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Gender Differences in Mood Stabilizer Medications Prescribed to Veterans with Serious Mental Illness

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Abstract

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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.

Keywords

mood stabilizer medications; weight gain; women; serious mental illness

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 (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, 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 (Arrone et al., 2003; 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, 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; Kilbourne et al., 2009b; Morden et al., 2012) and non-Veteran (Angst et al., 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, 1999; Daumit, 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 & Chengappa, 2007; Kenna et al., 2009; Seeman, 2009; Seeman, 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 & 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; McCloughen & 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 nonadherence to treatment (McCloughen & Foster, 2011; Weiden et al., 2004; Wong et al., 2011; Vandyk & 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.

Methods

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 freestanding 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). Of the 9,199 Veterans with these diagnoses, 3,823 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, 3,823 Veterans had 5,403 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 3,760 Veterans contributing 5,300 new starts of MSM treatment in the analyses.

Measures

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).

Demographic and Clinical Covariates—As we were interested in the effects of gender on mood stabilizer prescribing, beyond that of other demographics characteristics, we included age, race/ethnicity, marital status, and homelessness (in the prior 6 months) as covariates in the models. We included other covariates that could potentially influence mood stabilizer prescribing, for example service connected disability rating > 50%, indicating exemption from copayments for prescription medications. Service-connected disability benefits are paid to Veterans with disabilities resulting from conditions, including mental health disorders, incurred or exacerbated during active military service. The service connected disability rating reflects the severity of the disability and its impact on the Veteran's ability to work. We also included the presence of co-occurring psychiatric conditions (depression (ICD-9: 296.30–296.36), post-traumatic stress disorder (PTSD) (ICD-9: 309.81), substance use disorder (ICD-9: 303.0, 303.9, 304.x, and 305.x, except 305.1, which indicates nicotine abuse)), and opportunities for receipt of new mood stabilizer medication prescriptions (inpatient hospitalizations (yes/no) and number of outpatient mental health visits in the past 6 months). The presence of selected medical co-morbidities (coronary artery disease (ICD-9: 411, 413, 414), hyperlipidemia (ICD-9: 272.0–4), hypertension (ICD-9: 401), diabetes (ICD-9: 250, except 250.1)) and opportunities for identifying or treating them (number of outpatient primary care visits in the past 6 months), which could influence the metabolic risk level of the mood stabilizer selected, were included in the models as well.

Statistical Analyses

Univariate statistics were used to describe the demographic and clinical characteristics of the sample and bivariate statistics were used to compare the proportions of women versus men prescribed low (versus medium or high) risk MSMs during the 5-year study period. Multivariate logistic regression analysis was then used to examine gender differences in the likelihood of incident prescription of MSMs with low (versus medium or high) metabolic risk, adjusting for fiscal year of the MSM prescription and the aforementioned Veteran demographic, mental health, and physical health characteristics. We accounted for clustering due to repeated incident MSM prescriptions within Veteran by using a logistic mixed effects model with random effects. To determine whether our results were sensitive to our decision to select a single incident MSM prescription per Veteran-year at random, we conducted a separate analysis excluding those individuals. The logistic regression result for the gender difference was reported both as an adjusted odds ratio and as the covariate-adjusted probability of receiving a low metabolic risk MSM for women and for men. These covariate-adjusted means were estimated as predicted values by first assigning the entire sample

gender equal to male and then by assigning gender equal to female, holding constant the values of all other model covariates (Muller & MacLehose, 2014).

Results

Sample Description

Overall, the mean age of the sample was 49.9 (± 12.3), 17% (n=626) were female, 56% (n=2088) were non-Hispanic Caucasian, and 28% (n= 1066) were married. Seventy-seven percent (n=2895) had a diagnosis of bipolar disorder and 23% (n= 865) had a schizophrenia or schizoaffective disorder diagnosis. Co-occurring mental health diagnoses included depression (n=1634, 44%), alcohol or substance abuse disorder (n=1530, 41%), and post-traumatic stress disorder (n=1043, 28%). Twenty-nine percent (n=1082) had been hospitalized for their psychiatric condition in the prior 6 months. Twenty percent (n=744) had a diabetes diagnosis, 34% (n=1261) had a hyperlipidemia diagnosis, and 42% (n=1570) had a hypertension diagnosis.

Prescribing of MSMs According to Level of Metabolic Risk

In unadjusted analyses, across the entire study period, 47% of women were prescribed an MSM associated with a low risk of metabolic side effects compared to 26% of men ($p < 0.0001$), a pattern that was observable in each fiscal year (Figure 1). Women were 1.8 times as likely to be prescribed low risk agents compared to men (RR= 1.83; 95% CI= 1.65–2.02; $p < 0.0001$) in unadjusted analyses. In multivariable analysis (Table 1), the odds of being prescribed a low metabolic risk MSM were 2.19 times greater for women compared to men (AOR=2.19; 95% CI: 1.84–2.60, $p < 0.0001$). Based on these logistic regression results, the covariate-adjusted estimated mean probability of receiving a low metabolic risk MSM was 0.405 for women and 0.185 for men.

Several demographic and clinical covariates were also independently related to prescribing of MSMs by level of metabolic risk (Table 1). Older age was associated with a lower odds of receipt of a low metabolic risk MSM (AOR=0.99; 95% CI=0.98–1.00; $p = 0.006$). Homelessness in the prior 6 months was also associated with a 27% lower odds of receiving a low metabolic risk MSM (AOR=0.73; 95% CI=0.59–0.90; $p = 0.003$). Veterans who had been hospitalized for their psychiatric illness in the prior 6 months had a 44% lower odds of being prescribed a low metabolic risk MSM (AOR=0.56; 95% CI= 0.47–0.67; $p < 0.0001$). In addition, veterans diagnosed with schizophrenia had a 24 % lower odds of being prescribed a low metabolic risk MSM as compared to Veterans diagnosed with bipolar disorder (AOR=0.76; 95% CI=0.63–0.92; $p = 0.005$).

Conversely, there were several other covariates associated with a greater likelihood of being prescribed MSMs with a low risk of metabolic side effects. Veterans with a service connection $> 50\%$ (and thus no prescription co-pay) were 21% more likely to receive these agents (AOR=1.21; 95% CI=1.03–1.41; $p = 0.02$), as were Veterans with a hypertension diagnosis (AOR=1.21; 95% CI=1.03–1.43; $p = 0.02$). Greater numbers of outpatient psychiatric visits were also associated with a higher likelihood of being prescribed MSMs with a low risk of metabolic side effects (AOR=1.01; 95% CI=1.00–1.01; $p = 0.001$).

A sensitivity analysis was used to examine the impact of excluding from the sample the 781 individuals who had more than one incident MSM prescription during a year. There were no substantive changes in study findings when these individuals were excluded from the multivariate analyses.

Discussion

In a sample of VA patients with schizophrenia or bipolar disorder who began a new episode of a MSM, women had an approximately two-fold greater odds of receiving a prescription for a MSM with a lower risk of weight gain and other metabolic side effects compared to men, an effect that persisted over a 5-year period. These findings are consistent with a recent study in Sweden that found that women with bipolar disorder type II were significantly more likely than men to be prescribed lamotrigine, a MSM with a lower risk of metabolic side effects, while regardless of bipolar subtype, men were significantly more likely than women to receive lithium, a MSM with a higher risk of metabolic side effects (Karanti et al., 2014). Taken together, these findings suggest that both Veteran and non-Veteran women with serious mental illness may be subjected to fewer cardiovascular health risks from MSMs than men. Given that women are disproportionately affected by overweight/obesity, and by metabolic side effects associated with psychotropic medications, this strategy may be a rational approach by prescribers to improving the health status of their female patients. It may also reflect preferences by women for avoiding side effects that not only adversely affect their physical health, but also their appearance and psychological well-being.

While medication-induced weight gain has important implications for women's health and is particularly distressing for them, other potential effects of MSMs that are specific to women may also be influencing medication decision-making. For example, the mood stabilizer valproate, which is associated with a higher risk of metabolic side effects, is also linked with menstrual abnormalities, reproductive dysfunction, and the aforementioned PCOS, a neuroendocrine disorder that is one of the most common causes of anovulatory infertility (Burt & Rasgon, 2014; Kenna et al., 2009). While gender differences in valproate prescribing were not observed in the aforementioned Swedish study, the possibility of these effects may nevertheless help explain the lower use of valproate in female Veterans with serious mental illness in our study, particularly since almost half (48%) of the female Veterans in our sample were of reproductive age, which we defined as being 44 years of age or less.

Although the focus of this study was gender differences, the association of other demographic and clinical characteristics with MSM prescribing is noteworthy. For example, it is encouraging that Veterans with a diagnosis of hypertension were more likely to be prescribed MSMs with a lower risk for metabolic side effects. However, being diagnosed with other co-occurring cardiometabolic medical conditions, including Type 2 diabetes, coronary artery disease, or hyperlipidemia, was not significantly associated with the metabolic risk level of the MSM that was prescribed. In some respects, this contrasts with the primary finding of the study, in which women were more likely to receive the more metabolically neutral MSMs, which we hypothesize may have been in an effort to avoid weight gain and associated cardiovascular risk. Clearly, more research is needed to

determine the extent to which both prescribers and patients are aware of the weight gain potential and cardiovascular risks associated with mood stabilizer treatments, and whether patients' individual risk factors for adverse cardiovascular outcomes are considered as a part of the medication decision-making process.

It was also notable that while only comprising about a quarter of the study sample, individuals with schizophrenia were significantly less likely than those with bipolar disorder to be prescribed a mood stabilizer associated with a lower risk of weight gain and metabolic side effects. This finding is curious, since similar to individuals with bipolar disorder, those with schizophrenia also experience significant cardiovascular risk that may be due, in part, to concomitant treatment with multiple psychotropic medications with potentially adverse metabolic profiles. In contrast to bipolar disorder, however, robust empirical support for the efficacy of adjunctive treatment with MSMs in individuals with schizophrenia e.g., to mitigate residual psychotic symptoms, aggression, impulsivity, and mood disturbances, is lacking (Buchanan et al., 2010; Citrome 2009). Yet rates of prescribing of MSMs to individuals with schizophrenia are quite high, with an estimated 25–60% of patients receiving these agents (Citrome 2000; Citrome 2002; Horowitz et al., 2014; Olfson et al., 2009). Given the overall widespread use and the more frequent prescribing of high metabolic risk MSMs to individuals with schizophrenia, more research is needed to understand the potential harmful effects of such 'off-label' prescribing on the physical health of these individuals.

We also note that individuals in the study sample who were homeless or who had had an inpatient psychiatric hospitalization in the six months prior to the incident MSM prescription had a lower likelihood of being prescribed the more metabolically neutral MSMs, regardless of whether their primary psychiatric diagnosis was bipolar disorder or schizophrenia. This may suggest that prescribers are reserving the more metabolically problematic MSMs for individuals with a more severe course of illness, perhaps after trials of the more metabolically neutral agents have failed, a possibility that we were unable to investigate as it was beyond the scope of the current study. It may also be that prescribers have more clinical experience with the MSMs associated with greater metabolic risk (e.g., lithium, valproate, carbamazepine), which have been available for much longer than those with more favorable metabolic profiles (e.g., lamotrigine, topiramate). This study has some limitations, including several inherent in the use of electronic databases for research purposes. Importantly, our source of data did not permit us to understand *how* the MSM treatment decisions associated with the prescribing patterns we observed were made and by whom – particularly whether female Veterans had a substantial informed role in these decisions. Such information is critical to the overall health of female Veterans with serious mental illness and understanding their role in shared decision-making with respect to MSM treatment merits further research. Although available in VA administrative datasets, we did not have access to patients' body mass indices or results of metabolic monitoring to evaluate the influence of these parameters on prescribing choices and whether any difference in these parameters between male and female Veterans could have contributed to our results. Additionally, we were unable to evaluate individuals with a serious mental illness who were ultimately in the diagnostic sample but who declined mood stabilizer treatment, perhaps because of concerns

about metabolic or other side effects that could have been similar to those of individuals included in the study who accepted treatment.

Also, the results of this study may only generalize to VA patients with schizophrenia and bipolar disorder receiving care in an integrated healthcare system. It is worth noting that during the time period of the study (10/2006–9/2011), there were no restrictions within VA on prescribing of any of the mood stabilizer medications investigated in this study. During this time, the VA maintained an open national formulary and did not distribute any VA-specific treatment guidelines or algorithms to dictate prescribing of certain mood stabilizers. Further, while the VA promotes the use of evidenced-based physical and mental health treatments, it did not mandate that VA prescribers adhere to any other published recommendations e.g., for the treatment of bipolar disorder or schizophrenia. Finally, some of the measures we derived from administrative data, including that of recent homelessness and substance use, may not be particularly sensitive indicators of these problems. These limitations are mitigated by our ability to evaluate MSM prescribing patterns over an extended period of time in a large sample of female and male Veterans with serious mental illness.

In summary, we found that female Veterans with schizophrenia and bipolar disorder in a single VA healthcare network were more likely to be prescribed mood stabilizer medications with a lower risk of weight gain and adverse metabolic effects than males. These results suggest that prescribing choices for MSMs by VA mental health prescribers and the preferences of female Veterans reflect an awareness of the potential adverse health consequences of these treatments. More research is needed to better understand the impact of these treatment decisions on both the physical and mental health of female Veterans, which could be accomplished using the growing amount of clinical information, including weight and other metabolic indices, recently made available in VA administrative databases. Use of these data by VA clinicians and policymakers to facilitate medication risk monitoring in regular clinical practice is also a logical next step.

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References

- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am. J. Psychiatry*. 1999; 156:1686–1696. [PubMed: 10553730]
- American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development

conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004; 27:596–601. [PubMed: 14747245]

American Psychiatric Association (APA). Practice guideline for the treatment of patients with bipolar disorder (revision). *Am. J. Psychiatry*. 2002;1591–1650. [PubMed: 12202282]

Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J. Affect Disord*. 2002; 68:167–181. [PubMed: 12063145]

Aronne LJ, Segal KR. Weight gain in the treatment of mood disorders. *J. Clin. Psychiatry*. 2002; 64:22–29.

Baskaran A, Cha DS, Powell AM, Jalil D, McIntyre RS. Sex differences in rates of obesity in bipolar disorder: postulated mechanisms. *Bipolar Disord*. 2014; 16:83–92. [PubMed: 24467470]

Bauer M, Glenn T, Pilhatsch M, Pfennig A, Whybrow PC. Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. *Bipolar Disord*. 2014; 16:58–71. [PubMed: 24245529]

Bowersox, NW., Visnic, S., Valenstein, M., McCarthy, JF. VHA National Psychosis Registry. Ann Arbor, Mich: Serious Mental Illness Treatment Resource and Evaluation Center, Office of Mental Health Operations, VHA; Care for Veterans Health Administration (VHA) Clients with Psychosis, FY2013: 15th Annual report.

Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr. Bull*. 2010; 36:71–93. [PubMed: 19955390]

Burt VK, Rasgon N. Special considerations in treating bipolar disorder in women. *Bipolar Disord*. 2014; 6:2–13.

Chwastiak LA, Rosenheck RA, Desai R, Kazis LE. Association of psychiatric illness and all-cause mortality in the National Department of Veterans Affairs Health Care System. *Psychosom. Med*. 2010; 72:817–822. [PubMed: 20639387]

Citrome L, Levine J, Allingham B. Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatr. Serv*. 2000; 51:634–638. [PubMed: 10783182]

Citrome L, Jaffe A, Levine J, Allingham B. Use of mood stabilizers among patients with schizophrenia, 1994–2001. *Psychiatr. Serv*. 2002; 53:1212. [PubMed: 12364663]

Citrome L. Adding lithium or anticonvulsants to antipsychotics for the treatment of schizophrenia: useful strategy or exercise in futility? *J. Clin. Psychiatry*. 2009; 70:932–933. [PubMed: 19573487]

Covell NH, Weissman EM, Schell B, McCorkle BH, Summerfelt WT, Weiden PJ, Essock SM. Distress with medication side effects among persons with severe mental illness. *Adm. Policy Ment. Health*. 2007; 34:435–442. [PubMed: 17653845]

Daumit GL, Clark JM, Steinwachs DM, Graham CM, Lehman A, Ford DE. Prevalence and correlates of obesity in a community sample of individuals with severe and persistent mental illness. *J. Nerv. Ment. Dis*. 2003; 191:799–805. [PubMed: 14671456]

DeHert M, Correll CU, Bobes J, Cetkovich M, Cohen D, Asai I. Physical illness in patients with severe mental disorders. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011; 10:52–77. [PubMed: 21379357]

Druss BG, Zhao L, Von Esenwein S, Morrato EH, Marcus SC. Understanding excess mortality in persons with mental illness: 17-year follow up of a nationally representative US survey. *Med. Care*. 2011; 49:599–604. [PubMed: 21577183]

Fagiolini A, Chengappa KN. Weight gain and metabolic issues of medicines used for bipolar disorder. *Curr. Psychiatry Rep*. 2007; 9:521–528. [PubMed: 18221634]

Frayne, SM., Phibbs, CS., Saechao, F., Maisel, NC., Friedman, SA., Finlay, A., Berg, E., Balasubramanian, V., Dally, SK., Ananth, L., Romodan, Y., Lee, J., Iqbal, S., Hayes, PM., Zephyrin, L., Whitehead, A., Torgal, A., Katon, JG., Haskell, S. Sociodemographics, Utilization, Costs of Care, and Health Profile. Vol. 3. Women's Health Evaluation Initiative, Women's Health Services, Veterans Health Administration, Department of Veterans Affairs; Washington, D.C.: Feb. 2014 Sourcebook: Women Veterans in the Veterans Health Administration.

Horowitz E, Bergman LC, Ashkenazy C, Moscona-Hurvitz I, Grinvald-Fogel H, Magnezi R. Off-label use of sodium valproate for schizophrenia. *PLoS One*. 2014; 9:e92573. [PubMed: 24664210]

- Karanti A, Bobeck C, Osterman M, Kardell M, Tidemalm D, Runeson B, Lichtenstein P, Landen M. Gender differences in the treatment of patients with bipolar disorder: A study of 7354 patients. *J. Affect Disord.* 2015; 174:303–309. [PubMed: 25532077]
- Keck PE, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. *J. Clin. Psychiatry.* 2003; 64:1426–1435. [PubMed: 14728103]
- Kenna HA, Jiang B, Rasgon NL. Reproductive and metabolic abnormalities associated with bipolar disorder and its treatment. *Harv. Rev. Psychiatry.* 2009; 17:138–146. [PubMed: 19373621]
- Kilbourne AM, Ignacio RV, Kim HM, Blow FC. Datapoints: Are VA patients with serious mental illness dying younger? *Psychiatr. Serv.* 2009a; 60:589. [PubMed: 19411344]
- Kilbourne AM, Morden NE, Austin K, Ilgen M, McCarthy JF, Dalack G. Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. *Gen. Hosp. Psychiatry.* 2009b; 31:555–563. [PubMed: 19892214]
- Kriegshauser K, Sajatovic M, Jenkins JH, Cassidy KA, Muzina D, Fattal O, Smith D, Singer B. Gender differences in subjective experience and treatment of bipolar disorder. *J. Nerv. Ment. Dis.* 2010; 198:370–372. [PubMed: 20458200]
- Malone M. Medications associated with weight gain. *Ann. Pharmacother.* 2005; 39:2046–2055. [PubMed: 16278256]
- McCloughen A, Foster K. Weight gain associated with taking psychotropic medication: An integrative review. *Int. J. Ment. Health Nurs.* 2011; 20:202–222. [PubMed: 21492360]
- Morden NE, Lai Z, Goodrich DE, MacKenzie T, McCarthy JF, Austin K. Eight-year trends of cardiometabolic morbidity and mortality in patients with schizophrenia. *Gen Hosp. Psychiatry.* 2012; 34:368–379. [PubMed: 22516216]
- Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int. J. Epidemiol.* 2014; 43:962–970. [PubMed: 24603316]
- Olfson M, Marcus SC, Wan GJ. Treatment patterns for schizoaffective disorder and schizophrenia among Medicaid patients. *Psychiatr. Serv.* 2009; 60:210–216. [PubMed: 19176415]
- Ozderdem A, Tunca Z, Cimrin D, Hidioglu C, Ergor G. Female vulnerability for thyroid function abnormality in bipolar disorder: Role of lithium treatment. *Bipolar Disord.* 2014; 16:72–82. [PubMed: 24330379]
- Reschovsky JD, Rich EC, Lake TK. Factors contributing to variations in physicians' use of evidence at the point of care: A conceptual model. *J. Gen. Intern. Med.* 2015; 30:555–561.
- Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Arch. Gen. Psychiatry.* 2007; 64:1123–1131. [PubMed: 17909124]
- Seeman MV. Secondary effects of antipsychotics: Women at greater risk than men. *Schizophr. Bull.* 2009; 35:937–948. [PubMed: 18400811]
- Seeman MV. Schizophrenia: Women bear a disproportionate toll of antipsychotic side effects. *J. Am. Psychiatr Nurses Assoc.* 2010; 16:21–29. [PubMed: 21659259]
- Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, Crismon ML, Ketter TA, Sachs GS, Swann AC. Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J. Clin. Psychiatry.* 2005; 66:870–886. [PubMed: 16013903]
- Tham MSP, Jones SG, Chamberlain JA, Castle DJ. The impact of psychotropic weight gain on people with psychosis – patient perspectives and attitudes. *J. Ment. Health.* 2007; 16:771–779.
- Torrent C, Amann B, Sanchez-Moreno J. Weight gain in bipolar disorder: Pharmacological treatment as a contributing factor. *Acta Psychiatr. Scand.* 2008; 118:4–18. [PubMed: 18498432]
- Vandyk AD, Baker C. Qualitative descriptive study exploring schizophrenia and the everyday effect of medication-induced weight gain. *Int. J. Ment. Health Nurs.* 2012; 21:349–357. [PubMed: 22404848]
- Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. *Schizophr. Res.* 2004; 66:51–57. [PubMed: 14693352]

- Wong MMC, Chen EYH, Lui SSY, Tso S. Medication adherence and subjective weight perception in patients with first-episode psychotic disorder. *Clin. Schizophr. Relat. Psychoses*. 2011; 5:135–141. [PubMed: 21983497]
- Xiao S, Baker C, Oyewumi LK. Psychosocial processes influencing weight management among persons newly prescribed atypical antipsychotic medications. *J. Psychiatr. Ment. Health Nurs*. 2012; 19:241–247. [PubMed: 22074295]

Figure 1.

Prescription of Low Metabolic Risk Mood Stabilizer Medications by Gender among Veterans with Serious Mental Illness in VA VISN 5 (Fiscal Years 2007–2011)

¹The above results show that 47% of women were prescribed an MSM associated with a low risk of metabolic side effects compared to 26% of men ($p < 0.0001$), a pattern that was observable in each fiscal year.

Multivariate Analysis of Prescription of Mood Stabilizer Medications According to Liability for Weight Gain and Other Metabolic Risks among Veterans with Serious Mental Illness in VA VISN 5

Table 1

Characteristic	Prescribed low (vs. medium/high) risk Mood Stabilizer Medication				
	Yes (N=1,302)	No (N=3,998)	Multivariable analysis		
	N (%) or Mean (SD)	N (%) or Mean (SD)	AOR ^a	95% CI	p
Female gender	362 (27.8)	541 (13.5)	2.19	1.84–2.60	<0.0001
Other demographics					
Age, years	48.4 (± 12.0)	50.2 (± 13.5)	0.99	0.98–1.00	0.006
Black race (vs. other race)	455 (34.9)	1,594 (39.9)	0.81	0.62–1.07	0.13
White race (vs. other race)	741 (56.9)	2,145 (53.7)	0.99	0.76–1.28	0.91
Married	373 (28.6)	1,053 (26.3)	1.04	0.89–1.22	0.62
Homeless, past 6 months	140 (10.8)	713 (17.8)	0.73	0.59–0.90	0.003
Service connected > 50%	522 (40.1)	1,350 (33.8)	1.21	1.03–1.41	0.02
Mental health diagnoses/services use					
Schizophrenia (vs. bipolar disorder)	226 (17.4)	957 (23.9)	0.76	0.63–0.92	0.005
Depression	596 (45.8)	1,729 (43.2)	1.09	0.94–1.26	0.27
Post-traumatic stress disorder	395 (30.3)	1,118 (28.0)	1.03	0.87–1.21	0.73
Alcohol/substance use disorder	491 (37.7)	1,741 (43.5)	1.03	0.88–1.20	0.73
Psychiatric hospitalization, past 6 months	217 (16.7)	309 (7.7)	0.56	0.47–0.67	<0.0001
# outpatient clinic visits, past 6 months	8.0 (± 14.8)	7.1 (± 15.0)	1.01	1.00–1.01	0.001
Physical health diagnoses/service use					
Coronary artery disease	82 (6.3)	309 (7.7)	0.84	0.62–1.13	0.25
Hyperlipidemia	483 (37.1)	1,381 (34.5)	1.17	0.99–1.38	0.07
Hypertension	553 (42.5)	1,706 (42.7)	1.21	1.03–1.43	0.02
Type 2 diabetes	239 (18.4)	830 (20.8)	0.84	0.70–1.03	0.09
# outpatient primary care visits, past 6 months	4.3 (± 5.4)	4.3 (± 6.1)	0.99	0.98–1.01	0.52

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Adjusted odds of prescription of a low vs. medium/high metabolic risk MSM, controlling for all variables in the table and fiscal year (‘07, ‘08, ‘09, ‘10, ‘11) of prescription; analysis includes N=5,300 incident MSM prescriptions.