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Research report

The association between psychotic mania, psychotic depression and mixed affective episodes among 14,529 patients with bipolar disorder

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ABSTRACT

Background: Psychotic and mixed affective episodes are prevalent in the course of bipolar disorder. Despite many studies on the implications of psychotic mania (PM), psychotic depression (PD) and mixed affective episodes (MAE), relatively little is known about the relationship between the three subtypes. The present study aimed to investigate whether the occurrence of PM, PD and MAE were associated with one another.

Methods: This is a nationwide register-based, historical prospective cohort study. Data was obtained from the Danish Psychiatric Central Research Register. Subjects were defined as all individuals assigned with an ICD-10 diagnosis of bipolar disorder between January 1st 1994 and December 31st 2010. Potential associations among psychotic and mixed affective episodes were tested by means of logistic regression.

Results: We identified 14,529 individuals with bipolar disorder with lifetime incidences of PM, PD and MAE of 19%, 15% and 17% respectively. We detected significant associations between PM and MAE (Adjusted Odds Ratio (AOR)=1.26, $p=0.003$), PD and MAE (AOR=1.24, $p=0.001$), and PM and PD (AOR=1.28, $p=0.005$).

Limitations: Diagnoses were assigned as part of routine clinical practice.

Conclusions: According to this register-based study, PD, PM and MAE are all associated with one another. This knowledge should be taken into consideration by clinicians when monitoring patients with bipolar disorder and by nosologists when defining the criteria and potential subtypes for mixed affective episodes for the upcoming DSM-5 and ICD-11.

1. Introduction

Psychotic symptoms during episodes of mania and depression are common in the course of bipolar disorder (Kessing, 2006). In 1975 Guze et al. published the paper "The Significance of Psychotic Affective Disorders" based upon a study comparing psychotic and non-psychotic patients with bipolar disorder on a wide number of demographic and clinical variables (Guze et al., 1975). They concluded that "The results failed to support the validity of a classification of affective disorders based on the presence or absence of psychotic features" (Guze et al., 1975). Since then a number of studies have shown that this conclusion was wrong, as patients experiencing psychotic affective episodes in the course of bipolar disorder in fact do differ from their non-psychotic counterparts on several important domains. These include general affective symptomatology (Canuso et al., 2008), age at onset (Baldessarini et al., 2010a), predominant polarity (Baldessarini et al., 2010b), number of admissions (Mazzarini et al., 2010), duration of hospitalization (Kessing, 2004), psychiatric comorbidity (Hua et al., 2011) and degree of chronicity (Benazzi, 1999). In patients with bipolar disorder, the psychotic affective episodes are associated with poorer prognosis on all of these parameters, when compared to non-psychotic episodes. Accordingly, the clinical significance of psychotic episodes in bipolar disorder is emphasized in the classification of mental disorders as both psychotic mania (PM) and psychotic depression (PD) are classifiable subtypes in the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV) (American Psychiatric Association, 2000) and the International Classification of Disease, 10th revision (ICD-10) (World Health Organization, 1993).

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Mixed affective episodes (MAEs) are characterized by either a mixture or rapid alternation of manic and depressive syndromes (American Psychiatric Association, 2000) or symptoms (World Health Organization, 1993) and are common in the course of bipolar disorder (Kessing, 2006). Similar to the psychotic mood episodes, the MAEs are also associated with poor prognosis as evident by severe depressive morbidity (Baldessarini et al., 2010c), high use of antidepressants (Pacchiarotti et al., 2011a), risk of chronicity (Baldessarini et al., 2010b; Dodd et al., 2010), and pronounced suicidality (Baldessarini et al., 2012c; Undurraga et al., 2011; Valenti, et al., 2011). Unlike in depression and mania, the current diagnostic manuals do not allow the classification of psychotic symptoms during mixed affective episodes (American Psychiatric Association, 2000; Ostergaard et al., 2012; World Health Organization, 1993), although this clinical picture is relatively prevalent and has implications for the choice of treatment (Chou et al., 2009; Perugi et al., 2001).

Despite the high number of studies investigating the implications of PM, PD and MAE, only little is known about the relationship between these three types of affective episodes. In the present study we therefore addressed the following questions:

1. Do some patients with bipolar disorder have a general proneness to psychosis irrespective of polarity? I.e. compared to patients with a history of non-psychotic depression, are patients with a history of psychotic depression also more likely to experience psychotic symptoms when manic?
2. Are bipolar patients with a history of psychotic depression or psychotic mania more likely to experience mixed affective episodes than non-psychotic depressed/manic patients?
3. Do bipolar patients experiencing psychotic or mixed episodes differ from those not experiencing such episodes regarding age at onset, sex, the number of specific affective episodes and the number of psychiatric admissions and bed-days?

2. Methods

2.1. Design and data source

This is a nationwide register-based, historical prospective cohort study. Data was extracted from the Danish Psychiatric Central Research Register (DPCRR) (Mors, et al., 2011). All diagnoses assigned at psychiatric hospital-based settings throughout the country are reported to the DPCRR, which contains complete electronic data since 1969. The diagnoses are assigned at discharge by the treating psychiatrist based on clinical history, diagnostic procedures and response to treatment. Diagnoses were registered according to the International Classification of Diseases, 8th revision (ICD-8) (Danish National Board of Health, 1971) until January 1st 1994, when the ICD-8 was replaced by the ICD-10 (World Health Organization, 1993). Data assigned after outpatient treatment and contacts with psychiatric emergency rooms was included from January 1st 1995. The use of the DPCRR for research purposes is well established (Munk-Jorgensen and Ostergaard, 2011). Permissions to use the register were obtained from the Danish Data Protection Agency, The Danish National Board of Health and Statistics Denmark. The register-based data are rendered anonymous when used for research purposes.

2.2. Sample

All Danish residents assigned with their first ICD-10 diagnosis of bipolar disorder (F31) registered in the DPCRR in relation to admission, outpatient treatment or contact with a psychiatric emergency room between January 1st 1994 and December 31st 2010 entered as subjects. In order to get a homogenous sample of patients with bipolar disorder, individuals diagnosed with schizophrenia or schizoaffective disorder (ICD-8: 295, 296.8/ ICD-10: F20, F25) prior to the diagnosis of ICD-10 bipolar disorder were excluded from further analyses. The same was the case for patients diagnosed with bipolar disorder prior to the introduction of the ICD-10 (ICD-8: 296 (excl. 296.0, 296.2, 296.8), 298.1) since the psychotic and mixed affective episodes investigated in this study were not clearly defined in the ICD-8 (Danish National Board of Health, 1971).

2.3. Diagnostic variables

The lifetime occurrence of the following diagnostic subtypes of ICD-10 affective disorder was defined through the DPCRR: hypomania (F30.0, F31.0), mania (ICD-10: F30.1, F30.2, F30.8, F30.9, F31.1, F31.2), psychotic mania (PM) (F30.2, F31.2), depression (F31.3, F31.4, F31.5, F32, F33), severe depression (F31.4, F31.5, F32.2, F32.3, F33.2, F33.3), psychotic depression (PD) (F31.5, F32.3, F33.3) and mixed affective episodes (MAE) (F31.6, F38.00). The variables labeled as "episodes" of affective disorder in the present study are defined based on the number of these diagnoses assigned after admissions, contacts with emergency rooms or in relation to outpatient psychiatric treatment. For the variables regarding the number of specific affective episodes only patients registered with at least one of the episodes in question, were considered. The total number of psychiatric bed-days was also assessed through the DPCRR and for this variable, only patients admitted at least once were considered. The follow-up period for each subject regarding the ICD-10 began on the first day of their first contact registered in the DPCRR after the implementation of the of ICD-10 in Denmark (January 1st 1994) and ended at one of three events: death, lost to follow-up or August 9th 2011. For the admission and bed-days variables, the follow up began on the first day of their first contact registered in the DPCRR and ended at one of the same three events as mentioned above.

2.4. Statistical analysis

All statistical analyses were performed using Stata 12 at the Statistics Denmark Database via remote access. *Sample characteristics*: The dichotomously defined PM, PD, and MAE groups were individually compared to their bipolar counterparts not affected with the type of episode in question. Comparison of mean age at diagnosis of bipolar disorder and mean age at first psychiatric contact between groups was performed by two-sample t-tests. All comparisons of proportions were performed by chi-square tests. Potential difference in the number of episodes/admissions/bed-days recorded in the register was tested by Wilcoxon rank sum test.

Association between psychotic and mixed affective episodes: Due to the dichotomous nature of the PM, PD and MAE variables (lifetime occurrence: yes/no), potential associations between these affective episodes were tested pair-wise by means of logistic regression analyses, which were adjusted for sex and age at onset of bipolar disorder. The degree of association was expressed as Adjusted Odds Ratios (AOR). Only patients registered with a diagnosis of mania were considered in the analyses regarding association between PM and other affective episodes. Similarly for PD, only subjects with a history of depression were considered. I.e., the analysis of the association between e.g. PM and PD provides an answer to the following question: *Compared to patients with a history of non-psychotic depression, are patients with a history of psychotic depression also more likely to experience*