回归分析，控制了症状的严重程度、合并症和难治性抑郁症后，区分不同性别，考察儿童期虐待和自杀企图历史之间的关联。

**结果:** 结果显示，童年虐待与总样本中自杀未遂史之间具有显著的临床相关性。与没有儿童期虐待的患者相比，患有儿童期虐待的患者自杀未遂史的可能性是3.01倍。精神疾病的家族史也导致了自杀未遂的变异，但其与儿童期虐待的相互作用在统计学上并不显著。当分性别考察时，童年虐待对自杀未遂的影响在女性依然存在，而男性中MDD发病年龄和CTQ最小化-否认量表（minimization-denial scale）是预测变量。

**结论:** 童年虐待是MDD患者自杀行为的明确预测因素，在控制潜在混淆因素后，这种影响仍然很明显。此外，患者性别是可以预测自杀未遂的机制的一个相关因素。鉴于自杀是MDD患者早亡的主要原因，针对儿童期虐待的干预措施应纳入预防和临床方案。

## 1. Introduction

Over 300 million people are affected by depression worldwide (World Health Organization [WHO], 2017); that is, 4.4% of the global population. This disorder is the major contributor to suicide deaths, which number close to 800,000 per year (WHO, 2017). At the level of clinical psychiatry, it has been estimated that every sixth death among individuals receiving treatment for depression is by suicide (Wulsin, Vaillant, & Wells, 1999). In view of the substantial burden caused by the association between depression and suicide, there is an urgent need to identify the possible risk factors, which can then be targeted in prevention strategies and interventions.

Early life adversity is also one of the strongest risk factors for attempted suicide. Exposure to maltreatment during the early phases of a person's development increases the risk of suicidal behaviours throughout the lifespan by between two and five times (Ludwig, Roy, Wang, Birur, & Dwivedi, 2017). A helpful estimate to understand the scope and burden of this problem is the attributable risk fraction (ARF) measure, which indicates the proportion of cases that would not have occurred if no persons had been exposed to the risk factors (Rothman, Greenland, & Lash, 2008). Population-based studies have estimated that around 80% of suicide attempts occurring during childhood and adolescence would have been avoided if no child had been exposed to

maltreatment (Dube et al., 2001). The ARF estimate for suicide attempts during adulthood is similarly high (ARF = 64%, with childhood maltreatment as a risk factor) (Dube et al., 2001).

Key factors associated with suicide among patients with major depressive disorder (MDD) have been clearly recognized in systematic reviews, in which a history of suicide attempts appears as one of the most significant predictors of completed suicide [odds ratio (OR) = 4.84, 95% confidence interval (CI) 3.26–7.20] (Hawton, Casañas I Comabella, Haw, & Saunders, 2013). Therefore, the identification of risk factors for history of suicide attempts is clinically relevant and could help to build the basis for the prevention of completed suicide among MDD patients.

It has been consistently reported that around half of depressed patients have a history of childhood maltreatment (Nelson, Klumparendt, Doebler, & Ehring, 2017), which could at least partly explain suicide attempts in MDD. A surprisingly small number of studies have directly addressed this association, and the few studies available commonly report on special populations or lack information on crucial clinical variables such as severity of MDD or sex-related specificity (Dias de Mattos Souza, Lopez Molina, Azevedo Da Silva, & Jansen, 2016; Lopez-Castroman et al., 2013; Pompili et al., 2014; Tunnard et al., 2014). However, the effect of other known influences remains elusive. For example, while male sex is more commonly associated with

completed suicide in the general population, the effect of sex on attempted or completed suicide among MDD patients is still under discussion (Hawton et al., 2013; Rihmer, 2007). Also, childhood sexual abuse is more commonly reported in females (Barth, Bermetz, Heim, Trelle, & Tonia, 2013), but males are less likely to disclose it (O’Leary & Barber, 2008), and when they do, they are two to three times more likely to attempt suicide than females (Duke, Pettingell, McMorris, & Borowsky, 2010). In this line, in a community sample of adolescents, suicidal thoughts were associated with self-reported sexual abuse in boys, and with depression, hopefulness, and family dysfunction in females, pointing to sex-specific mechanisms linking childhood abuse and suicidal thoughts (Martin, Bergen, Richardson, Roeger, & Allison, 2004).

It has been proposed that childhood abuse predicts suicidal behaviour among MDD patients with comorbid borderline personality disorder (BPD) (Pompili et al., 2014) or even with BPD traits (Aaltonen et al., 2017). This is an important finding that may help in understanding the increased risk of suicide in this particular group of patients. However, it is still not clear whether a similar mechanism can be confirmed for MDD patients without personality disorders, who also present a high risk of suicide attempts (Zeng et al., 2015) and represent the vast majority (55–85%) of MDD patients (Friborg et al., 2014). Also, women are overrepresented among patients with MDD (Kuehner, 2003), which could be indicative of differential susceptibility associated with a number of sex-related factors such as psychobiological response to early adversity (Elton et al., 2014). Exploring the sample from a sex-specific point of view may help researchers to identify factors particularly influenced by sex.

In the present study, we hypothesize that early exposure to maltreatment will be a significant predictor of history of suicide attempts in adult patients with MDD, above and beyond other explanatory risk factors. We highlight that this association is evident among MDD patients with no history of other alterations that could better explain suicidal behaviour, such as substance abuse, neurological illness, or personality disorders. To test this hypothesis, we examined the association between childhood maltreatment and history of suicide attempts in a well-characterized sample of patients with a principal diagnosis of MDD. We used a model that controlled for the impact of specific risk factors for suicide attempts in MDD patients defined in previous reviews. We further explored putative sex-specific mechanisms underlying this association by testing the model in males and females independently. In this regard, we expected a higher percentage of female patients to report maltreatment, and sex-specific factors involved

in the association between childhood maltreatment and suicide attempts.

## 2. Methods

### 2.1. Participants

The study sample comprised 165 Caucasian outpatients consecutively admitted to the Mental Health Unit at Parc Taulí University Hospital (Sabadell, Spain). Only patients with MDD (past or present diagnosis of MDD), according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR), as the main reason for seeking consultation were enrolled in the study; secondary diagnoses of anxiety disorders and dysthymia were allowed, given the high rates of these disorders among MDD patients (Ressler & Mayberg, 2007). Patients with dysfunctional personality traits but who did not fulfil DSM-IV criteria for Axis II diagnosis were also included. All diagnoses were confirmed by an expert psychiatrist using the Structured Clinical Interview for DSM-IV (Clinician Version) (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1997). Exclusion criteria were: age under 18 or over 65 years old; and current or past history of substance abuse, neurological disorder, and/or DSM-IV diagnosis of personality disorders. All patients provided written informed consent prior to inclusion. The Ethics Committee at the Parc Taulí University Hospital approved the study and all procedures were carried out in accordance with the Declaration of Helsinki.

### 2.2. History of suicide attempt

History of suicide attempt was defined as a ‘yes’ response to the question ‘Have you ever attempted suicide?’ (Dube et al., 2001). The question was asked during the interview and the responses provided by the patients were contrasted with the clinical records. Following a ‘yes’ response, further information was collected regarding the number and types of attempts.

### 2.3. Demographic and clinical assessment

Trained psychologists performed direct interviews to assess demographic and clinical features of the patients. Demographics included age, sex, years of education, and socio-economic status (SES).

Clinical variables of interest for our study were identified based on a systematic review of the risk factors for completed suicide in patients with MDD (Hawton et al., 2013) and the information provided by recent original studies (Courtet, 2010; Janiri et al., 2018; Tunnard et al., 2014; Zoltan, 2007). The variables of interest identified were: family history of psychiatric

disorder, age at onset of MDD, MDD symptom severity, MDD with psychotic symptoms, treatment-resistant depression, and comorbidities.

Family history of psychiatric disorder in first- and second-degree relatives was assessed through direct interviews with the patients and with relatives when possible. Presence of family history was recorded only when the identified relatives had been diagnosed by an expert psychiatrist and had been treated for the disorder.

Age at onset of MDD was defined as the age at which symptoms became a significant source of distress and interfered with the patient's functioning (Goldberg et al., 2015). Symptom severity at time of inclusion in the study was assessed with the 17-item Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1960). Comorbidities and MDD with psychotic symptoms were identified based on DSM criteria (SCID). Dysfunctional personality traits were classified as present/absent based on clinical impressions, although none of the patients fulfilled DSM-IV criteria for Axis II diagnosis. Treatment-resistant depression was assessed with the Maudsley Staging Method (MSM) (Fekadu et al., 2009), a model staging treatment resistance that ranges from 5 (no resistance) to 15 (highest level of resistance).

#### 2.4. Childhood abuse and neglect

Maltreatment experiences during childhood and adolescence were assessed using the short form of the Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998); Spanish validation by Hernandez et al. (2013). The reliability and validity of this questionnaire have been proven (Bernstein et al., 2003). In brief, the CTQ assesses five types of maltreatment experiences through 25 items scored on a five-point Likert-type scale ranging from never true (= 1) to very often true (= 5). Each type of maltreatment experience is scored on a specific subscale: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN). Scores on these subscales range from 5 to 25 and can be classified according to severity following the original guidelines (Bernstein & Fink, 1998). In agreement with previous reports, and to enhance the statistical power (Catalan et al., 2017; De Sanctis, Nomura, Newcorn, & Halperin, 2012), a dichotomous variable was created in which individuals were categorized as maltreated (in contrast to not-maltreated) if they presented moderate to severe criteria for one or more subtypes of maltreatment (PA  $\geq$  10; EA  $\geq$  13; SA  $\geq$  8; PN  $\geq$  10; EN  $\geq$  15).

The CTQ also includes a minimization–denial scale, which comprises three items. This scale detects socially desirable responses that suggest underreporting of childhood maltreatment and have been found to moderate the questionnaire's discriminative

validity (MacDonald et al., 2016). The presence or absence of minimization and denial attitudes was explored in our study, with 0 = no minimization.

#### 2.5. Data analysis

All data were analysed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). We first obtained a description of the characteristics of the complete sample. We then classified the patients as maltreated versus not maltreated, and examined the distribution of the variables of interest between groups using Pearson chi-squared or Student's *t*-test as appropriate (Table 1).

Next, we performed a binomial logistic regression analysis on the total sample to test the impact of childhood maltreatment on the history of suicide attempts while controlling for other variables of interest. First, we ran an unadjusted model that included history of suicide attempts as the outcome, and the following variables as predictors: presence of childhood maltreatment, sex, age at onset, family history of psychiatric disorders, comorbidities, MDD symptom severity, MDD with psychotic symptoms, treatment-resistant depression, and CTQ minimization–denial score. This test of the unadjusted model was followed by the analysis of a fully adjusted model. Because the unadjusted model was a preliminary examination of the data, we used a *p*-value  $<$  0.15 to inform the decision about the variables to be included in the fully adjusted model. For the rest of the statistical analyses, we used a *p* value of  $<$  0.05.

To further explore potential sex-related differences in the mechanisms underlying these associations, we ran independent binomial logistic regression analysis in the group of male patients and in the group of female patients. For these unadjusted models we included history of suicide attempts as the outcome, and the following variables as predictors: presence of childhood maltreatment, age at onset, family history of psychiatric disorders, comorbidities, MDD symptom severity, MDD with psychotic symptoms, treatment-resistant depression, and CTQ minimization–denial score. As was the case for the total sample, the final step was to run a fully adjusted model within each group, including only the variables that reached a *p*-value  $<$  0.05.

### 3. Results

#### 3.1. Sample description

The distribution of age and sex in the total sample was as expected for a sample of adult MDD patients, with a mean age in older adulthood (mean = 52.3, *SD* = 9.6, range = 18–65) and a large presence of female patients (69.5%).

**Table 1.** Distribution of demographic and clinical characteristics for the complete sample and according to childhood maltreatment group.

	Total sample (N = 165)	Childhood maltreatment (N = 94)	No childhood maltreatment (N = 71)	t-Test/ $\chi^2$	p
<b>Demographic variables</b>					
Age (years)	52.3 ± 9.6	51.5 ± 9.7	53.4 ± 9.4	1.261	0.21
Sex (female)	114 (69.5)	66 (70.2)	48 (68.6)	0.051	0.87
Years of education	10.4 ± 4.3	10.7 ± 3.9	11 ± 3.9	0.480	0.63
<b>Socio-economic status</b>					
Low	54 (32.9)	29 (30.9)	25 (35.7)	5.084	0.08
Middle	94 (56.7)	59 (62.8)	35 (48.6)		
High	17 (10.4)	6 (6.4)	11 (15.7)		
<b>Clinical characteristics</b>					
Age at onset (years)	41.7 ± 12.2	41.1 ± 11.4	42.5 ± 13.2	0.731	0.47
Treatment-resistant depression	6.4 ± 2.1	6.6 ± 2.0	6.1 ± 2.2	-1.378	0.17
MDD symptom severity	14.3 ± 8.6	15.2 ± 8.3	13.1 ± 8.9	-1.559	0.12
MDD with psychotic symptoms	17 (10.7)	9 (9.8)	8 (11.9)	0.189	0.80
<b>Comorbidities</b>					
Anxiety	10 (6.1)	5 (5.3)	5 (7.1)	0.233	0.75
Dysthymia	35 (21.3)	25 (26.6)	10 (14.3)	3.622	0.08
Dysfunctional personality traits <sup>a</sup>	20 (12.2)	10 (10.6)	10 (14.3)	0.498	0.48
Family history of psychiatric disorders	133 (81.6)	74 (79.6)	59 (84.3)	0.591	0.54
History of suicide attempt	33 (20.1)	23 (24.5)	10 (14.3)	2.588	0.11
CTQ minimization–denial scale = 1	79 (47.9)	34 (36.2)	45 (63.4)	12.001	0.001

Data are presented as mean ± SD or frequency (%) as appropriate.

<sup>a</sup>Do not fulfil Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for personality disorder. MDD, major depressive disorder; CTQ, Childhood Trauma Questionnaire.

The most frequent socio-economic level was middle SES (56.7%), with 10.4% identified as low SES and 32.9% as high. The majority of the sample (144 patients, 88.9%) lived in an urban environment.

Mean depression severity score at time of inclusion in the study was 14.3 ( $SD = 8.6$ ), ranging from no current acute depression (i.e. total HAM-D scores between 0 and 7: 28.7% of the sample) to very severe acute depression (i.e. total HAM-D scores over 23, 17.8%). Mean age at onset of the disorder was 41.7 years ( $SD = 12.2$ ), mean treatment-resistant depression as estimated by MSM score was 6.4 ( $SD = 2.1$ ), and 17 patients (10.7%) presented MDD with psychotic symptoms. Ten patients (6.1%) had a comorbid diagnosis of anxiety, 35 (21.3%) of dysthymia, and 20 (12.2%) presented dysfunctional personality traits that did not fulfil a DSM-IV Axis II diagnosis of personality disorder.

Thirty-three patients (20.1%) had a history of suicide attempt(s) during their lifetime. Twenty-six of these patients were female (78.8%). The comparison of the proportion of female and male patients in the groups with and without suicide attempt was not statistically significant ( $\chi^2 = 1.68$ ,  $p = 0.195$ ). Among all the patients who attempted suicide, nine (5.7%) presented more than one attempt. Suicide attempts were distributed as follows among the 164 participants: 123 patients (78.8%) had no history of suicide attempts, 24 (15.4%) had made one suicide attempt, seven patients had made two, and two patients (1.2%) had made three or more attempts. No sex-related differences were found in number of attempts. The most frequent type of attempt was medication overdose, reported by 28 patients of the total of 33 with a history of attempted suicide (21 female, seven male).

A total of 133 patients (81.1%) reported a family history of mental disorder including major depressive, bipolar, psychotic and anxiety disorders, or drug abuse. Eleven patients reported a family history of suicide; seven of these also presented a personal history of suicide attempts while four did not.

### 3.2. Frequency of childhood maltreatment in the total sample

Considering the total sample of MDD patients ( $N = 165$ ), the results showed that 57% reported childhood maltreatment. Almost half of the sample (47.9%) scored positive on the minimization–denial scale, indicating that the presence of childhood maltreatment may be higher than reported.

Emotional neglect was the most frequent type of maltreatment, reported by 42.4% of the sample ( $n = 70$ ), followed by physical neglect (27.9%), emotional abuse (28.5%), sexual abuse (20%), and physical abuse (13.9%). These frequencies are within the ranges reported in review studies (Nelson et al., 2017). When taking sex into consideration, although there were no differences in the prevalence of maltreatment, the percentage of women suffering emotional abuse was higher than in men (see Table 2 for more details).

### 3.3. Distribution of demographic and clinical characteristics according to presence of childhood maltreatment

The distribution of the demographic characteristics in the two groups of patients according to experience of childhood maltreatment is presented in Table 1.

**Table 2.** Presence and type of maltreatment divided by sex.

	Female (N = 114)	Male (N = 51)	$\chi^2$	p
Maltreatment (presence)	66 (57.9)	28 (54.9)	0.129	0.720
Emotional abuse	39 (34.2)	8 (15.7)	5.936	0.015*
Physical abuse	16 (14.0)	7 (13.7)	0.003	0.958
Sexual abuse	27 (23.7)	6 (11.8)	3.129	0.077
Emotional neglect	48 (42.1)	22 (43.1)	0.015	0.901
Physical neglect	29 (25.4)	17 (33.3)	1.092	0.296
CTQ minimization–denial scale = 1	51 (44.7)	27 (54.0)	1.196	0.274

Data are presented as frequency (%) within each category.

CTQ, Childhood Trauma Questionnaire.

\*Significant difference between groups ( $p < 0.05$ ).

Results showed no statistically significant differences according to age, sex, years of education, or SES. Nor were differences found in clinical variables including age at onset of MDD, treatment-resistant depression, MDD symptom severity, MDD with psychotic symptoms, family history of psychiatric disorders, and comorbidities.

A history of suicide attempts was present in 24.5% of the patients in the childhood maltreatment group while the percentage was lower in the no-maltreatment group (14.3%), although the comparison did not reach statistical significance ( $\chi^2 = 2.59$ ,  $p = 0.11$ ).

The results also showed differences in the tendency to provide a socially desirable response, as assessed by the CTQ minimization–denial scale. Patients in the no-maltreatment group were more prone to minimization–denial (62.9% vs 36.2% of patients in the maltreatment group;  $p = 0.01$ ).

### 3.4. Impact of childhood maltreatment on history of suicide attempts in MDD patients in the total sample

Next, we tested the unadjusted model to explore the impact of childhood maltreatment on the history of suicide attempts in the total sample of MDD patients, while controlling for the effect of other risk factors for suicide attempts and the score on the CTQ minimization–denial scale. This unadjusted model showed a

significant association between childhood maltreatment and a history of suicide attempts, and indicated an impact of family history of psychiatric disorders with a trend towards significance ( $p = 0.07$ ) (Table 3).

Therefore, the adjusted model was tested including only these two predictors. A test of the full model against a constant-only model was statistically significant, indicating that childhood maltreatment and family history of psychiatric disorders as a set reliably distinguished between MDD patients with and without a history of suicide attempts ( $\chi^2 = 9.330$ ,  $df = 2$ ,  $p < 0.01$ ). The model accounted for 9% of the variance (Nagelkerke's  $R^2 = 0.093$ ). Prediction success overall was 80.6%. In the total sample, childhood maltreatment increased the odds of having a history of suicide attempts three-fold (OR = 3.01, 95% CI 1.19–7.61,  $p < 0.05$ ). The association between family history of psychiatric disorders and history of suicide attempts showed a trend towards significance in the fully adjusted model (OR = 3.87, 95% CI 0.84–17.67,  $p = 0.08$ ). We tested an interaction term between childhood maltreatment and family history, which was not statistically significant.

### 3.5. Sex-specific impact of childhood maltreatment on history of suicide attempts in MDD patients

We tested the unadjusted model as mentioned before, independently in the group of female patients and in the group of male patients (Table 3). The exploration in the group of female patients ( $N = 114$ ) showed only a significant association between childhood maltreatment and a history of suicide attempts ( $p < 0.05$ ), while the effect of the other predictors remained non-significant. The fully adjusted model accounted for 6% of the variance (Nagelkerke's  $R^2 = 0.06$ ). Prediction success overall was 77.3% and the test of the full model against a constant-only model was statistically significant ( $\chi^2 = 4.44$ ,  $df = 1$ ,  $p < 0.05$ ). In this group, childhood maltreatment increased the

**Table 3.** Binomial logistic regression analysis results for the model entering all variables of interest (unadjusted model) and the model entering only statistically significant variables (fully adjusted model).

Variable	Unadjusted model			Fully adjusted model								
	Total sample (N = 165)			Total sample (N = 165)			Female (N = 114)		Male (N = 51)			
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Sex	2.53	0.85–7.51	0.10									
Age at onset	1.01	0.98–1.05	0.53							1.18	0.99–1.38	0.06
Family history of psychiatric disorders	4.32	0.94–20.65	0.07*	4.0	0.87–18.37	0.08						
Comorbidities	0.72	0.48–2.87	0.72									
MDD symptom severity	0.98	0.93–1.03	0.50									
MDD with psychotic symptoms	0.50	0.09–2.90	0.44									
Treatment-resistant depression	1.07	0.84–1.35	0.59									
CTQ minimization–denial scale	1.11	0.45–2.73	0.82							10.21	0.90–116.33	0.06
Childhood maltreatment	3.33	1.23–9.03	0.02*	3.01	1.19–7.09	0.02*	2.82	1.02–7.74	0.04*	3.92	0.44–34.80	0.22

MDD, major depressive disorder; CTQ, Childhood Trauma Questionnaire.

\*Significant difference between groups (Unadjusted model  $p < 0.15$ ; Fully adjusted model  $p < 0.05$ ).

odds of having a history of suicide attempts almost three-fold (OR = 2.82, 95% CI 1.02–7.74,  $p < 0.05$ ).

For the group of male patients ( $N = 51$ ), in the test of the unadjusted model, age at onset of the disorder and CTQ minimization–denial scale showed statistically significant effects ( $p < 0.05$ ), while the association between childhood maltreatment and history of suicide attempts presented a trend towards significance ( $p = 0.07$ ). A test for the fully adjusted model that included these three predictors showed 33% of the variance accounted for by the model (Nagelkerke's  $R^2 = 0.326$ ). Prediction success overall was 86% and the test of the full model against a constant-only model was statistically significant ( $\chi^2 = 9.97$ ,  $df = 3$ ,  $p < 0.05$ ). However, the association between the predictors and the outcome showed only a trend towards significance in the case of age at onset and CTQ minimization–denial scale ( $p = 0.06$  in both cases), while the association for childhood maltreatment was not statistically significant ( $p = 0.22$ ). Of note, six out of the seven male patients who had attempted suicide in our sample presented minimization and denial attitudes.

### 3.6. Complementary analysis: impact of type of childhood maltreatment on suicide attempts in MDD patients

As previous studies have suggested that different types of childhood maltreatment constitute distinct constructs representing different facets of the phenomenon (Bernstein et al., 2003), we performed a complementary analysis consisting of a separate binomial logistic regression with history of suicide attempts as the outcome and the five types of childhood maltreatment as predictors.

We further investigated whether the association found between childhood maltreatment and history of suicide attempts could be attributed to a specific type of maltreatment as assessed by the CTQ subscales: PA, EA, SA, PN, and EN.

Among the 94 patients with childhood maltreatment, 31.9% reported exposure to only one type of maltreatment, while the remaining 68.1% of the patients reported exposure to two or more types. Specifically, 28.7% reported two types, 21.3% reported three, 11.7% reported four, and 6.4% reported exposure to all five.

In view of the results of the regression analyses, we performed a binomial logistic regression analysis with history of suicide attempt(s) as the outcome variable, and the following predictive variables: family history of psychiatric disorders, presence of PA, presence of EA, presence of SA, presence of PN, and presence of EN. As in the exploration of the main analysis, we first ran an unadjusted model that included all variables of interest. None of the types of childhood maltreatment reached significance in this model.

The percentage of the variance accounted for by the model (10%), prediction success overall (81.3%), and impact of family history of psychiatric disorders (OR = 4.34, 95% CI 0.93–20.30,  $p = 0.06$ ) were similar to those found in the main analysis.

## 4. Discussion

As expected, childhood maltreatment was a significant predictor of history of suicide attempts in the total sample of patients with MDD. Importantly, the impact of childhood maltreatment was clinically relevant after adjusting for previously proposed risk factors for suicide attempts, and evident in MDD patients without other alterations that could better explain suicidal behaviour. Patients who had suffered childhood maltreatment were 3.01 times more likely to have a history of suicide attempt (95% CI 1.19–7.09,  $p < 0.05$ ) than MDD patients with no childhood maltreatment. This result is in line with published estimates of risk in the general population (Aguilera et al., 2009; Dube et al., 2001; Hoertel et al., 2015) and in special populations (Tunnard et al., 2014).

Our study suggests a clear role of childhood maltreatment in the presence of suicide attempts in MDD patients, which may shape the course and outcome of the treatment. Although the mechanisms underlying this association are not yet completely understood, a number of theories have been proposed based on findings in the general population. A widely accepted model proposes that high psychosocial stress acts as a disruptive force over the normal developmental processes, leading to maladaptive emotion regulation and social skills (Danese & McEwen, 2012). Accordingly, childhood maltreatment would promote enduring changes in the nervous, endocrine, and immune systems that may limit the person's resources to cope with future stressful situations (De Bellis & Zisk, 2014; Tafet & Nemeroff, 2016). Furthermore, the relationship between childhood maltreatment and suicide attempts has been hypothesized to be mediated by different psychological and social variables, such as interpersonal difficulties during middle adolescence (Johnson et al., 2002), being abused by an immediate family member (Brezo et al., 2008), affective lability (Aas et al., 2017), hopelessness (Meadows & Kaslow, 2002), or experiential avoidance (Fiorillo, Papa, & Follette, 2013; Kingston, Clarke, & Remington, 2010; Marx & Sloan, 2002). If this were the case, clinical treatment could be oriented towards the mechanisms involved in stress response, at the levels of both behaviour and pharmacotherapy, to promote a more adaptive coping strategy in challenging situations.

In our analysis, childhood maltreatment and family history of psychiatric disorders as a set explained 9% of the variance of history of suicide attempts in MDD

patients. This estimate is significant and relevant in clinical settings, although it is clear that other factors need to be added to achieve a fuller understanding of this outcome, with particular attention being paid to the context surrounding the attempt (Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013). The results provide support for the theories of a joint influence of genetic vulnerability and stressful early environmental factors on suicide attempts in MDD patients. These theories have proposed different mechanisms, including a diathesis–stress model (Mann, 2003; Monroe & Simons, 1991), a differential susceptibility model (Belsky & Pluess, 2009), and a ‘two-hit hypothesis’ (originally proposed in cancer studies by Knudson, and commonly used in schizophrenia research) (Davis et al., 2016). During the past decade, an epigenetic approach has gained support to describe the joint action of genes and environment and its impact on adult health (Fiori & Turecki, 2016; McGowan et al., 2009; Teicher & Samson, 2013) and specifically on MDD (Bao & Swaab, 2014; Mann & Currier, 2010). Also related to our topic, a recent article using post-mortem samples of MDD patients who completed suicide reported DNA methylation changes in those with a history of childhood abuse, but not in MDD patients without this history (Lutz et al., 2017). This research highlights a close interaction between genetic and environmental backgrounds that is assumed to shape human adaptive behaviour and coping.

In this article we also explored the effect of sex on the association between childhood maltreatment and suicide attempts, not only as a covariate in the general model, but – importantly – as a relevant factor in such associations. Among female patients, besides their having a higher rate of emotional abuse, results showed evidence to further support a specific role of childhood maltreatment as a key risk factor to attempt suicide, above and beyond other clinical influences. This association was not evident among male patients. In this group, the association presented a trend towards significance between the CTQ minimization scale – a measure of denial of trauma – and suicide attempts and between age at onset and suicide attempts ( $p = 0.06$ ). These results call for a discussion regarding sex-related differences in the impact of childhood maltreatment on suicide attempts among MDD patients.

When contrasting findings according to sex-based differences, both biological and psychosocial explanations should be taken into consideration. As commented above, the neurobiological effects of childhood maltreatment comprise dysfunctional responses of the endocrine stress system and brain development alterations that impact the amygdala and prefrontal network. Sex-related differences are evident in these processes, specifically those including the involvement of the amygdala in emotional and behavioural responses (Janak & Tye, 2015) and the

presence of sex-hormone receptors (Bender et al., 2017; Engman, Linnman, Van Dijk, & Milad, 2016), which may confer girls and boys different vulnerabilities to early stress (Rhodes et al., 2014).

From a gene–environment interaction perspective, it is relevant to highlight the role of key genotypic variants involved in these processes that are expressed in different time windows and also differ between sexes (Schwarz, Nugent, & McCarthy, 2010; Wilson et al., 2009). In this sense, the sex differences found in our study could be derived from the potential impact of childhood maltreatment during critical windows of development that represent different sensitive periods for boys and girls (Rhodes et al., 2014). As a consequence, childhood maltreatment increases further risks during pubertal transition through early timing of puberty, early sexual relationships, and an increased risk of physical and sexual victimization by an intimate partner in adulthood (Arias, 2004; Desai, Arias, Thompson, & Basile, 2002). Particularly in women, revictimization has, in turn, been associated with depressive symptoms and suicide attempts (Devries et al., 2013), and hence should be considered when exploring the specific relationship between childhood maltreatment and suicide attempts among women.

Among male patients, two other factors presented a clear trend towards statistically significant effects ( $p = 0.06$ ) and deserve further attention. First, age at onset showed a relevant effect indicating that a later age at onset might be associated with suicide attempts among male MDD patients. Inconsistent results have been reported regarding early and late onsets as risk factors for more severe forms of depression (Kornstein & Schneider, 2001). These inconsistencies are probably due to the potential interaction of other variables, including the sex of the subjects. The only study found specifically looking at this relationship from a sex perspective (Lavretsky, Lesser, Wohl, & Miller, 1998) suggests that men with late-onset depression have an increased risk of presenting diffuse brain abnormalities. These abnormalities could underlie a more severe course of the disease, including suicide attempts. Secondly, the CTQ minimization–denial scale had an impact on suicide attempts among male MDD patients. This three-item response bias subscale detects artificially desirable responses. Such responses are not necessary intentional but rather denote a ‘naïvely positive, almost idyllic representation of childhood experiences’ (MacDonald et al., 2016) and may be approached as an indicator of a more complex mechanism of denial of trauma (MacDonald, Thomas, MacDonald, & Sciolla, 2015). It is therefore noticeable that this effect was only evident among male MDD patients, suggesting: (1) a specific psychological mechanism that may be mainly present among male MDD patients (as opposed to female patients);

and (2) underreporting of maltreatment among male MDD patients that could explain the lack of statistically significant associations between childhood maltreatment and suicide attempts in this group. The results of the fully adjusted model showed only a trend towards significance and the large estimate (CTQ minimization–denial scale OR = 10.21, 95% CI 0.90–116.33) may be related to the fact that almost all male patients in our sample who attempted suicide also presented denial attitudes (six out of seven patients).

#### 4.1. Clinical implications

The results of this study support that childhood maltreatment is a risk factor for suicide attempts, and suggest that the mechanisms involved in this association are probably mediated by emotional (affective lability, hopelessness) and behavioural (interpersonal difficulties, experiential avoidance) factors. Hence, therapies that focus on developing skills to distress tolerance and affect regulation might be applied in individuals at risk. Third-generation psychosocial treatments that include components to work with trauma-related memories may be successful, particularly among women (Lang & Sharma-Patel, 2011). For male MDD patients, especially for those with late onsets, it may be also helpful to include clinical strategies directed at treating denial of trauma and to discuss childhood maltreatment with the assistance of tools that are sensitive to the reality that young boys could have been exposed to.

#### 4.2. Limitations

Although the total sample size has a good statistical power, when splitting the analysis by sex, the proportion of males ( $N = 51$ ) is modest. Hence, further studies should be run to overcome the limited sample size of these analyses and conclusions must be considered cautiously. In any case, choosing a male MDD sample could better resolve this issue, as women tend to be overrepresented in naturalistic studies such as ours.

The results showed no significant increase in the risk of history of suicide attempts associated with any of the subscales. Although this result may suggest the absence of a specific mechanism associated with a particular form of maltreatment, this analysis presents certain limitations: (1) subtypes of maltreatment are highly correlated and frequently co-occur (Green et al., 2010), as was the case in 68.1% of the patients in our sample; (2) the CTQ provides a solid measure of a broad dimension of childhood maltreatment, but it has been recommended that the assessment of its subtypes should be complemented with a semi-structured interview (Spinhoven & Penninx,

2014); and (3) previous research has proposed that different types of childhood maltreatment provide a common liability to adult psychopathology (Keyes et al., 2012), and therefore the impact of specific types of maltreatment may not be as relevant. Against this background, the effect of the different subtypes of maltreatment on outcome may be better approached in the context of in-depth interviews.

In addition, we found no evidence of a more severe clinical form of MDD (in terms of symptom severity and treatment resistance) among patients who had suffered childhood maltreatment (Table 1), in contrast with previous reports (Nelson et al., 2017). This may be attributed to the design of our study, which explicitly excluded patients with DSM-IV Axis II diagnoses of personality disorders, history of drug abuse, and neurological comorbidities. Hence, the distribution of the scores of treatment-resistant depression in our sample might have been different if we had included patients with these alterations.

Although patients with a diagnosis of personality disorder were not included, the fact that the dysfunctional personality traits were classified only on the basis of clinical impression makes this information difficult to replicate. The lack of reliable information regarding perceived social support may also limit the findings, as this has been demonstrated to be an important factor in mitigating the effects of childhood maltreatment (Evans, Steel, & DiLillo, 2013). Finally, the fact that our sample comprises late-adult MDD patients with a mean age at onset around 40 years old could be viewed as a limitation. It is clear that specific analyses in samples of MDD patients with an earlier age at onset are warranted to confirm our results among young-adult patients. On the other hand, the risk for transition from MDD to bipolar disorder in late-adult MDD patients is low, and therefore the mean age at onset of our sample argues against the changes in diagnosis at follow-up.

#### 4.3. Conclusions

In summary, we provide evidence that childhood maltreatment increases the risk of suicide attempts among MDD patients, and that this association is apparent even in the absence of previously proposed risk factors. These findings provide further support to the notion that childhood maltreatment has a clear impact on the history of suicide attempts. This is especially relevant given that history of suicide attempts is the single most important predictor of completed suicide – the primary cause of premature death among MDD patients. Childhood maltreatment should be emphasized as a key predictive factor for suicide attempts in MDD patients, and the joint action of a genetic background and environmental stressors should be

considered in the design of interventions and strategies for promoting healthy behaviour (McEwen, 2017). Importantly, while these conclusions seem to be true for female MDD patients, suicide attempts in male patients may respond to a different configuration of the factors involved in this phenomenon. Clinicians attending MDD patients are strongly recommended to carefully consider family predisposition, history of childhood maltreatment, and sex to facilitate the early identification of potential suicidal behaviour in patients experiencing stressful life events.

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