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The impact of comorbid post-traumatic stress disorder in patients with major depressive disorder on clinical features, pharmacological treatment strategies, and treatment outcomes – Results from a cross-sectional European multicenter study

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Abstract
This international, multicenter, cross-sectional study comprising 1346 adult in- and outpatients with major depressive disorder (MDD) investigated the association between MDD as primary diagnosis and comorbid post-traumatic stress disorder (PTSD). In a cross-sectional data collection process, the presence of comorbid PTSD was determined by the Mini International Neuropsychiatric Interview (MINI) and the patients' socio-demographic, clinical, psychopharmacological, and response information were obtained. Clinical features between MDD with and without concurrent PTSD were compared using descriptive statistics, analyses of covariance (ANCOVA), and binary logistic regression analyses. 1.49% of the MDD patients suffered from comorbid PTSD. Significantly more MDD + comorbid PTSD patients exhibited atypical features,

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comorbid anxiety disorders (any comorbid anxiety disorder, panic disorder, agoraphobia, and social phobia), comorbid bulimia nervosa, current suicide risk, and augmentation treatment with low-dose antipsychotic drugs. In the binary logistic regression analyses, the presence of atypical features (odds ratio (OR) = 4.49, 95%CI:1.01-20.12; $p \leq .05$), any comorbid anxiety disorder (OR = 3.89, 95%CI:1.60-9.44; $p = .003$), comorbid panic disorder (OR = 6.45, 95% CI:2.52-16.51; $p = .001$), comorbid agoraphobia (OR = 6.51, 95%CI:2.54-16.68; $p \leq .001$), comorbid social phobia (OR = 6.16, 95%CI:1.71-22.17; $p \leq .001$), comorbid bulimia nervosa (OR = 10.39, 95%CI:1.21-88.64; $p = .03$), current suicide risk (OR = 3.58, 95%CI:1.30-9.91; $p = .01$), and augmentation with low-potency antipsychotics (OR = 6.66, 95%CI:2.50-17.77; $p < .001$) were associated with concurrent PTSD in predominant MDD. Major findings of this study were (1.) the much lower prevalence rate of comorbid PTSD in predominant MDD compared to the reverse prevalence rates of concurrent MDD in primary PTSD, (2.) the high association to comorbid anxiety disorders, and (3.) the increased suicide risk due to concurrent PTSD.

1. Introduction

Major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are chronic diseases with 12-month prevalence rates of 6.9% and 1.1-2.9%, respectively (Wittchen et al., 2011). Both disorders are associated with reduced quality of life, functional impairment, and substantial economic burden (Gustavsson et al., 2011; Wittchen et al., 2011). A meta-analysis based on 57 individual studies with altogether 6670 participants found a prevalence rate of 52% for comorbid MDD in patients with a primary diagnosis of PTSD (Rytwinski et al., 2013). However, only very few surveys examined the reverse prevalence, i.e. the occurrence of comorbid PTSD in patients with predominant MDD. They suggest much lower prevalence rates of less than 5% for concurrent PTSD in MDD (Balestri et al., 2016; Thaipisuttikul et al., 2014).

To investigate PTSD as comorbidity of MDD in a large representative MDD patient sample (n=1346) for the first time, we aimed to explore differences in socio-demographic, clinical, psychopharmacological, and response characteristics between MDD subjects with and without comorbid PTSD and to determine the association between various variables and the presence of concurrent PTSD in MDD employing binary logistic regression analyses.

2. Experimental procedures

This international, multicenter, non-interventional, cross-sectional trial of the European Group for the Study of Resistant Depression (GSRD) (Dold et al., 2016; Schosser et al., 2012; Souery et al., 2007) was carried out in 10 university/academic sites across Europe: (1.) Psychiatry Section, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy; (2.) Division of Psychiatry, Department of Neuroscience, University of Siena School of Medicine, Siena, Italy; (3.) Department of Psychiatry, University Hospital of Geneva, Geneva, Switzerland; (4.) Psy Pluriel, European Centre of Psychological Medicine, Université Libre de Bruxelles, Brussels, Belgium; (5.) Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; (6.) Department of Psychiatry, Psychotherapy, and Psychosomatics, University of Halle, Halle, Germany; (7.) Department of Psychiatry, Athens University Medical School, Eginition Hospital, Athens, Greece; (8.) Department of Psychiatry, Chaim Sheba Medical Center, Tel Hashomer, Israel; (9.) Clinical Investigation Center Dr. Gailledreau, Elancourt, France; and (10.) Clinical Investigation Center Dr. Modavi, Toulouse, France. The study was approved by the ethics committees at each site and all patients provided written informed consent.

Between November 2012 and February 2016, we included adult in- and outpatients with predominant MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR criteria (classification code: 296.2x or 296.3x). The MDD diagnosis had to be confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Prior to study entry, all participants had to be treated with at least one antidepressant during their current MDD episode (≥ 4 weeks in adequate dose [Supplementary online Table 1]). Exclusion criteria were (1.) any other primary psychiatric disorder than MDD, (2.) any substance disorder (except nicotine and caffeine) in the previous six months, and (3.) any severe personality disorder.

The socio-demographic, clinical, treatment, response, and pharmacological information of the participants were gathered in a detailed clinical interview (cross-sectional data collection process). For the evaluation of current comorbid PTSD and other psychiatric comorbidities, the patients were interviewed using the MINI. The present depressive symptom severity was measured by the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the 17- and 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). In addition, the symptom severity at the onset of the present MDD episode was evaluated by calculating a retrospective MADRS score based on the patient's statements and medical record information. Hence, symptom changes during the current depressive episode could be operationalized by MADRS total score changes (retrospective MADRS score - present MADRS score). Treatment response was defined by $\geq 50\%$ MADRS total score reduction during the pharmacotherapy with 1 antidepressant agent (≥ 4 weeks at an adequate dose). Treatment resistance was evidenced by treatment failures to ≥ 2 consecutive adequate trials with antidepressants or combination/augmentation medications.

The data analysis was performed using SPSS version 23.0. We allocated the participants into two different study groups according to the presence of comorbid PTSD (MDD with vs without PTSD). We employed descriptive statistics (means, standard deviations (SD), and/or percentages) to present the characteristics of the study arms. For between-group comparisons, we used chi-squared tests (categorical variables) and analyses of covariance (ANCOVA) (continuous variables) with presence of comorbid PTSD (fixed effect), center

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