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Research report

Gender differences in the treatment of patients with bipolar disorder: A study of 7354 patients

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ABSTRACT

Background: Gender differences in treatment that are not supported by empirical evidence have been reported in several areas of medicine. Here, the aim was to evaluate potential gender differences in the treatment for bipolar disorder.

Methods: Data was collected from the Swedish National Quality Assurance Register for bipolar disorder (BipoläR). Baseline registrations from the period 2004–2011 of 7354 patients were analyzed. Multiple logistic regression analysis was used to study the impact of gender on interventions.

Results: Women were more often treated with antidepressants, lamotrigine, electroconvulsive therapy, benzodiazepines, and psychotherapy. Men were more often treated with lithium. There were no gender differences in treatment with mood stabilizers as a group, neuroleptics, or valproate. Subgroup analyses revealed that ECT was more common in women only in the bipolar I subgroup. Contrariwise, lamotrigine was more common in women only in the bipolar II subgroup.

Limitations: As BipoläR contains data on outpatient treatment of persons with bipolar disorder in Sweden, it is unclear if these findings translate to inpatient care and to outpatient treatment in other countries.

Conclusions: Men and women with bipolar disorder receive different treatments in routine clinical settings in Sweden. Gender differences in level of functioning, bipolar subtype, or severity of bipolar disorder could not explain the higher prevalence of pharmacological treatment, electroconvulsive therapy, and psychotherapy in women. Our results suggest that clinicians' treatment decisions are to some extent unduly influenced by patients' gender.

1. Introduction

Bipolar disorder is a serious psychiatric disease with an estimated lifetime prevalence of 0.6% for bipolar disorder type I (BP I), 0.4% for bipolar disorder type II (BP II), and 2.4% for bipolar spectrum disorders (BPS) according to a recent study conducted by the World Health Organization (Merikangas et al., 2011). Although the lifetime prevalence of bipolar disorder appears to be roughly equal in both genders (Angst, 1998; Bebbington and Ramana, 1995; Gold, 1998; Grant et al., 2005), a number of reports suggest gender differences in the symptomatic picture among bipolar patients. Many, but not all, studies report that women with bipolar disorder are more likely to suffer from subsyndromal depressed mood and dysphoria (Altshuler et al., 2010; Diflorio and Jones, 2010; Morgan et al., 2005; Rasgon et al., 2005a), even though the number of depressives episodes and the time spent in syndromal depression do not differ between men and women (Baldassano et al., 2005; Diflorio and Jones, 2010; Grant et al., 2005; Hendrick et al., 2000; Kawa et al., 2005; Kessing, 2004; Suominen et al., 2009). A majority of studies shows that women are more likely than men to be diagnosed with the BP II subtype, and to experience hypomanic episodes (Angst, 1998; Baldassano et al., 2005; Cassano et al., 1992; Diflorio and Jones, 2010; Merikangas et al., 2011; Schneck et al., 2008). Finally, a number of studies point out that women are more likely than men to suffer from mixed episodes (Benazzi, 2003; Diflorio and Jones, 2010; Grant et al., 2005; Kessing, 2004, 2008; Suppes et al., 2005).

There is a range of treatment options for bipolar disorder, including mood stabilizers such as lithium, neuroleptics (both first and second generation neuroleptics), electroconvulsive treatment

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(ECT), psychotherapy, and psychoeducation. By and large, there is no clear-cut evidence suggesting that treatment response to these modalities differs between men and women, and hence no justification for adjusting the bipolar disorder treatment according to gender. Data are inconclusive with respect to the response to mood stabilizers; some studies find possible gender differences (Hendrick et al., 2000; Kawa et al., 2005; Leibenluft, 1996; Viguera et al., 2000) while others do not (Arnold et al., 2000; Dilsaver et al., 1993; Freeman et al., 1992; Post et al., 1987; Secunda et al., 1985; Swann et al., 1997; Viguera et al., 2001). There is no evidence to suggest that bipolar men and women respond differently to ECT or psychotherapy. High teratogenic risk in some mood stabilizers, such as valproate and carbamazepine (Yonkers et al., 2004), as well as risk for menstrual abnormalities and polycystic ovary syndrome (PCOS) (O'Donovan et al., 2002; Rasgon et al., 2005b), should, however, be taken into account when treating women. Reproductive considerations for women of a fertile age could therefore lead to gender differences in prescribing patterns of these specific medications. Kriegshauser et al. (2010) found that women have more fear than men of gaining weight as an adverse effect of medication, which could affect the choice of medication in women.

The importance of gender to treatment choice for bipolar disorder has not previously been systematically studied. Hence, it is not known whether men and women are offered different treatments in clinical practice. In the STEP-BD study (Systematic Treatment Program for Bipolar Disorder), there was no gender difference in the use of antidepressants in bipolar patients (Baldassano et al., 2005), but we lack data on potential gender differences with respect to the use of lithium, mood stabilizers, ECT, and psychotherapy in bipolar patients in routine clinical practice. We know from studies of other medical disorders, such as coronary artery disease, that there have been unjustified differences in treatment between men and women, and attention to this has led to adjustments in clinical practice (Heer et al., 2002; Tsuyuki et al., 1994).

The aim of this study was to survey whether men and women with bipolar disorder in psychiatric outpatient care receive different treatments. The null hypothesis was that we would find no gender difference in the treatment of bipolar disorder.

2. Subjects and methods

2.1. Sources of data and study population

Data were derived from the Swedish national quality assurance register for bipolar disorders (BipoläR). BipoläR contains individualized data concerning case-mix, medical interventions, and treatment outcomes. It was established in 2004 with the aim of improving the quality of care for bipolar patients in Sweden. The register captures basic clinical epidemiological data along with longitudinal data on the natural history and clinical course of the disease. Data is collected by the treating psychiatrist and entered into a web-based application. Participation in this register is voluntary for the clinician as well as the patients, even though there have been incentives from health care providers to increase the clinician's rate of participation. Registering units include both private and public psychiatric outpatient health care units in Sweden.

The baseline data include a multi-axial psychiatric DSM-diagnosis [bipolar I, II, schizoaffective disorder or NOS, other psychiatric disorders; axis II-disorders; somatic diseases; axis IV data; and a global assessment of functioning (GAF)]. Data on the number of lifetime depressive, hypomanic, manic and mixed episodes, suicide attempts, educational level, occupation, sick benefits, history of compulsory institutional care, current psychotropic drugs, electroconvulsive treatment (ECT), psychological treatment, Clinical Global Impression Severity (CGI-S), weight, and height are also collected. The treating physician receives reminders by email when the annual follow-up is due. At the annual follow-up, the following data are collected: psychiatric diagnoses as above, the number of depressive, hypomanic, manic, and mixed episodes during the past 12 months, suicide attempts, occupation, sick benefits, compulsory institutional care during the past 12 months, current psychotropic drug treatment, ECT, psychological treatment, psychoeducation, Clinical Global Impression Improvement (CGI-I), weight, and height. By the time of data extraction for this study in 2011, 7354 baseline registrations were analyzed to identify differences in treatment choice between bipolar men and women in Sweden.

2.2. Measures

Gender was the main exposure of interest in this study. The outcome measures were ECT, antidepressants, lithium, valproate, lamotrigine, mood stabilizers as a group (i.e., lithium, valproate, lamotrigine, carbamazepine, and oxcarbazepine), neuroleptics (both first and second generation), benzodiazepines, and psychotherapy. All these outcomes were binary measures (yes/no) derived from baseline registrations. Data on ECT was missing for 168 individuals. Data on the use of benzodiazepines was only available for a subset of the patients ($n=4827$).

As potential confounders in the model, we used age, bipolar subtype, GAF-symptom score, comorbid anxiety disorder, comorbid substance use disorder, previous suicide attempts, and number of depressive, manic, and mixed episodes. "Comorbid anxiety disorder" is coded as a group in BipoläR and includes panic disorder, agoraphobia, generalized anxiety disorder, social phobia, obsessive–compulsive disorder, and specific phobias, but not post-traumatic or acute stress disorders. The number of affective episodes was coded as "none", "1–3 episodes", and "4 or more episodes" (see Table 1).

2.3. Statistics

The statistical analyses were based on logistic regressions, where female gender was chosen as the reference category. Thus, an odds ratio over one corresponds to an increased probability for a man to have a certain medicine or therapy. The significance level to reject the null hypothesis was set to $P<0.05$. Separate analyses were conducted for bipolar types I and II. A subanalysis was performed for patients 45 years of age or younger, in order to investigate possible gender differences in the use of valproate in light of adverse effects of valproate for women in reproductive age. We tested for multicollinearity using the variance inflation factor (VIF). There were no signs of multicollinearity.

2.4. Ethics

The study was approved by the Regional Ethics Committee in Gothenburg and conducted in accordance with the latest Helsinki Protocol. All analyses were conducted on a de-identified dataset.

3. Results

Demographic and clinical characteristics of the analyzed group are summarized in Table 1. There was an overrepresentation of women (61%) in our study population with a mean (SD) age of 47.9 (23.3) years for women and 50.1 (15.5) years for men. With respect to diagnostic subgroups, 46% of the patients were diagnosed with BP I, 37% with BP II, 14% with NOS, and 3% with SAD (percentages not shown in table). Women were more likely than men to be diagnosed with BP II and BP NOS, while men were more likely to be diagnosed with BP I. Women had more depressive and mixed episodes, and men had more manic episodes. Comorbid anxiety disorder as well as previous suicide attempts was more frequent in women while comorbid substance