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Original article

Asenapine prescribing patterns in the treatment of manic in- and outpatients: Results from the MANACOR study

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ABSTRACT

Background: Asenapine is the most recent compound that has been FDA- and EMA-approved for treatment of mania. Its efficacy and safety have been assessed in placebo-controlled trials, but little is known about its performance in routine clinical conditions. In this study, we compared features of patients treated with adjunctive asenapine or other adjunctive antipsychotics and the costs of the treatment.
Methods: A combined prospective and retrospective data collection and analysis was conducted from January 2011 to December 2013 following a clinical interview and assessment of manic and depressive symptoms (YMRS, HDRS-17), clinical state (CGI-BP-M), psychosocial functioning (FAST), sexual dysfunction (PRSexDQ) and health resource costs associated with treatment with adjunctive asenapine versus other adjunctive antipsychotics.
Results: Hundred and fifty-two patients from different university hospitals were included. Fifty-three patients received adjunctive asenapine and 99 received other adjunctive antipsychotics concomitantly to mood stabilizers. Considering inpatients, those treated with adjunctive asenapine presented a significantly less severe manic episode ($P = 0.001$), less psychotic symptoms ($P = 0.030$) and more comorbid personality disorder ($P = 0.002$). Regarding outpatients, those treated with adjunctive asenapine showed significantly less severe manic episode ($P = 0.046$), more previous mixed episodes ($P = 0.013$) and more sexual dysfunction at baseline ($P = 0.036$). No significant differences were found in mean total costs per day.
Conclusion: Clinicians tended to use adjunctive asenapine in patients with less severe manic symptoms but more complex clinical profile, including more mixed episodes in the past, concomitant personality disorder, and sexual problems. Treatment with adjunctive asenapine was not associated with higher costs when compared to other options.

1. Introduction

Bipolar disorder (BD) is one of the leading causes of time lost to death or disability among people aged between 15–55 years [6]. The WHO and the World Mental Health recently updated this data in a survey carried out in 24 countries and raised BD to the second illness with the strongest individual-level impact in days out of role per year [1]. As BD is mostly diagnosed in young adulthood, it involves the active population and therefore connotes high costs to society. In the United States, the total annual costs in 1991 were estimated at 45.2 billion dollars [22]. In the United Kingdom (UK), the annual costs to society attributable to BD were estimated to be 2 billion pounds in 1999–2000 [11]. Ten percent of this cost was attributable to National Health Service (NHS) resource use, 4% to non-health-care resource use and 86% to indirect costs. Despite advances in pharmacotherapy and outpatient therapy, some hospitalizations are hardly unpreventable and entail a substantial portion of the NHS costs. In a recent study carried out in Catalonia (Spain), 77% of the total costs of a manic episode corresponded to hospitalization [19]. In addition, manic episodes are associated with occupational disability in bipolar

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patients, hence increasing society costs [15]. However, above all, intangible costs such as family burden and impaired health-related quality of life stand still out as the economic and social burden of greatest concern in the community.

Evidence of the antimanic properties of atypical antipsychotics and their value in long-term management have made the pharmacological options for the treatment of BD at our disposal actually extensive [42]. Despite the economical disbursement in the acute and long-term treatment that atypical antipsychotics might imply, these drugs may critically prevent hospital admissions and, thus, may restrain the social budget invested in BD [11,13]. Despite the body of evidence being limited, asenapine, a multimodal antipsychotic recently marketed, seems to be an effective treatment for mania and in particular in mania with mixed features [21,29]. In clinical trials, the patients in a manic episode with mixed features treated with asenapine showed a stable remission rate regardless of baseline depressive symptom severity, whereas remission decreased with increasing severity with olanzapine and placebo [29]. Moreover, recent economical evaluation studies about this treatment in BD have demonstrated the cost-effectiveness of asenapine versus olanzapine regarding costs and quality adjusted life years (QALYs) in both manic and mixed episodes from a healthcare perspective [5,23,35]. These studies suggested that asenapine is a cost-effective strategy compared to olanzapine at least in three countries around the world. In the Canadian study of Lachaine et al. [23], asenapine was associated with lower treatment costs and a lower risk of weight gain and consequently, a lower risk of developing metabolic complications. In the study by Sawyer et al. focused on mixed episodes in the UK [35], asenapine generated 0.0187 more QALYs for an additional cost of 24 pounds compared to olanzapine over a 5-year period, corresponding to a 1302 pound incremental cost-effectiveness ratio in the UK. Finally, in the recent article by Caresano et al. in Italy [5] based on the pharmacoeconomic model of Sawyer et al., the results suggested that the management of bipolar I patients with mixed episodes using asenapine rather than olanzapine could lead to cost saving to the Italian NHS and improve the patient quality of life.

In the present study, we aimed to describe the features of a representative sample of everyday-clinical-practice patients diagnosed with BD in a manic episode treated either in an inpatient or outpatient setting with adjunctive asenapine compared to other adjunctive antipsychotic treatments as well as the cost of these treatments.

2. Methods

2.1. Study population and participants

A combined prospective and retrospective data collection and analysis was conducted in this study. Clinical data were prospectively collected from January 2011 to December 2013 as part of the systematic assessment of the Barcelona Bipolar Disorders Program [38,43] and retrospectively analyzed to ensure no sponsor bias in medication choice. The naturalistic 6-month follow-up study sample involved 169 consenting, systematically followed, adult patients from four different psychiatric hospitals and outpatient clinics from Catalonia, Spain. One hundred fifty-two patients finished the study. The study protocol was reviewed and approved by the respective hospital Ethics Committees. The patients included were 18 years or older and according to DSM-IV-TR [2] and were diagnosed with bipolar I disorder in a manic episode considering a score $\geq$15 in the Young Mania Rating Scale (YMRS) or other comorbid disorders whenever required [8,46].

2.2. Procedure and data collection

Psychiatrists in charge of attending inpatients and outpatients were asked to identify patients who could meet inclusion criteria during the study. Under this premise, the psychiatrist responsible for the study in each center carefully evaluated every indicated case. Socio-demographic and work information as well as medical and psychiatric history were extracted from the medical records including the number and type of the first and following episodes, suicide attempts, previous hospitalizations and predominant polarity (defined as at least a two-fold number of episodes of one polarity) [9]. The clinical setting, either outpatient unit or inpatient ward and the treatment administered were also collected [14,16]. The pharmacological treatment was at the psychiatrist's discretion including lithium, anticonvulsants, antipsychotics, antidepressants and benzodiazepines. In a previous study [19], a general description of the pharmacological treatment has been reported being the most commonly prescribed drug lithium, followed by valproic acid. Prescribed antipsychotics in the sample were aripiprazole, asenapine, clotiapine, clozapine, haloperidol, levomepromazine, olanzapine, paliperidone, perphenazine, quetiapine, risperidone, ziprasidone, and zuclopentixol.

2.3. Clinical assessments

Assessments were performed at baseline and after one and six months according to the systematic protocol of the Barcelona Bipolar Disorders Program which consists of a clinical interview and assessment of the manic symptoms with the YMRS, the depressive symptoms with the 17-item Hamilton Depression Rating Scale (HDRS-17) [18,32] and the clinical state using the Clinical Global Impression scale-Bipolar Disorders-Modified (CGI-BP-M) [36,41]. Psychosocial functioning was assessed following the Functioning Assessment Short Test (FAST) [33,34] and sexual dysfunction related to psychiatric drugs following the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) [30].

2.4. Cost estimates

Although the centers involved belonged to the Spanish NHS, the individual services costs were not standardized. Therefore, health resource costs were calculated considering a mean cost per day taking into account the value of a day in ward (255.20 €), an outpatient visit (82.20 €) and an emergency visit (178.40 €). Visits due to medical disorders were not counted. Pharmacological treatment costs were calculated according to an average dose per day of the treatment during the admission and follow-up at the current retail list prices (alprazolam: 0.20 €/day, amisulpride: 1.98 €/day, aripiprazole: 10.06 €/day, asenapine: 5.22 €/day, biperidene: 0.50 €/day, bromazepam: 0.15 €/day, bupropion: 2.94 €/day, carbamazepine: 0.32 €/day, citalopram: 0.36 €/day, clonazepam: 0.20 €/day, clorazepate dipotassium: 0.25 €/day, clotiapine: 0.07 €/day, clozapine: 0.30 €/day, diazepam: 0.25 €/day, escitalopram: 1.70 €/day, flunitrazepam: 0.15 €/day, fluoxetine: 0,20 €/day, flurazepam: 0.15 €/day, gabapentine: 0.28 €/day, haloperidol: 0.06 €/day, lamotrigine: 0.94 €/day, levomepromazine: 0.08 €/day, lithium: 0.15 €/day, lorazepam: 0.09 €/day, lormetazepam: 0.14 €/day, midazolam: 0.15 €/day, mirtazapine: 0.57 €/day, olanzapine: 3.75 €/day, oxcarbazepine: 0.44 €/day, paliperidone: 4.92 €/day, paroxetine: 0.44 €/day, perphenazine: 0.04 €/day, quetiapine: 3.27 €/day, risperidone: 0.84 €/day, sertraline: 0.39 €/day, topiramate: 1.23 €/day, trazodone: 0.12 €/day, valproate; 0.47 €/day, valpromide: 0.30 €/day, venlafaxine: 0.68 €/day, ziprasidone: 3.75 €/day, zolpidem: 0.09 €/day, and zuclopentixol: 0.83 €/day). Direct total