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Predictors of switch from depression to mania in bipolar disorder

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ABSTRACT

Manic switch is a relevant issue when treating bipolar depression. Some risk factors have been suggested, but unequivocal findings are lacking. We therefore investigated predictors of switch from depression to mania in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample. Manic switch was defined as a depressive episode followed by a (hypo)manic or mixed episode within the following 12 weeks. We assessed possible predictors of switch using generalized linear mixed models (GLMM).

8403 episodes without switch and 512 episodes with switch (1720 subjects) were included in the analysis. Several baseline variables were associated with a higher risk of switch. They were younger age, previous history of: rapid cycling, severe manic symptoms, suicide attempts, amphetamine use and some pharmacological and psychotherapeutic treatments. During the current depressive episode, the identified risk factors were: any possible mood elevation, multiple mania-associated symptoms with at least moderate severity, and comorbid panic attacks.

In conclusion, our study suggests that both characteristics of the disease history and clinical features of the current depressive episode may be risk factors for manic switch.

1. Introduction

Bipolar disorder (BD) is a chronic disease characterized by the alternation of periods of (hypo)mania and depression, resulting in high personal and socio-economic burden in terms of poor quality of life, increased rates of suicide, direct and indirect costs (Ferrari et al., 2012; Conus et al., 2013; Fagiolini et al., 2013; Kleine-Budde et al., 2013; Whiteford et al., 2013). The course of BD is highly variable, thus the identification of individuals at higher risk of experiencing a more severe course has relevant implications for both patients and public health care.

Switch from depression to (hypo)mania or mixed status is a critical issue since its high impact on disease severity. Indeed, patients with one or more episodes of switch have longer periods of illness lifetime and higher risk of suicide; further, they experience more comorbidities (e.g. substance abuse) (Maj et al., 2002; MacKinnon et al., 2003a, 2003b, 2005). Thus, the identification of switch risk factors represents a pivotal issue in order to prevent this detrimental event and improve BD prognosis. Previous studies investigated antidepressant (AD)-related switch in patients with BD, and they suggested a number of risk factors (see Supplementary Table S1 for a summary). On the basis of the results observed in the largest samples, the most replicated risk factors were previous history of switch or rapid cycling, younger onset age, and BD I diagnosis (Serretti et al., 2003; Perlis et al., 2010; Valenti et al., 2012). One of these studies was performed on the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) sample and it reported several associations between switch and baseline clinical-demographic features (greater number of past depressive episodes, recent or lifetime rapid cycling, alcohol use disorder, previous suicide attempt, past history of AD-emergent switch, and greater manic symptom severity) (Perlis et al., 2010). Some of these risk factors were dependent from AD exposure (younger onset age in patients not treated with ADs; previous suicide attempt and BD type I diagnosis in AD-exposed patients).

Previous studies were mainly focused on the risk of switch during AD treatment (Supplementary Table S1), but some patients with BD experience switch even in the absence of AD treatment. Indeed, some randomized controlled trials (RCTs) suggested that a mood stabilizer plus adjunctive AD therapy, compared with a mood stabilizer plus a placebo or mood stabilizer monotherapy, showed no association with higher risk of AD-emergent affective switch (Keck et al., 2005; Sachs et al., 2007). The first of these RCTs (Sachs et al., 2007) was carried out on a subsample of the STEP-BD study

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and its results could have been biased due to the intervention of clinicians in the process of randomization (tendency to avoid the randomization of patients at higher risk of switch). Despite the risk of inclusion bias deriving from this type of study design, several neurobiological mechanisms support the risk of spontaneous switch (Salvadore et al., 2010), thus risk factors of switch should not be investigated only in relation to concomitant AD treatment.

Previous studies focused on the risk of AD-induced mood switch suggested that tricyclic ADs (Boerlin et al., 1998; Bottlender et al., 2001; Nemeroff et al., 2001; Bottlender et al., 2004), monoamine oxidase inhibitors (MAOIs) (Boerlin et al., 1998) and venlafaxine (Leverich et al., 2006; Post et al., 2006) may be associated with higher risk than SSRIs or bupropion.

All the above-mentioned studies (with the exception of a small naturalistic study (Boerlin et al., 1998)) investigated a patient-based phenotype of switch from depression to (hypo)mania, i.e. they compared patients with and without switch, but they did not consider an episode-based phenotype, i.e. the comparison between depressive episodes followed or not by switch. Despite the fact that the disease course usually keeps a similar pattern in the same patient during time (van Rossum et al., 2008; Uher et al., 2013), the recurrence of acute episodes increases the level of functional impairment (Bonnin et al., 2013) and it possibly affects the clinical features and frequency of the following episodes. Thus, the specific features of each episode should be considered in addition to the general characteristics of BD in each patient in order to provide an accurate prognosis and suitable treatment interventions.

Given the hypothesized clinical relevance of each episode in every subject, the present study investigated the clinical predictors of switch from major depressive episodes to (hypo)manic/mixed episodes including into the analysis all the depressive episodes occurring for each patient during follow-up. Previous evidence suggested that the risk of switch is not influenced only by concomitant AD treatment, thus supporting our choice. Thus, baseline clinical-demographic characteristics, past clinical history, and current clinical characteristics (including treatment) at each depressive episode were investigated for a possible correlation with the risk of switch from depression to (hypo)manic/mixed state.

2. Methods

2.1. Study overview

The STEP-BD was a large, multi-center and naturalistic cohort study, conducted in the USA between 1999 and 2005. The aim of the STEP-BD was to evaluate prospective outcomes among patients with bipolar disorder treated in a naturalistic setting. STEP-BD clinicians were encouraged to treat patients in accordance with contemporary practice guidelines. The study design was approved by the Human Subjects Panel from each site. More detailed methods of the STEP-BD are described elsewhere (Sachs et al., 2003; Perlis et al., 2006).

2.2. Participants

Entry criteria involved meeting DSM-IV criteria for BD I, II or not otherwise specified, or schizoaffective disorder bipolar type, and ability to provide informed consent. All patients were outpatients; inpatients were eligible to enter the study following discharge (Sachs et al., 2003; Perlis et al., 2006). Overall, 4360 participants were included. Participants received pharmacological interventions as clinically indicated and clinicians were encouraged to follow the principles of evidence-based treatment and published guidelines, updated annually in the STEP-BD Clinicians Handbook. The protocol promoted the application of evidence-based treatments at regular clinical assessments during follow-up, in accordance with the needs of the participant and did not follow compliance to a specific treatment algorithm. This naturalistic study employed ongoing assessments of treatment and outcome information.

For the present study, further inclusion criteria were: (i) 6 months (180 days) or more follow-up duration; (ii) at least one depressive clinical episode during follow-up, according to the Clinical Monitoring Form (CMF) (Sachs et al., 2002, 2003) of the STEP-BD Standard Care Pathway (SCP).

2.3. Assessments

The diagnosis of BD was assessed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and Affective Disorder Evaluation (ADE) form (Sachs et al., 2003; Sachs, 2004) upon study entry together with a socio-demographic form (Demographic Form (DF)) (Sachs et al., 2003; Sachs, 2004). The CMF was used as source document for key prospective outcome measures and provided the progress note in the patient's medical record (Sachs et al., 2002).

Regarding symptoms of depression and mania, sums of classified scores for depression (SUM-D) and mania (SUM-M) were calculated using the Scoring Conventions and Rules for Imputation (Sachs et al., 2002).

2.4. Definition of “depressive episode with switch” and “patient with switch”

We used the clinical status variable in the CMF form to define the occurrence of switch. A “depressive episode with switch” was defined as a depressive episode that was followed by a manic, hypomanic or mixed episode within 12 weeks (84 days). The 12 weeks cut-off was chosen according to previous literature (Vieta et al., 2009). The other depressive episodes were defined as “depressive episode without switch”. Patients with at least one “depressive episode with switch” during follow-up were defined as “patients with switch”, otherwise they were considered “patients without switch”.

2.5. Hypothesis under analysis

The risk of switch from depression to (hypo)manic/mixed state was tested for association with: 1) past clinical history, including previous treatments and disease course; 2) clinical-demographic characteristics at study inclusion; and 3) the clinical features of the current depressive episode, including treatment(s).

2.6. Statistical analysis

We employed a generalized linear mixed model (GLMM) (Stroup, 2012) for investigating predictors of switch, because this model allowed the inclusion of data from all depressive episodes for each patient. A dichotomous variable coding for the affective switch was used as dependent variable, and a binomial distribution was applied. Identification ID Number of each patient was considered as a random effect, while the other clinical variables were considered as fixed effects.

To identify possible confounders mediating the association between switch and clinical variables, several regression models were constructed in a stepwise manner. Schemas of data structure and of each model are shown in Supplementary Figure S1. Firstly, we assessed crude associations between switch and each clinical variable (Model 1). Secondly, on the base of clinical considerations and the STEP-BD design, we included baseline demographic and