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Gender Differences in Antipsychotics Prescribed to Veterans with Serious Mental Illness

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Abstract

Objective—To examine gender differences in prescribing of antipsychotic medications (APMs) according to their liability for weight gain and other metabolic side effects.

Method—We identified 4,510 patients with schizophrenia or bipolar disorders receiving usual care in a VA healthcare network in the U.S. mid-Atlantic region who initiated treatment with an APM between 10/2006 and 9/2011. We used multivariable logistic regression to examine gender differences in the likelihood of incident prescription of APMs with low versus medium/high metabolic risk, adjusting for fiscal year of prescribing and selected Veteran demographic, mental health, and physical health characteristics.

Results—Overall, 58% of women were prescribed an APM with a low risk of metabolic side effects compared to 45% of men ($p < 0.001$). In multivariable analysis, women Veterans were 1.47 times as likely as men to be prescribed a low metabolic risk APM (95% CI: 1.26–1.73, $p < 0.001$). Several demographic and clinical covariates were also independently related to prescribing of APMs by level of metabolic risk.

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Conclusions—The results may suggest that prescribing choices for APMs by VA mental health prescribers and female Veterans reflect a growing awareness of the potential adverse health consequences of these treatments in women.

Keywords

women's health; serious mental illness; veterans; antipsychotic medication

1. Introduction

Women are one of the fastest growing groups of Veterans [1], and antipsychotic medications (APMs) are widely prescribed among both male and female Veterans with serious mental illnesses including schizophrenia and bipolar disorder [2]. Awareness has grown over recent years that APMs are associated with weight gain and other metabolic side effects (e.g., hyperglycemia, hyperlipidemia) that vary depending on the specific medication [3–5] and for which expert guidelines recommend ongoing monitoring [3]. Increasing attention is being paid to the potential impact of weight gain and other metabolic side effects associated with APMs on the physical health status of individuals with serious mental illness, which may be an important determinant of their use [6].

Studies in both Veteran [7–10] and non-Veteran [11–13] 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 [7,9]. Heart disease is the leading cause of premature mortality in both Veterans and non-Veterans with serious mental illness, which is largely attributable to the higher prevalence of several risk factors for cardiovascular disease, including overweight and obesity [4,8,10,14–16], in these individuals. Several lines of evidence suggest that the prevalence of overweight/obesity is higher in women than men with serious mental illness [5,16], which may be due in part to women being more susceptible to psychotropic medication-induced weight gain, diabetes and cardiovascular risks than men [17–20]. While considerable, 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 [21–22], who are more vulnerable to the many psychosocial consequences of obesity, including bias and stigma from others, low self-esteem and self-image, and diminished quality of life related to being overweight [23]. While the negative effects of weight gain on physical health and psychological well-being are better known, emerging research also suggests that medication-induced weight gain and its resulting distress may also be associated with nonadherence to treatment [21,24–27], an effect that may be more pronounced in women.

The growing awareness of gender differences in the impact of weight gain from psychotropic medications may be expected to result in gender differences in the rate of use of medications with less significant versus more significant metabolic side effects, because women and men may differ in their ranking of the importance of these side effects in comparison to other medication attributes. 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 APMs to women versus men is scant. In this study, we examined whether differences in APMs' 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. Material and Methods

2.1 Data and Study Population

Data for the study were obtained from the VA pharmacy and health care utilization databases for patients in the mid-Atlantic 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 (January 1, 2007 to December 31, 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 [2]. Of the 9,199 Veterans with these diagnoses, 4,586 had at least one new (i.e., incident) prescription for an APM during the study period, defined as an APM 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 1,074 Veterans had incident APM 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, 4,586 Veterans had 6,945 incident prescriptions for APMs that met inclusion criteria for the study. After excluding 76 Veterans (and 134 corresponding incident APM prescriptions) with missing data on age, gender, race, marital status, or service connected disability status, the final sample consisted of 4,510 Veterans contributing 6,811 new starts of APM 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 receipt of a low versus a medium or high metabolic risk APM. The medium and high risk APMs were clozapine, olanzapine, chlorpromazine, iloperidone, loxapine, paliperidone, quetiapine, risperidone, thioridazine, thiothixene, and trifluoperazine. The low risk APMs were aripiprazole, asenapine, fluphenazine, haloperidol, lurasidone, perphenazine, pimozide, and ziprasidone [3–5].

2.2.2 Demographic and Clinical Covariates—As we were interested in the effects of gender on antipsychotic 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 also included other covariates that could potentially influence antipsychotic prescribing: service connected disability rating >50% (indicating exemption from copayments for prescription medications), the presence of co-occurring psychiatric conditions (depression (ICD-9: 296.30–296.36), posttraumatic stress disorder (PTSD) (ICD-9: 309.81), substance use disorder (ICD-9: 303.0, 303.9, 304, and 305, except 305.1, which indicates nicotine abuse)) and opportunities for receipt of new antipsychotic 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 antipsychotic selected, were included in the models as well.

2.2.3 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 APMs with low (versus medium or high) risk during the 5-year study period. Multivariate logistic regression analysis was then used to examine gender differences in the likelihood of incident prescription of APMs with low (versus medium or high) metabolic risk, adjusting for fiscal year of the APM prescription and the aforementioned Veteran demographic, mental health, and physical health characteristics. We accounted for clustering due to repeated incident APM 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 APM prescription at random for inclusion in the analysis for those who had more than one in a given year, we conducted a separate analysis excluding those individuals.

3. Results

3.1 Sample Description

Overall, the mean age of the sample was 51.3 ($\pm$ 12.3) years, 14% (n=634) were female, 53% (n=2,386) were non-white, and 25% (n=1,126) were married. Fifty-five percent (n=2,519) had a diagnosis of bipolar disorder and 45% (n=1,991) had a schizophrenia or schizoaffective disorder diagnosis. Co-occurring mental health diagnoses included depression (n=1,820, 40%), alcohol or substance use disorder (n=1,833, 40%) and post-traumatic stress disorder (n=1,183, 26%). Thirty-two percent (n=1,440) had been hospitalized for their psychiatric condition in the prior 6 months. Twenty percent (n=931) had a diabetes diagnosis, 34% (n=1,550) had a hyperlipidemia diagnosis, and 43% (n=1,972) had a hypertension diagnosis.

3.2 Prescribing of APMs According to Level of Metabolic Risk

In unadjusted analyses, across the entire study period, 58% of women were prescribed an APM associated with a low risk of metabolic side effects compared to 45% of men ($X^2 = 38.16$; $df=1$; $p < 0.0001$), a pattern that was observable in each fiscal year (Figure 1). Consistent with unadjusted analyses, multivariable logistic regression analysis showed that

women Veterans were approximately 1.5 times as likely as men (AOR=1.47; 95% CI=1.26–1.73; $p < 0.001$) to be prescribed a low metabolic risk APM across the entire study period.

Several demographic and clinical covariates were also independently related to prescribing of APMs with a low risk of metabolic side effects (Table 1). Veterans who were older (AOR=0.99; 95% CI=0.98–0.99; $P < 0.001$) had lower odds of being prescribed these agents as did Veterans with co-occurring PTSD (AOR=0.81; 95% CI=0.71–0.92; $p < 0.001$).

Conversely, several other covariates were associated with a greater likelihood of being prescribed APMs with a low risk of metabolic side effects. Veterans with service connection $>50\%$ (and thus no prescription co-pay) had a 13% higher likelihood of receiving a low metabolic risk APM (AOR=1.13; 95% CI=1.01–1.27; $p=0.04$), and Veterans with co-occurring substance use disorders had a 9% higher likelihood (AOR=1.09; 95% CI=1.03–1.16; $p = 0.005$). Veterans with co-occurring hyperlipidemia (AOR=1.18; 95% CI=1.05–1.34; $p = 0.008$) or Type 2 diabetes (AOR=1.49; 95% CI=1.29–1.72; $p < 0.001$) also had a higher likelihood of being prescribed an APM associated with fewer metabolic side effects, as did those with a greater number of outpatient primary care visits (AOR=1.02; 95% CI=1.01–1.03; $p = 0.003$).

There were no substantive changes in study findings when the 1,312 individuals with more than one incident APM prescription in a given year were excluded from the multivariate analyses.

4. Discussion

In a sample of VA patients with schizophrenia or bipolar disorder who began a new episode of antipsychotic treatment, controlling for other factors, women were 50% more likely to receive a prescription of an antipsychotic 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 prescribing patterns suggest that women Veterans with serious mental illness may be subjected to *fewer* cardiovascular health risks from APMs than men. Given that these women are disproportionately affected by overweight/obesity, and particularly that 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.

On the other hand, the use of fewer APMs with increased risks for metabolic effects may lead to lower utilization of treatments with superior efficacy, at least for schizophrenia, in some women. Clozapine has been shown to be the most effective antipsychotic medication for refractory schizophrenia [28], and some evidence suggests that olanzapine may be marginally more effective than other APMs [29] or to be slightly less likely to be discontinued [30]. In addition, while limited data suggests that switching APM treatment to a medication with a lower propensity for inducing weight gain produces modest weight loss and improvements in selected metabolic parameters, switching to a more weight-neutral APM may also lead to an increase in psychiatric symptoms or to treatment discontinuation

in some patients [31–32]. As such, it may be that some of the physical health benefits associated with the more metabolically neutral APMs may be offset by negative effects on psychiatric status, of which female Veterans may be differentially affected. Understanding the impact of APM treatment decisions in women with serious mental illness, including possible trade-offs between physical and mental health effects, was beyond the scope of the current work but represents an important avenue of future research with clear clinical implications.

Although gender differences in receipt of APMs with lower metabolic risks have not been previously reported, other studies of Veterans have identified gender differences in medication prescribing. Notably, in these studies, women Veterans were receiving lower quality treatment than men [33–35]. For example, in a recent study, women Veterans were found to be more likely than men to be prescribed all classes of pharmacotherapy for PTSD (antidepressants, antipsychotics, hypnotics) except for prazosin, with marked increases in prescribing of benzodiazepines in women despite guideline recommendations against their use for PTSD [33].

Although the focus of this study was gender differences, it is encouraging to note that VA mental health prescribers and VA patients appear to be taking multiple indicators of physical health status into account when selecting APM treatment [6]. For example, we found that Veterans with serious mental illness and co-occurring hyperlipidemia or Type 2 diabetes were more likely to receive the more metabolically neutral APMs, as were Veterans with other indicators of potentially compromised medical status, including those with substance use disorders and those with a greater number of visits to primary care providers. However, we also found that Veterans with serious mental illness who had co-occurring PTSD were *less* likely to be prescribed APMs associated with fewer metabolic problems. This is consistent with other work showing quetiapine, an agent with medium/high metabolic risk and significant sedating properties, to be the most frequently prescribed second-generation APM for individuals with co-occurring PTSD, in which insomnia and nightmares are common [36]. Further, another agent with medium-high risk metabolic effects, risperidone, has been the most widely studied APM for PTSD. Despite not having greater overall efficacy versus fluoxetine alone, risperidone was shown to significantly increase sedation and improve symptoms of hyper-arousal and re-experiencing in the largest study of its effects in PTSD [37]. Use of higher metabolic risk APMs in this group is of concern given the growing evidence that PTSD is associated with an increased risk for metabolic syndrome [38], an effect shown to be independent of APM treatment [39] that may impose additive cardiovascular risk in individuals with serious mental illness who are already predisposed to these conditions. As such, efforts to inform mental health prescribers and patients alike about the less well known cardiovascular risks of PTSD may be needed.

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 APM 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

APM treatment merits further research. We also did not have access to patients' body mass indices to evaluate the role that weight or BMI played in prescribing practices as well as potential BMI differences between male and female SMI Veterans that 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 antipsychotic 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.

Other limitations of the study include that some of the APMs examined were introduced on the market and became available in VA during the study period, one associated with a medium/high risk of metabolic side effects (iloperidone introduced in 2009) and two associated with a low risk (asenapine (2009) and lurasidone (2010)). More research is needed to determine the extent to which the gender differences in prescribing we observed apply to the prescribing of these newer (more expensive) treatments. Also, the results of this study may only generalize to VA patients with schizophrenia and bipolar disorder receiving care in an integrated healthcare system. 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 to some extent by our ability to evaluate APM prescribing patterns over an extended period of time in a large sample of female and male Veterans with serious mental illness.

5. Conclusions

In summary, we found that female Veterans with serious mental illness in a single VA healthcare network were more likely to be prescribed antipsychotic treatments with a lower risk of weight gain and adverse metabolic effects than males. The limitations of administrative data notwithstanding, these results suggest that prescribing choices for APMs by VA mental health prescribers and the preferences of female Veterans reflect a growing awareness of the potential adverse health consequences of these treatments. On the other hand, as some APMs with a higher risk for metabolic side effects also demonstrate superior efficacy for schizophrenia, the mental health status of some women Veterans may be compromised due to lower utilization of evidence-based treatments for schizophrenia, in particular. More research is needed to better understand the impact of these treatment decisions on both the physical and mental health of female Veterans.

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Appendix

Figure A.1.
Prescription of Low Metabolic Risk Antipsychotic Medications by Gender among Veterans with Serious Mental Illness in VA VISN 5 (Fiscal Years 2007–2011)

Table A.1

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

Characteristic	Prescribed low (vs medium/high) risk Antipsychotic Medication				
	Yes (N= 2,661)	No (N = 4,150)	Multivariable Analysis		
	N (%) or Mean (SD)	N (%) or Mean (SD)	AOR ^a	95% CI	p
Female Gender	473 (17.7)	501 (12.1)	1.47	1.26–1.73	<0.001
<u>Other Demographics</u>					
Age, Years	50.5 (±11.7)	51.7 (±11.8)	0.99	0.98–0.99	<0.001
Black Race (vs other)	1,338 (50.3)	2,507 (49.6)	0.90	0.71–1.13	0.35
White race (vs other)	1,146 (43.1)	1,863 (44.9)	0.88	0.70–1.10	0.26
Married	596 (22.4)	961 (23.2)	0.93	0.81–1.06	0.26
Homeless, past 6 months	452 (22.4)	821 (19.8)	0.94	0.81–1.08	0.39
Service Connected >50%	1,116 (43.1)	1,494 (36.0)	1.13	1.01–1.27	0.04
<u>Mental Health Diagnoses/Service Use</u>					
Schizophrenia (vs Bipolar Disorder)	1,303 (49.0)	1,908 (46.0)	1.10	0.98–1.24	0.12
Depression	1,076 (40.4)	1,660 (40.0)	0.98	0.86–1.11	0.77
Post-Traumatic Stress Disorder	717 (26.9)	1,095 (26.4)	0.81	0.71–0.92	<0.001
Alcohol/Substance Use Disorder	1,017 (38.2)	1,856 (44.7)	1.09	1.03–1.16	0.005
Psychiatric Hospitalization, Past 6 months	662 (24.9)	1,182 (28.5)	0.90	0.79–1.02	0.10
No. Outpatient Visits, past 6 months	9.6 (±19.0)	8.1 (±15.8)	1.00	0.99–1.04	0.71
<u>Physical Health Diagnoses/Service Use</u>					
Coronary Artery Disease	204 (7.7)	296 (7.1)	1.03	0.83–1.28	0.79
Hyperlipidemia	1,059 (39.8)	1,401 (33.8)	1.18	1.05–1.34	0.008
Hypertension	1,235 (46.4)	1,827 (44.0)	1.03	0.91–1.17	0.62
Type 2 Diabetes	701 (26.3)	766 (18.5)	1.49	1.29–1.72	<0.001
No. Outpatient Primary Care Visits, past 6 months	5.4 (7.5)	4.4 (6.6)	1.02	1.01–1.03	0.003

^a Adjusted odds of prescription of a low vs medium/high risk metabolic risk antipsychotic medication, controlling for all variables in the table and fiscal year (2007, 2008, 2009, 2010, 2011) of prescription; analysis includes N=6,811 incident antipsychotic medication prescriptions.

Highlights

- We examined gender differences in prescribing of antipsychotic medications (APMs).
- APMs were examined by liability for weight gain and other metabolic side effects.
- Women were more frequently prescribed a low metabolic risk APM.
- This may reflect a growing awareness of adverse health effects of some APMs in women.