Journal of Affective Disorders 125 (2010) 61–73

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Prevalence of mixed mania using 3 definitions

E. Vieta [a,*], C. Morralla [b]

[a] Bipolar Disorder Programme, Institut Clínic de Neurociencies, Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERSAM, Barcelona, Catalonia, Spain
[b] Medical Department, Sanofi-Aventis, SA, Barcelona, Spain

ARTICLE INFO

Article history:
Received 20 May 2009
Received in revised form 22 December 2009
Accepted 23 December 2009

Keywords:
Mixed mania
Prevalence
Bipolar disorders

ABSTRACT

Objectives: Mixed episodes are a combination of depressive and manic symptoms in bipolar disorder (BD). We want to identify the proportion of patients who have depressive symptoms during an acute episode and also the validity of current methods for its diagnosis.
Material and method: Cross-sectional multicentre study of patients with type I BD who are admitted to specialized units. 368 patients in 76 centres were included. The patients should have a well established diagnosis of BD and need hospitalisation. The severity of the disorder and clinical status were evaluated upon admission and discharge using CGI-BP-M clinical impression scales, the Hamilton depression scale (HAMD-17) and the Young mania rating scale (YMRS). Upon admission, the necessary criteria for diagnosing a mixed type episode were recorded according to DSM-IV-TR, ICD-10 and McElroy criteria. Clinical judgment of the current type of episode was also recorded.
Results: Prevalence estimations for mixed episodes were: 12.9% according to DSM-IV-TR ($n=45$), 9% according to ICD-10 ($n=31$), 16.7% according to McElroy criteria ($n=58$), and 23.2% according to clinical judgment ($n=81$). Statistically significant differences were found between the estimated prevalence rates (Cochrane's Q-test, $p<0.0001$), with the maximum concordance level found between the McElroy and ICD-10 (Kappa = 0.66, 95% CI, 0.54–0.77). The DSM-IV-TR criteria only present moderate concordance with ICD-10 (Kappa = 0.65, 95% CI, 0.52 to 0.78) and McElroy criteria (Kappa = 0.62, 95% CI, 0.50 to 0.74).
Conclusions: The definition of mixed episodes for BD must be revised to improve consensus and, consequently, therapeutic management. Current diagnostic systems, based on DSM-IV and IDC-10, only capture a limited proportion of patients suffering from mixed episodes, giving rise to important limitations concerning the therapeutic management of BP patients.

1. Introduction

The prevalence of type I bipolar disorder in general population samples ranges from 0.4% to 1.6%. It is a recurring disorder in which over 90% of the subjects who have suffered a single manic episode will present future episodes (American Psychiatric Association, 2002). Mixed episodes have been described since Kreapelin in 1907, not only receiving different names but also giving rise to different descriptions related to the same concept. This type of episode is common and will occur throughout the lifetime of 30–40% of the patients affected by the disease (Akiskal et al., 2000). Such episodes are commonly found in bipolar patients, but are less apparent for clinicians than pure manic conditions.

The identification of mixed episodes is one of the main issues in the diagnosis of bipolar disorder; they are usually difficult to treat, potentially severe and not only involve a high risk of suicide (Henry et al., 2007) but are also associated to a substantial increase in the risk of suffering future episodes (Kessing, 2008). Diagnosis of these episodes is crucial, and it is now accepted that, due to different factors, these patients must be monitored more closely on a practical level; their evolution and prognosis are usually worse in the

* Corresponding author. Hospital Clinic & CIBERSAM, Villarroel, 170, 08036 Barcelona, Spain. Tel./fax: +34 932 275 477.
E-mail address: evieta@clinic.ub.es (E. Vieta).
URL: http://www.bipolarclinic.org (E. Vieta).

0165-0327/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2009.12.019

short–medium term, with expected higher recurrence rates and psychotic readmission rates. Not only do they present a worse response to monotherapy treatment but they are also associated to comorbidity with substance abuse (Gonzalez-Pinto et al., 2007). Correct recognition of mixed episodes, therefore, is important in order to select appropriate anti-manic agents.

A great deal of effort has been made to establish definitions which enhance sensitivity in detection. Some patients in the manic phase simultaneously present depressive symptoms, without reaching complete depressive syndrome status; thus, they do not meet conventional diagnostic criteria for a mixed episode, because it is only applied when a complete manic and depressive syndrome occurs (American Psychiatric Association, 2002).

Different definitions currently co-exist and the attempts made to validate the criteria for the syndrome are hindered by the difficulty of selecting an appropriate external validator. Eventually, prevalence for mixed episodes largely depends on the definition used; when categorical definitions are considered, the prevalence rate can range from 13.8% to 27.4%, according to strict DSM-III-R or broader criteria, respectively. Although it is accepted that prevalence tends to be lower, the stricter the criteria, mean global prevalence has been established at 30% (McElroy et al., 1992).

Among categorical definitions, DSM-IV (American Psychiatric Association, 2002) mixed episode criteria contemplate the presence of both complete depressive syndrome and complete manic syndrome for at least a week. The CIE-10 (World Health Organisation, 1992) criteria establish that the diagnosis is only applied when the two groups of symptoms are prominent most of the time during the current episode and for at least two weeks. Finally, the criteria created by McElroy et al. (i.e. Cincinnati criteria) (McElroy et al., 1992; McElroy et al., 1995), which represent the broader definition, contemplate the simultaneous presence of mania and at least two independent depressive symptoms (Cassidy et al., 2000).

It is accepted that there is a need to find or adopt a less restrictive definition than those conventionally used, in relation to the severity and characterisation of the depressive component.

In our study, we aimed to identify the proportion of patients presenting symptoms of depression among a cohort of bipolar patients admitted for an acute manic or mixed episode and determine the prevalence of mixed episodes by applying different diagnostic criteria to the same cohort. We also aimed to establish the differences between them and describe the degree of consensus. Finally, we analysed the differences between definitions with regard not only to the depressive components of patient's clinical status but also to other factors such as clinical evolution at discharge. The study provides data aimed at improving the definition of mixed episode for its detection in clinical practice.

2. Materials and methods

Cross-sectional epidemiological study conducted during hospitalisation in a sample of patients with bipolar disorder admitted to psychiatric units. The study was conducted in 76 centres in different autonomous regions in Spain. Bipolar patients were recruited consecutively from those admitted to the participating centres. The information was collected as part of clinical routine.

2.1. Subjects

The inclusion criteria for patient selection were: patients aged from 18 to 65, well established diagnosis of type I bipolar disorder according to DSM-IV-TR criteria (American Psychiatric Association, 2002) and the need for hospitalisation for an acute manic or mixed episode. Patients presenting a manic episode in the context of a schizophrenic disorder or substance abuse were excluded, as were patients with a manic episode directly or indirectly due to any other organic cause (i.e. brain tumour, corticoid therapy, cerebrovascular accident, Parkinson's disease, multiple sclerosis, etc.) or who were participating in any other clinical study or trial. Patients were required to grant their informed consent in writing for data to be collected and processed.

2.2. Evaluations

The investigators evaluated the patients at admission and at discharge. Depressive symptoms were evaluated following a routine clinical assessment and by a SCID-I structured interview (American Psychiatric Association, 2002). The severity of the patient's clinical status was evaluated with the 17-item Hamilton Depression Rating Scale (HDRS-17) (Bobes et al., 2003), the Young Mania Rating Scale (YMRS) (Colom et al., 2002) and the Modified Clinical Global Impression Scale for Bipolar Disorder (CGI-BP-M) (Vieta et al., 2002). Regarding the type of current episode upon admission, different mixed episode criteria were applied, as occurs in clinical practice, using DSM-IV-TR (American Psychiatric Association, 2002), CIE-10 (World Health Organisation, 1992) and clinical judgment. Functional impact on the patient's social-occupational life in the two weeks prior to admission was evaluated by the Social and Occupational Functioning Assessment Scale (SOFAS).(American Psychiatric Association, 2002) Changes in the patient's functioning were evaluated by the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) at admission and discharge. The study was approved by the Independent Ethics Committee of one of the participating centres (Tormo Díaz et al., 1998; Dal-Re et al., 1998). Patients were included from July 2007 to November 2007.

2.3. Data analysis

The prevalence of mixed episodes was determined for each group of criteria (i.e. DSM-IV-TR (American Psychiatric Association, 2002), CIE-10 (World Health Organisation, 1992), McElroy/Cincinnati and clinical judgment). We analysed the differences between the estimated prevalence rates obtained from each definition by Cochrane's *Q*-test and the degree of consensus between definitions by the Kappa statistic (HDRS-17 scores were not considered in these analyses).

The presence of meaningful depressive component was defined as "mild depression" on HDRS-17, with a total score of 7 to 17 taken as a summary measure of depressive component.

Differences related to sociodemographic and clinical variables between the groups of mixed and non-mixed patients and under each system were described. The categorical data were analysed with a chi2 test and the continuous data by means of