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Research paper

# Changes in mood stabilizer prescription patterns in bipolar disorder

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ABSTRACT

*Background:* Lithium is a first line treatment option in bipolar disorder, but several alternative treatments have been introduced in recent years, such as antiepileptic and atypical antipsychotic drugs. Little is known about how this has changed the prescription patterns. We investigated possible changes in the use of mood stabilizers and antidepressants in Sweden during 2007–2013.
*Methods:* Data was collected from Swedish registers: the National Quality Assurance Register for bipolar disorder (BipoläR), the Prescribed Drug Register, and the Patient Register. Logistic regression models with drug use as outcomes were used to adjust for confounding factors such as sex, age, year of registration, and subtypes of bipolar disorder.
*Results:* In both bipolar subtypes, lithium use decreased steadily during the study period, while the use of lamotrigine and quetiapine increased. The use of valproate decreased in bipolar II disorder and the use of olanzapine decreased among women. The use of antidepressant remained principally unchanged but increased somewhat in bipolar I disorder.
*Limitations:* We only report data from 2007 as the coverage of BipoläR prior to 2007 was too low to allow for reliable analyses.
*Conclusion:* Significant changes in the prescription of drugs in the treatment of bipolar disorder have occurred in recent years in Sweden. Further studies are needed to clarify whether these changes alter the outcome in bipolar disorder.



## 1. Introduction

Bipolar disorder affects around 1.5% of the population (Altshuler et al., 2010) and entails high costs for the society, mainly due to long periods of sick leave (Ekman et al., 2013). The course of the disorder varies considerably between individuals. Some patients are free from affective recurrences for decades, while others frequently recurrent into severe manic or prolonged depressive episodes (Goodwin, 2007). While some persons recover completely between mood episodes, others suffer persisting, debilitating symptoms. The subdivision into bipolar disorder type I and II is established but not undisputed (Akiskal, 1996; Akiskal et al., 2000; Cassano et al., 1989, 1992; Paris, 2009), and bipolar disorder type II does not exist as a diagnosis of its own in ICD-10.

In addition to treatment for acute depressive and manic episodes, there is effective prophylactic treatment available for bipolar disorder. It has been known for more than half a century that lithium effectively prevents new episodes (Geddes and Briess, 2007; Goodwin, 2002; Goodwin and Geddes, 2003), and lithium is still recommended as a first line maintenance treatment option according to national and international treatment guidelines (APA, 2002; Goodwin, 2009; NCCMH, 2006; SBU, 2004; Suppes et al., 2005; Yatham et al., 2013, 2009). Lithium is known as a *mood stabilizer*. The definition of mood stabilizer is a treatment that is effective against either depression or mania without increasing the risk for an opposite episode. Some antipsychotic drugs are effective against mania, but may increase the risk of depression (Goikolea et al., 2013; Tohen et al., 2003; Zarate and Tohen, 2004). Contrariwise, antidepressant drugs may trigger mania when given as monotherapy to bipolar patients (Viktorin et al., 2014). In addition to lithium, several other drugs have now been proven effective not only for treatment of acute episodes but also for prophylaxis and are included among first line treatment options. Thus, besides lithium the mood stabilizer group comprises some antiepileptic drugs (valproate, carbamazepine, lamotrigine) and

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some atypical antipsychotic drugs (quetiapine, olanzapine, aripiprazole) (Coryell, 2009).

It has been suggested that the classic manic-depressive disorder with euphoric manias and full recovery between recurrences would respond particularly well to lithium (Dilsaver et al., 1993; Keller et al., 1993), while persons with mixed episodes and persons with rapid cycling would respond better to valproate (Bowden, 1995; Calabrese et al., 1996; Freeman et al., 1992; Swann et al., 1997). Olanzapine is prescribed mostly for mania but may also be used for acute bipolar depression in combination with fluoxetine (Taylor et al., 2014; Yatham et al., 2013). Lamotrigine is considered primarily to protect against depressive recurrences (Calabrese, 2004; Calabrese et al., 2003a, 2008, 2003b; Frye et al., 2000) and could therefore earn its place when preventing mania is less critical, as in bipolar disorder type II. Quetiapine is used for both depression and mania, but is also the only medication with indication acute treatment of bipolar depression. The use of standard antidepressants to treat bipolar depression is controversial and the evidence base is inconclusive (Pacchiarotti et al., 2013; Sidor and Macqueen, 2011; Taylor et al., 2014; Yatham et al., 2013). Quetiapine might therefore be more likely to be prescribed to patients with predominantly depressive episodes, which is mostly the case in bipolar II disorder. Hence, a possible increased prescription of drugs with antidepressant profile (such as lamotrigine or quetiapine) might stem from changes in case-mix or diagnostic shifts with respect to bipolar subtypes.

Bipolar disorder has received increased attention in the 2000s, not least because of the launching of new treatments. It is not known if this has affected the prescription pattern. The purpose of this study was therefore to study possible changes in the prescription of mood stabilizers and antidepressants for bipolar disorder during the period 2007–2013.

## 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, established in 2004, contains individualized data concerning case-mix, medical interventions, and treatment outcomes. Data is typically collected by the treating physician 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 clinicians' rate of participation. Registering units include both private and public psychiatric outpatient health care units in Sweden.

Registration is carried out by the treating physician or nurse. After initial registration, the patients are followed up annually. In this study, we used de-identified data from 32,019 registrations in BipoläR, including both initial registrations and follow-ups, to study changes in mood stabilizer and antidepressant prescriptions during 2007–2013. BipoläR has the advantage to the Swedish National Patient register (NPR) of containing information about bipolar subtypes I, II and NOS, as well as other clinical variables that allow for in-depth analyzes such as Global Assessment of Function (GAF), a measure of clinical severity and psychosocial functioning. The disadvantage with BipoläR is, however, that it not yet includes all patients with bipolar diagnosis in Sweden. To get complete coverage of the Swedish population, we also conducted sensitivity analyzes using data from the NPR (Ludvigsson et al., 2011; Sellgren et al., 2011) and the Prescribed Drug Register (PDR) (Wettermark et al., 2007) for the same period. NPR contains all Swedish psychiatric inpatient admissions since 1973, and all psychiatric outpatient admissions, excluding primary care, since 2001. PDR contains data on all dispensed prescribed drugs in Sweden since July 2005.

### 2.2. Statistics

For BipoläR data, we built a logistic regression model with use of mood stabilizers and antidepressants as outcome, adjusting for confounding factors such as sex, age, and bipolar type (Table 2). To investigate whether there were sex differences in drug use changes, we performed a logistic regression with bipolar type and age as confounding factors (Table 2). Finally, we used a logistic regression model to study if drug use changes differed between bipolar I and II disorder after adjusting for sex and age (Table 3). Regarding data from PDR and NDR, we performed $\chi 2$ tests to study if the changes between 2007 and 2013 were statistically significant.

### 2.3. Ethics

The study was approved by the Regional Ethics Committee in Gothenburg. All analyses were conducted on a de-identified dataset.

## 3. Results

Demographic and clinical characteristics of the BipoläR-cohort ($N=32{,}019$) are summarized in Table 1. Women were overrepresented (61%). The mean (SD) age was 49.6 (15.9) years for women and 51.9 (15.3) years for men. 45% of the patients were diagnosed with Bipolar I disorder, 34% with Bipolar II disorder, 18% with Bipolar disorder NOS, and 3% with schizoaffective disorder, bipolar type. Women were more likely than men to be diagnosed with Bipolar II disorder and Bipolar disorder NOS, while men were more likely to be diagnosed with Bipolar I disorder. The Global Assessment of Functioning (GAF) score was higher in men ($t=-8.6$; $p<0.05$).

### 3.1. Treatment with lithium

In BipoläR, the prevalence of lithium use in women decreased from 64% to 53% over the period 2007–2013; in men, the prevalence was down from 71% to 59% (Fig. 1). Men were more likely to be treated with lithium than women throughout the period. The decrease was statistically significant for both sexes after adjusting for bipolar type and age (Table 2). Sensitivity analyses using data from NPR and PDR revealed that 51% of patients with bipolar diagnosis in Sweden were prescribed lithium in 2007, which was down to 41% in 2013. The use in women decreased from 49% to

**Table 1**
Demographic and clinical characteristics of the study population ($N=32{,}019$). Data from the quality register BipoläR.

| | Men | Women |
|---|---|---|
| Registrations, *n* (%) | 12,380 (39) | 19,639 (61) |
| Age, mean (SD) years | 51.9 (15.3) | 49.6 (15.9) |
| Diagnosis, *n* (%) | | |
| BD I | 5730 (19) | 7894 (26) |
| BD II | 3698 (12) | 6920 (22) |
| BD NOS | 2080 (7) | 3530 (11) |
| SAD | 407 (1) | 610 (2) |
| GAF Symptom, mean (SD) | 63.9 | 61.8 |
| GAF Function, mean (SD) | 64.2 | 62.4 |

Abbreviations: BD I: Bipolar I disorder; BD II: Bipolar II disorder; BD NOS: Bipolar disorder not otherwise specified; SAD: Schizoaffective syndrome of bipolar type; GAF: Global Assessment of Functioning.