Journal of Affective Disorders 188 (2015) 112–117

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Gender differences in mood stabilizer medications prescribed to Veterans with serious mental illness

Melanie Charlotte [a,*], Elana Schwartz [b], Eric Slade [a,b], Deborah Medoff [a,b], Lan Li [a], Lisa Dixon [c], Amy M. Kilbourne [d,e], Julie Kreyenbuhl [a,b]

[a] University of Maryland School of Medicine, Department of Psychiatry, Division of Psychiatric Services Research, Baltimore, MD, United States
[b] VA Capitol Healthcare Network (VISN 5) Mental Illness Research, Education, and Clinical Center (MIRECC), Baltimore, MD, United States
[c] Center for Practice Innovations, New York State Psychiatric Institute, Department of Psychiatry, Columbia University, New York, NY, United States
[d] Quality Enhancement Research Initiative, VA Health Services Research and Development (HSR&D Program), Washington DC, United States
[e] Department of Psychiatry, University of Michigan, Ann Arbor, MI, United States

ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form
13 August 2015
Accepted 28 August 2015
Available online 3 September 2015

Keywords:
Mood stabilizer medications
Weight gain
Women
Serious mental illness

ABSTRACT

Background: Mood stabilizer medications (MSMs) can induce significant weight gain and other metabolic side effects. Research suggests that women are more susceptible to psychotropic medication-induced metabolic side effects than men. We examined gender differences in the likelihood of receiving an MSM with a lower liability for weight gain using data from the U.S. Department of Veterans Affairs (VA) healthcare system.

Methods: We identified 3823 VA patients with a schizophrenia or bipolar disorder diagnosis who initiated treatment with a MSM between 10/2006 and 9/2011. We used multivariable logistic regression analysis to examine gender differences in the likelihood of incident prescription of MSMs with low versus medium/high metabolic risk, adjusting for fiscal year of prescribing and demographic, mental health, and physical health characteristics.

Results: Overall, 47% of women were prescribed a low metabolic risk MSM compared to 26% of men ($p < 0.0001$). In multivariable analysis, women were 2.19 times as likely as men to be prescribed a low metabolic risk MSM (95% CI: 1.84–2.60, $p < 0.0001$). Several demographic and clinical covariates were also independently related to prescribing of MSMs by level of metabolic risk.

Limitations: This study used retrospective administrative data collected from a VA healthcare system database, which does not allow us to understand the context in which MSM treatment decisions were made.

Conclusions: Prescribing choices for MSMs by VA mental health prescribers and female Veterans may reflect a growing awareness of the potential adverse health consequences of these treatments in women.

1. Introduction

Treatment with mood stabilizer medications (MSMs) such as lithium and valproate alone or in combination with antipsychotic medications (APMs) are considered first-line treatments for various phases of bipolar disorder (American Psychiatric Association (APA), 2002; Suppes et al., 2005). Awareness has grown over recent years that psychotropic medications, including APMs and MSMs, are associated with weight gain and other metabolic side effects (e.g., hyperglycemia, hyperlipidemia) that vary depending on the specific medication (Allison et al., 1999; American Diabetes Association et al., 2004; Baskaran et al., 2014; DeHert et al., 2011; Kenna et al., 2009; Torrent et al., 2008). Among MSMs, lithium and valproate have been associated with substantial weight gain in many patients, whereas carbamazepine and gabapentin have been associated with more modest effects on weight gain and associated metabolic parameters. On the other hand, oxcarbazepine and lamotrigine have not been shown to have appreciable effects on weight, whereas topiramate has been associated with weight loss in some patients (Aronne and Segal, 2002; Fagiolini and Chengappa, 2007; Keck and McElroy, 2003; Malone, 2005). While the propensity of certain APMs to induce these effects requires physicians to regularly monitor patients' weight, lipid profiles, and other metabolic indices (American Diabetes Association et al., 2004), MSMs have attracted less scrutiny and many fewer calls for routine monitoring, despite having similar metabolic effects.

Studies in both Veteran (Chwastiak et al., 2010; Kilbourne et al., 2009a, 2009b; Morden et al., 2012) and non-Veteran (Angst et al.,

* Corresponding author. Fax: +1 410 706 0022.
E-mail address: Mcharlot@psych.umaryland.edu (M. Charlotte).

http://dx.doi.org/10.1016/j.jad.2015.08.065
0165-0327/

2002; Saha et al., 2007; Druss et al., 2011) samples have shown that serious mental illness is associated with an increased risk for morbidity and premature mortality, though the effect is somewhat less pronounced in Veterans (Chwastiak et al., 2010; Kilbourne et al., 2009a). Heart disease is the leading cause of premature mortality in individuals with serious mental illness, which is largely attributable to their higher prevalence of risk factors for cardiovascular disease (CVD), including overweight and obesity (Allison et al., 2009; Baskaran et al., 2014; Daumit et al., 2003; DeHert et al., 2011; Kilbourne et al., 2009b; Morden et al., 2012). Several lines of evidence suggest that the prevalence of overweight/obesity among individuals with serious mental illness is higher in women than men (Allison et al., 1999; Daumit et al., 2003). This association may be due in part to women being more susceptible to psychotropic medication-induced weight gain, diabetes and cardiovascular risks than men (Fagiolini and Chengappa, 2007; Kenna et al., 2009; Seeman, 2009, 2010). While most attention has been focused on the metabolic effects of APMs in women with schizophrenia (Seeman, 2009), there are similar concerns associated with MSMs, which are widely prescribed for bipolar disorder, and which are associated with side effects that affect women in particular (Kenna et al., 2009). For example, valproate is associated with polycystic ovary syndrome (PCOS), a neuroendocrine disorder that can lead to obesity and further elevate the risk of early onset CVD and Type 2 diabetes in women (Kenna et al., 2009). Also, women with serious mental illness are more vulnerable than men to lithium-induced thyroid dysregulation, which may contribute to both overweight and psychiatric instability (Baskaran et al., 2014; Bauer et al., 2014; Burt and Rasgon, 2014; Ozerdem et al., 2014).

The negative impact of excess weight in women is not limited to its effects on physical health, as weight gain is reported to be the most distressing side effect of psychotropic medications, particularly among women (Covell et al., 2007; McCloughlen and Foster, 2011). In bipolar disorder, women express more concerns than men about their weight and are more than twice as likely as men to report this as the most worrisome medication-related side effect of their prescribed MSM (Kriegshauser et al., 2010). Emerging research also suggests that medication-induced weight gain and its resulting distress may also be associated with non-adherence to treatment (Tham et al., 2007; McCloughen and Foster, 2011; Weiden et al., 2004; Wong et al., 2011; Vandyk and Baker, 2012; Xiao et al., 2012), an effect that may be more pronounced in women.

Conceptually, prescription decisions are reached as providers balance the risks and benefits of particular medications, taking into account a multitude of factors known to influence clinical decision making (Reschovsky et al., 2015). These factors include patients' preferences and prior experiences with both beneficial and adverse effects of treatment (which may differ by e.g., gender), prescribers' understanding of the scientific literature and their own clinical experiences with particular medications, and practice site characteristics including mandated drug formularies and prescribing guidelines. With regard to MSMs, the growing awareness of gender differences in the impact of weight gain and other metabolic side effects from these agents may be expected to result in gender differences in the rate of prescribing according to the metabolic risk of the medication. and documentation of these differences may provide insight into whether patient gender moderates the clinical effectiveness of these treatments. However, evidence that metabolic side effect risk profile differentially impacts the prescribing of MSMs to women versus men is scant. As women are among the fastest growing groups of Veterans (Frayne et al., 2014), we examined whether differences in MSMs' metabolic side effect risk profiles differentially affect their prescribing to women versus men, using administrative data from the U.S. Department of Veterans Affairs (VA) healthcare system.

2. Methods

2.1. Setting, data and study population

Mental health care services for Veterans with serious mental illness are typically provided in specialty mental health outpatient clinics located at VA tertiary hospitals. In these settings, psychotropic medications are usually prescribed by a psychiatrist or nurse practitioner. Medication switching often occurs and may result from inadequate response, medication side effects, or patient non-adherence. Normally a Veteran will be seen by the same provider over time, which helps sustain continuity of treatment. However, relapses and inpatient admissions may result in a Veteran being seen by a different provider and being prescribed a different medication.

Data for the study were obtained from the VA's pharmacy and health care utilization databases for patients in the mid-Atlantic VA service region that encompasses Maryland and Washington DC as well as Northern Virginia and northeastern West Virginia. These areas are served by four VA hospitals and by a network of free-standing VA hospital-affiliated outpatient medical clinics. Using the diagnostic codes from inpatient and outpatient encounter data, we identified all VA patients with diagnoses of schizophrenia/schizoaffective disorder or bipolar disorder during the study period of fiscal years 2007–2011 (October 1, 2006 to September 30, 2011). A patient was assigned a diagnosis of schizophrenia or schizoaffective disorder if an ICD-9 code of 295.0-295.4 or 295.6-9 was recorded in the majority of instances in the administrative records (relative to other ICD-9 codes indicative of a serious mental illness). A patient was assigned a diagnosis of bipolar disorder if an ICD-9 code of 296.0-1 or 296.4-8 occurred most frequently (Bowersox et al., 2013). Of the 9199 Veterans with these diagnoses, 3823 had at least one new (i.e., incident) prescription for an MSM during the study period, defined as an MSM prescription that was preceded by a period lasting at least 183 days during which no other prescriptions were filled for the same medication. A total of 781 Veterans had incident MSM prescriptions in more than one year during the study period that were included in the analyses. For Veterans with more than one incident prescription within the same year, we randomly selected one incident prescription from that year to be included in analyses. Overall, 3823 Veterans had 5403 incident prescriptions for MSMs that met inclusion criteria for the study. After excluding 63 Veterans (and 103 corresponding incident MSM prescriptions) with missing data on age, gender, race, marital status, or service connected disability status, the final sample consisted of 3760 Veterans contributing 5300 new starts of MSM treatment in the analyses.

2.2. Measures

2.2.1. Primary independent and dependent variables

The primary independent variable was gender. The dependent variable was a binary indicator for the receipt of a low versus a medium or high metabolic risk MSM. The medium and high risk MSMs were carbamazepine, gabapentin, lithium and valproate/divalproex sodium/valproic acid. The low risk MSMs were lamotrigine, oxcarbazepine, and topiramate (Baskaran et al., 2014; Kenna et al., 2009; Torrent et al., 2008).

2.2.2. Demographic and clinical covariates

As we were interested in the effects of gender on mood stabilizer prescribing, beyond that of other demographics