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Journal of Affective Disorders 106 (2008) 63 – 72

JOURNAL OF AFFECTIVE DISORDERS

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Research report

Olanzapine monotherapy and olanzapine combination therapy in the treatment of mania: 12-week results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) observational study☆

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Received 26 March 2007; received in revised form 11 May 2007; accepted 13 May 2007
Available online 20 June 2007

Abstract

Background: To evaluate the 12-week outcomes (effectiveness, tolerability, and patterns of medication use) of olanzapine (either in antimanic monotherapy or in combination with other antipsychotics, anticonvulsants, and/or lithium) in patients with bipolar mania or mixed mania.

Method: EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication) is a 24-month prospective observational study of in- and outpatients with acute mania/mixed mania conducted in 14 European countries. Primary outcome measures included Clinical Global Impressions–Bipolar Disorder scale (overall, mania, and depression); 5-item Hamilton Depression Rating Scale; and Young Mania Rating Scale. Tolerability measures included a questionnaire to assess patients' symptomatic complaints.

Results: Overall, 2004 patients received olanzapine (olanzapine monotherapy, $n=673$; olanzapine combination, $n=1331$). Concomitant therapy with antidepressants and/or anxiolytics was possible in both groups. The countries significantly differed in the use of olanzapine monotherapy versus olanzapine combination ($p<.0001$). Baseline-to-endpoint changes on the CGI-BP subscales, YMRS, and HAMD-5 were significant within both treatment groups ($p<.0001$). Olanzapine monotherapy was generally better tolerated than olanzapine combination, particularly with regard to sedation (12% vs 17%; $p<.001$), tremor (2% vs 5%; $p<.001$), and akathisia (3% vs 6%; $p<.001$).

☆ Role of funding source: The EMBLEM study is funded by Eli Lilly and Company Limited, Windlesham, Surrey, UK. Contributors: All the authors have been sufficiently involved in the study submitted. Conflict of interest: Eduard Vieta, has acted as a consultant, received grants, or been hired as a speaker by the following companies: Almirall, AstraZeneca, Bial, Bristol-Myers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Sanofi Aventis, Servier, UCB. He has acted as consultant and has received grants from the Spanish Ministry of Health, Instituto de Salud Carlos III, RETICS RD06/0011 (REM-TAP) and from the Stanley Medical Research Institute. Iris Goetz, Catherine Reed, and Mauricio Tohen are Eli Lilly and Company employees. Francesco Panicali and Merce Comes have no conflict of interest.

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0165-0327/$ - see front matter
doi:10.1016/j.jad.2007.05.009

Discussion: The acute-phase EMBLEM results suggest that in naturalistic settings, olanzapine (both as monotherapy and combination) may be effective in treating patients with bipolar mania. The use of olanzapine monotherapy or combination varies significantly across countries, but combination is generally the rule, rather than the exception.

Keywords: Olanzapine; Mania/mixed; Bipolar disorder; Prospective observational study

1. Introduction

Over the last 5 years, our knowledge on the treatment of mania has outstandingly increased due to the data from randomized clinical trials: Atypical antipsychotics such as olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole have been compared with placebo and with active compounds (haloperidol, lithium, and divalproex), and the evidence base for the use of all these compounds has been considerably enriched (Vieta and Goikolea, 2005). The knowledge of the actual use of antimanic agents in routine clinical conditions is quite limited, however, and large observational studies are rare (Vieta et al., 2001). Observational studies are more likely to be challenged for their internal validity than randomized clinical trials, but provide relevant data about the actual use of therapies either as monotherapy or combination therapy in "real world" patients (that is, without excluding comorbidities or suicide risk, including flexible and broader dose ranges, and across all ranges of illness severity).

Olanzapine has been tested in randomized designs in mania and compared with placebo (Tohen et al., 1999, 2000), haloperidol (Tohen et al., 2003), divalproex (Zajecka et al., 2002; Tohen et al., 2002a), and risperidone (Perlis et al., 2006). Olanzapine cotherapy with lithium or divalproex was also compared with lithium and divalproex alone in one trial (Tohen et al., 2002b, 2004). Olanzapine proved to be effective for the acute treatment of mania and beyond (Vieta, 2004). Hence, a good number of studies provide an excellent evidence base for the use of olanzapine (both in mono- and combination therapy) as an antimanic agent, but less is known about the factors that drive the choice of olanzapine as monotherapy or combination, its dosages in routine clinical practice, and the patterns of use across different countries.

To close this gap, we conducted the EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication), one of the largest observational studies ever conducted in patients suffering form bipolar mania. The objectives of the EMBLEM were to learn about the clinical and functional outcomes and patterns of use of antimanic therapy including olanzapine (both in monotherapy and in combination therapy) across several European countries.

2. Methods

2.1. Study objective

EMBLEM is a large, prospective, multicentre, observational study on the outcomes of patients after an episode of mania. From December 2002 to June 2004, 530 investigators enrolled patients from 14 European countries (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, The Netherlands, Norway, Portugal, Spain, Switzerland, and the UK). Observations were completed with 5 further data collections as part of the acute phase, which lasted for 12 weeks, until October 2004. Further observations are currently ongoing in the ≤24-month maintenance phase. All countries applied the same core set of measures at each data collection point to capture a broad range of clinical outcomes. The primary objective of the study was to assess the course of bipolar disorder in patients who experienced a manic/mixed episode and started new oral treatment antipsychotics, anticonvulsants and lithium as monotherapy or treatment combinations.

Depending on the health-care system in each country, the EMBLEM included investigators from both inpatient and outpatient settings. Both rural and urban locations, as well as public and private facilities, were involved to allow for an accurate representation of current treatment settings for patients with mania across Europe. Participating investigators were psychiatrists practicing in the setting in which the patient was being treated. Data were collected by either the investigators or by their designee.

2.2. Patients

Patients were considered for enrolment if they presented within the standard course of care and if, according to the decision of the treating psychiatrist, oral medication with antipsychotics, lithium and/or anticonvulsants was initiated or changed (excluding dose changes) for the treatment of a manic or mixed bipolar episode. Psychiatric diagnosis to determine the presence of a manic/mixed episode was made by each site's leading investigator using the site's usual standard diagnostic criteria (generally DSM-IV or ICD-10). Patients with comorbidity, substance abuse, and suicidiality, or those