Utilization and Safety of Antipsychotic Medications in Special Populations

UTILIZATION AND SAFETY OF ANTIPSYCHOTIC MEDICATIONS IN SPECIAL POPULATIONS

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Abstract

Antipsychotic medications are widely used in the United States (US). Understanding the extent of use and comparative safety of antipsychotics is especially important for certain groups of people such as pregnant women or hospitalized patients, for whom the evidence on safety and effectiveness is limited. Previous studies lacked power to detect difference in safety endpoints or suffered from potential confounding bias. In this dissertation, we used large administrative claims databases to provide evidence for antipsychotic use among vulnerable population subgroups.

In Chapter 1, we describe the pattern of antipsychotic utilization among publicly insured pregnant women in the US using a nationwide Medicaid claims database. We found that atypical antipsychotics are increasingly used in this population between 2001 and 2010, with a notable increase in the diagnosis of and antipsychotic use for bipolar spectrum disorders. More than 50% of women discontinue treatment after becoming pregnant and polytherapy with other psychoactive drugs was common. These findings require further attention with respect to safety of antipsychotic in this population.

In Chapter 2, we examine the association between the use of atypical antipsychotic and the risk of gestational diabetes (GDM) among pregnant women in Medicaid. Comparing women who continue treatment to those who discontinue among prevalent users of antipsychotic without pre-existing diabetes at the beginning of pregnancy, we observed a potentially increased risk of

GDM among continuers of quetiapine and olanzapine but not for the continuers of aripiprazole, ziprasidone, or risperidone. Olanzapine showed the strongest evidence of increased risk of GDM across multiple analyses, but the variability in results was not large enough to comment on comparative safety of different antipsychotics.

In Chapter 3, we examine the comparative safety of antipsychotics in hospitalized patients with acute myocardial infarction, where antipsychotics are often used to manage delirium-related agitation. We found that the hazard ratio of 7-day mortality was greater for patients who received haloperidol compared to those who received atypical antipsychotics after adjusting for a large number of confounders. While residual confounding is a possible alternative explanation, our result is consistent with what has been reported from outpatient studies and in nursing home population.

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Chapter 1. Introduction

Over the last decade, there has been a significant increase in the prevalence and severity of psychiatric disorders in the United States (US).[1] In 2012, there were an estimated 43.7 million adults in the US with mental illness in the past year, representing 18.6% of all US adults. [2,3] The growing prevalence of psychiatric disorders has led to a dramatic increase in the proportion of population being treated with psychotropic medications as well as in prescription drug spending in the US.[4] In 2012, 12.4 % of the adult population US used prescription medication for a mental health problem.[2]

One of the most widely used psychotropic medication classes are antipsychotic medications, a class of drugs approved for treatment of conditions such as schizophrenia, bipolar disorder, or major depressive disorder.[1] Antipsychotics are classified into first-generation or 'typical' antipsychotics and second-generation or 'atypical' antipsychotics. Typical antipsychotics show treatment effect by inhibiting dopamine receptor (D2) in the brain.[5] The exact mechanisms of action of atypical antipsychotics are yet to be explained, but they are thought to act through dopaminergic, serotonergic, or combined modulation of both systems.[5]

In recent years, it has been reported that antipsychotics are increasingly used not only for the approved indications but also as off-label treatment for conditions such as anxiety, attention-deficit hyperactivity disorder (ADHD), or behavioral disorders.[1,6,7] With the broadened use of antipsychotics, people have raised concerns about adverse effects of these drugs and lack of safety or effectiveness data to support its use.[8] Typical antipsychotics are associated with extrapyramidal symptoms (EPS) and related motor dysfunctions, cardiac arrhythmia, hyperprolactinemia, and neuroleptic malignant syndrome.[9] Atypical antipsychotics are generally considered safer with respect to EPS and motor dysfunctions, but they are associated with

weight gain, dyslipidemia, diabetes, sedation, postural hypotension, and anticholinergic side effects.[9] Normally, evidence on safety and efficacy is obtained from randomized clinical trials (RCTs). However, there are subgroups of patients that are generally excluded from RCTs: Children and adolescents, pregnant women, and elderly with comorbidity are a few examples. They are not eligible for trials due to safety or ethical reasons, and the increasing use of antipsychotic medication in these groups of people not supported by scientific evidence[8] is concerning in terms of patient safety and well-being as well as appropriate use of healthcare resources. For these patients, post-marketing observational studies are an important source of safety and effectiveness evidence. Therefore, in this dissertation we aimed to describe the extent of use and examine the comparative safety of antipsychotic medications in two of such vulnerable populations, pregnant women and hospitalized patients with severe comorbidity, using large administrative databases.

In Chapter 1, we analyze the patterns of antipsychotic use during pregnancy in a large cohort of publicly insured pregnant women in the US. The utilization of antipsychotics among pregnant women in private insurance programs has been reported, but the utilization in Medicaid, the largest payer of mental health treatment in the US, has not been reported previously. We describe the extent of use over calendar time (2001-2010) and over defined windows during pregnancy. We show how many women who were taking antipsychotics before the start of pregnancy period discontinue the medication once they become pregnant, and how polytherapy with other major psychotropic medication is common in this population.

In Chapter 2, we evaluate the risk of gestational diabetes (GDM) subsequent to specific atypical antipsychotic drug continuation during pregnancy. Metabolic side effects following atypical antipsychotic use are well recognized, but the evidence is limited for pregnant women.

Especially, we raise a clinically relevant question of whether a prevalent user of antipsychotic should consider treatment discontinuation once she becomes pregnant given the possibility of increased risk of GDM, and whether there is variability in risk between five different antipsychotic agents. We demonstrate that continuation of olanzapine or quetiapine treatment compared to discontinuation may increase the risk of GDM, although the degree of variability between different antipsychotics was not large enough to draw conclusions on comparative safety.

In Chapter 3, we compare the safety of antipsychotics used in hospital with respect to in-hospital mortality among patients who were admitted with acute myocardial infarction. In contrast to a large number of outpatient studies, the comparative safety information is scarce for in-hospital use of antipsychotics. We show that haloperidol, the most frequently used typical antipsychotic, is associated with increased in-hospital mortality compared to atypical antipsychotics when used to treat the symptoms of delirium. We also observe that the potential harmful effect of haloperidol may occur acutely, increasing the risk of death right after the initiation of treatment.

Chapter 2. Antipsychotic Medication Use among Publicly-insured Pregnant Women in the US

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ABSTRACT

Objective: Given the increasing use and broadening of indications for antipsychotic medications in the general population, as well as the paucity of information on the safety of this drug class during pregnancy, the study aim was to document patterns of antipsychotic medication use in pregnant women.

Method: We used Medicaid Analytic eXtract data (2001-2010) from pregnant women who delivered live-born infants. Antipsychotic use at both the class and individual drug level was defined based on dispensed outpatient prescriptions. Users' characteristics, including mental disorder diagnoses, were described. Temporal trends in use, as well as discontinuation patterns and polytherapy with other psychotropic medications during pregnancy were evaluated.

Results: Among 1,522,247 pregnancies, the prevalence of atypical antipsychotic use at any time during pregnancy increased three-fold, from 0.4% to 1.3%, over the 10-year period while the use of typical antipsychotics remained stable around 0.1%. The increase in atypical use was largely driven by more frequent use in patients with bipolar disorder. Quetiapine and aripiprazole were the most frequently dispensed drugs, and polytherapy with antidepressants (65.2%), benzodiazepines (24.9%), and/or other mood stabilizers (22.0%) was common among women using antipsychotics during pregnancy. More than 50% of women receiving an antipsychotic in the 3 months prior to pregnancy discontinued during pregnancy.

Conclusions: A growing number of pregnant women in Medicaid are exposed to atypical antipsychotics, frequently in combination with other psychotropic medications. This study highlights the importance of documenting the use and safety of these drugs during pregnancy to inform therapeutic decision making for pregnant women with psychiatric disorders.

INTRODUCTION

Over the past two decade, the use of antipsychotic medications to treat psychiatric disorders has greatly expanded in the United States (US).[8] Schizophrenia and other psychotic disorders have long been treated with both typical and atypical antipsychotics. However, since 2000, a number of atypical antipsychotics have received approvals for broader indications including irritability in autism, mood stabilization in bipolar disorder and adjunct therapy for major depressive disorder (MDD). Increasing off-label use of antipsychotics to treat attention-deficit hyperactivity disorder (ADHD) or behavioral disorders has also been reported in recent years.[1,6,7]

For women, psychiatric disorders that are treated with antipsychotics often present during the childbearing years[10] and the risk-benefit trade-off of treatment during pregnancy is challenging. While continuous treatment may be important to prevent symptomatic episodes or relapse,[11] maternal and fetal safety concerns exist related to antipsychotic treatment. Case reports and studies with small samples have reported conflicting findings on the association between typical antipsychotic use and the risk of congenital anomalies.[12-14] There are few large, well-controlled studies examining the teratogenicity of atypical antipsychotics,[15,16] but the results from a recent large study with 9,258 women exposed to atypical antipsychotics did not find increased risk of congenital malformation.[17] Atypical antipsychotics are known to cause weight gain and increase the risk of Type 2 diabetes mellitus in the general population,[18] which may translate into higher risks for diabetes associated adverse pregnancy outcomes like fetal macrosomia or increased risk of gestational diabetes and its attendant effects.

In light of the rising use in the general population and the broadening of the indications for antipsychotic treatment observed in the last decade,[1,6,8] as well as the limited information on the

safety profile of this drug class during pregnancy, it is important to understand the extent and patterns of use of antipsychotics among pregnant women. Describing antipsychotic utilization trends in a publicly insured population is especially important since Medicaid covers the costs for approximately 80% of all antipsychotic prescriptions[19] and close to 50% of all deliveries in the US.[20] We used nationwide Medicaid data to investigate the patterns of antipsychotic use among publicly insured women in the US.

METHODS

Data Source and Study Population

We used Medicaid Analytic eXtract (MAX) data from 2001 to 2010 from the Centers for Medicare and Medicaid Services (CMS). MAX contains person-level information on demographics, hospitalizations and outpatient visits, as well as outpatient pharmacy dispensings. We created a linked cohort of pregnant women and their live-born babies based on a process described elsewhere in detail.[21] Linkage provided delivery dates that were used to estimate the last menstrual period (LMP) based on a previously validated algorithm.[22] Women were required to have continuous coverage from three months before the LMP to one-month after delivery and to not have other private insurance or restricted benefits during pregnancy to ensure complete capture of healthcare use information.

Antipsychotic Medication Use

To define exposure and patient characteristics, the time period was divided into four different windows: 3 months prior to the LMP (baseline), the LMP to gestational day 90 (first trimester), from gestational day 91 to 180 (second trimester), and from gestational day 181 to delivery (third trimester). Antipsychotic exposure during each of these time windows was defined as filling at least one prescription during the respective window, as documented based on National Drug Codes and dispensing dates in the outpatient pharmacy dispensing file. The full list of antipsychotics considered in this study is provided in Appendix 2.1. Prochlorperazine and promethazine were excluded because they are more commonly used for non-psychiatric conditions.[23] We examined antipsychotic use at the class level (atypical or typical) and at the generic level for the six most frequently used drugs (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and haloperidol). When a woman was dispensed more than one type of antipsychotic, each dispensing was counted separately toward each drug exposure category since the main purpose of this study was to describe the extent of antipsychotic use in this population.

Psychiatric Disorder Diagnoses

To document psychiatric disorders, we searched for the presence of International Classification of Diseases, Ninth Revision (ICD-9) codes for anxiety disorder, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, depression, schizophrenia or other psychotic disorder from 90 days prior to LMP to delivery (see Appendix 2.1 for specific diagnostic codes for these conditions). Following the approach from Crystal et al,[8] we created mutually exclusive hierarchical diagnosis categories since multiple diagnoses often occur concurrently.[10] Subjects

were classified into the highest possible category among 1) ADHD only, 2) anxiety with or without ADHD, 3) depression with or without anxiety or ADHD, 4) bipolar disorder with or without depression, anxiety or ADHD, and 5) schizophrenia or other psychotic disorder with or without bipolar disorder, depression, anxiety or ADHD (i.e., the highest category).

Analyses

Trends in Use

Temporal trends of antipsychotic use at both the class and generic level were examined by delivery year and the p-value for trend was reported. The prevalence of any antipsychotic use was examined stratified by age at time of delivery (under 20, 20 to < 30, 30 to <40, 40 or above) and race (White, Black/African American, Hispanic/Latino, Asian/other pacific islanders, others). To evaluate changes in drug use as a function of changes in diagnoses, we examined the yearly prevalence of each diagnosis using the hierarchical definitions, as well as the proportion receiving any antipsychotic medication among those with the diagnosis.

Characteristics of Study Population

We used descriptive statistics to characterize the study population in terms of demographics, comorbid diagnoses such as other mental disorders, pain disorders, hypertension, or diabetes, and use of other medications such as anxiolytics, hypnotics, or opioids during the baseline period and the first trimester. Additionally, we investigated concomitant treatment with major psychotropic medications (antidepressants, benzodiazepines, and other mood stabilizers defined in this study as lithium, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and

valproate) in women who received antipsychotic medication during pregnancy.

Discontinuation and Switching

To evaluate the potential impact of pregnancy on the decision to continue or to discontinue treatment at different time points during pregnancy, we investigated the patterns of use during pregnancy. 'Continuation' was defined as filling a prescription for the same antipsychotic class (class level) or specific drug (generic level) during pregnancy as before pregnancy and 'initiation' was defined as filling a prescription during pregnancy among those without a record of use during the 3 months before the start of pregnancy. A 'Switch' was defined as filling a prescription for a different antipsychotic (class or generic level) than during the baseline. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

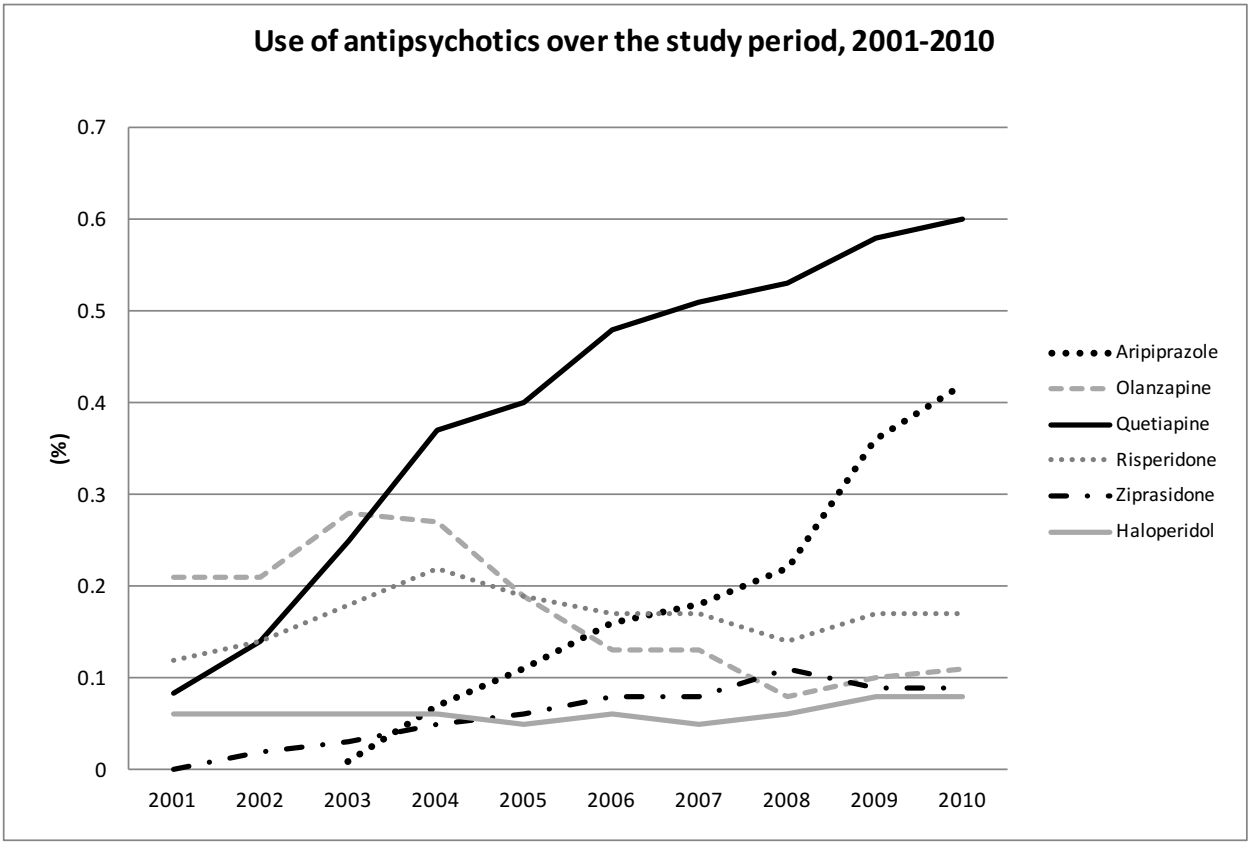
RESULTS

Trends in Use

Between 2001 and 2010, we identified 1,522,247 pregnancies meeting our inclusion criteria. Over this 10-year period, the number of women who filled at least one prescription for an atypical antipsychotic during pregnancy increased from 0.4% (n=376) to 1.3% (n=2,044; p-value for trend < 0.0001), representing a three-fold increase. The increasing trend was similar across the age and race groups considered. In all years, use was higher among women older than 30 years (Appendix 2.2 A). The proportion of atypical antipsychotic users increased in all race groups and remained higher among whites than among Hispanics and blacks (Appendix 2.2 B).

The proportion of women who received a typical antipsychotic remained stable at around 0.1% over the entire study period. At the individual drug level, we observed different trends for each of the 6 antipsychotics considered (Figure 2.1). The proportion using quetiapine increased substantially from 0.08% in 2001 to 0.6% in 2010. Since its introduction to the market in 2002, aripiprazole became the second most frequently used antipsychotic by 2010 with 0.4% of all women filling a prescription during pregnancy. In contrast, we observed a decreasing trend in the proportion of olanzapine users from 0.2% to 0.1%.

Figure 2.1 Proportion of women who were dispensed an antipsychotic medication during pregnancy in Medicaid, 2001 to 2010



We observed a temporal increase both in the prevalence of the five psychiatric disorder diagnoses of interest and, for some diagnoses, also in the proportion of women with such diagnoses receiving antipsychotic medication during pregnancy (Figure 2.2). Most strikingly, the prevalence of bipolar disorder diagnosis increased more than 3-fold over 10 years from 0.7% to 2.5% and the proportion of women with the diagnosis receiving antipsychotics increased from 13.6% in 2001 to 23.6% by 2010. Women with depression, but no schizophrenia, bipolar or other psychotic disorders, represented 6.7% of the study population in 2001 and 8.5% in 2010; the proportion treated with antipsychotics changed from 1.9% to 3.9% representing about a twofold increase. The extent of antipsychotic use in women with apparent off-label indications such as anxiety or ADHD was small but increased over time. The proportion of women with an anxiety diagnosis but without a diagnosis for any of the approved indications receiving antipsychotics doubled from 1.0% in 2001 to 2.0% in 2010. Among women with an ADHD diagnosis only, 3.4% were treated with an antipsychotic in 2010, increased from 1.6% in 2001.

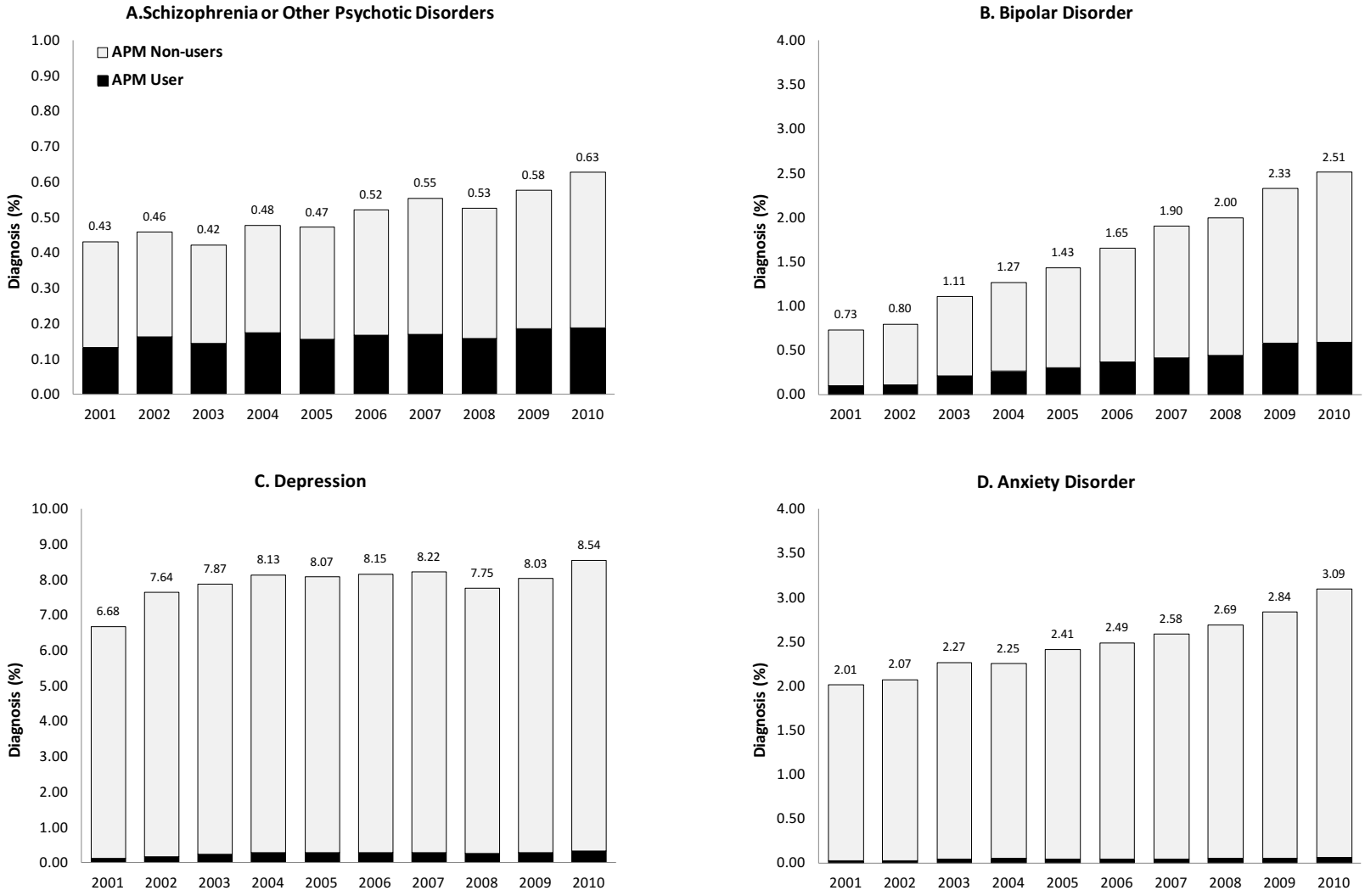
Characteristics Study Population

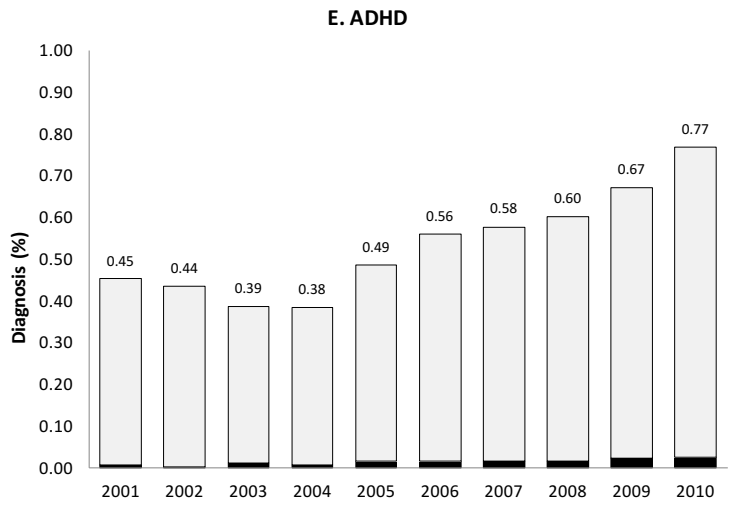
Compared to non-users during pregnancy, antipsychotic users were older, disproportionately white, and had a higher prevalence of non-psychiatric comorbidities and medication use, smoking, alcohol use, and recorded drug abuse or dependence (Table 2.1). Polytherapy with other psychotropic medications during pregnancy was common (Figure 2.3). Among the 15,196 women who used antipsychotics at any time during pregnancy, 65.2% also received antidepressants, 24.9% benzodiazepines, and 22.0% mood stabilizers. Five percent (765 women) received at least one prescription for all four drug classes at some point during pregnancy. Opioids were prescribed to more than 40% of women who received antipsychotics during pregnancy.

Discontinuation and Switching

Of the16,608 women (1.1%) who filled an atypical antipsychotic prescription during the 3 months before the LMP, about half (50.2%) did not fill any additional prescription from LMP until delivery and 15.4% continued use of the same medication throughout pregnancy, defined as filling at least one prescription in each trimester of pregnancy (Figure 2.4). Of all women who did not use atypical antipsychotics during the baseline period (n=1,505,639), 5,583 (0.4%) filled a prescription at some point during pregnancy: 65.2% (n=3,641) initiated in the first, 20.1% (n=1,123) in the second, and 14.7% (n=819) in the third trimester. For women who used typical antipsychotics prior to the LMP (n=774), the discontinuation rate was similar (51.7%). A greater number of women compared to the baseline users (n=1,403) initiated treatment during pregnancy without use during the 3 months before the LMP.

Figure 2.2 Prevalence of each psychiatric disorder diagnosis (hierarchical[a]) among pregnant women in Medicaid and proportion of women with the diagnosis who had one or more dispensing of antipsychotic medication, 2000 to 2010





APM: Antipsychotic medication; ADHD: Attention-deficit hyperactivity disorder
Note that the y-axis scales are different for each diagnosis

[a] Hierarchy of diagnoses: the highest possible category among 1) ADHD only, 2) anxiety with or without ADHD, 3) depression with or without anxiety or ADHD, 4) bipolar disorder with or without depression, anxiety or ADHD, and 5) schizophrenia or other psychotic disorder with or without bipolar disorder, depression, anxiety or ADHD

Table 2.1 Characteristics of antipsychotic users vs. non-users among pregnant women in Medicaid, 2001 to 2010

	Users (N=15196)		Non-users (N=1507051)		Standardized Difference
	N	(%)	N	(%)	
Demographics					
Age under 20	2888	19.01	364962	24.22	0.13
Age 20 to <30	8246	54.26	880000	58.39	0.08
Age 30 to <40	3745	24.64	242338	16.08	0.21
Age 40 or older	317	2.09	19751	1.31	0.06
White	9144	60.17	602772	40.00	0.41
Black/African American	3766	24.78	504884	33.50	0.19
Hispanic/Latino	827	5.44	225390	14.96	0.32
Asian/Other Pacific Islanders	267	1.76	53318	3.54	0.11
Others	1192	7.84	120687	8.01	0.01
Mental disorders					
Schizophrenia or other psychotic disorder	2526	16.62	5273	0.35	0.61
Bipolar disorder	6488	42.70	20383	1.35	1.15
Depression	7910	52.05	127273	8.45	1.08
Anxiety disorder	4470	29.42	65747	4.36	0.71
ADHD	1374	9.04	15433	1.02	0.37
Other comorbid conditions					
Personality disorder	589	3.88	2724	0.18	0.26
Adjustment disorder	329	2.17	8249	0.55	0.14
Sleep disorder	598	3.94	9639	0.64	0.22
Epilepsy	774	5.09	17378	1.15	0.23
Neuropathic pain	603	3.97	18462	1.23	0.17
Fibromyalgia	431	2.84	12541	0.83	0.15
Other pain disorder	433	2.85	12984	0.86	0.15
Migraine/headache	2378	15.65	105806	7.02	0.28

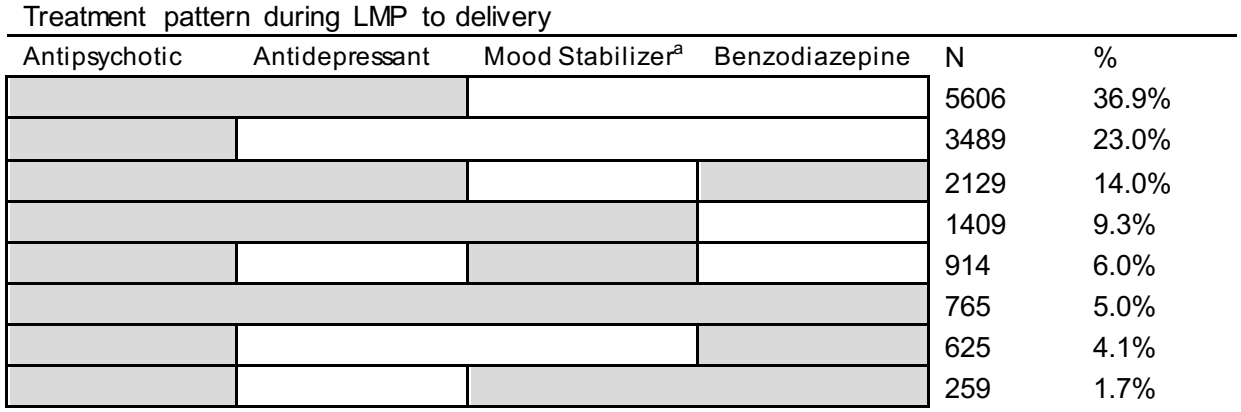
Table 2.1 Characteristics of antipsychotic users vs. non-users among pregnant women in Medicaid, 2001 to 2010 (Continued)

	Users (N=15196)		Non-users (N=1507051)		Standardized Difference
	N	(%)	N	(%)	
Hypertension	761	5.01	32717	2.17	0.15
Diabetes	506	3.33	23043	1.53	0.12
Tobacco use	1446	9.52	45623	3.03	0.27
Alcohol use	603	3.97	7780	0.52	0.24
Other drug abuse or dependence (2001-2006)	942	12.76	13418	1.55	0.45
N of outpatient visits (median, IQR)	10	(6-17)	4	(2-8)	0.73
Other Medication use[a,b]					
Anxiolytics	644	4.24	4641	0.31	0.27
Barbiturates	695	4.57	24574	1.63	0.17
Other hypnotics[c]	3633	23.91	94835	6.29	0.51
Opioids	6112	40.22	306000	20.30	0.44

ADHD: Attention-deficit hyperactivity disorder; IQR: Interquartile range; ED: Emergency department; NSAIDs: Non-steroidal antiinflamatory drugs

[a] Defined based on the information during 90 days prior to LMP to 90 days after LMP.
[b] Use of psychotropic medication (antidepressants, mood stabilizers, and benzodiazepines) is presented in Figure 3.
[c] Hypnotic drugs other than barbiturates, benzodiazepines, antidepressants, or antipsychotics

Figure 2.3 Treatment patterns with other psychotropic medication among women receiving antipsychotic during pregnancy

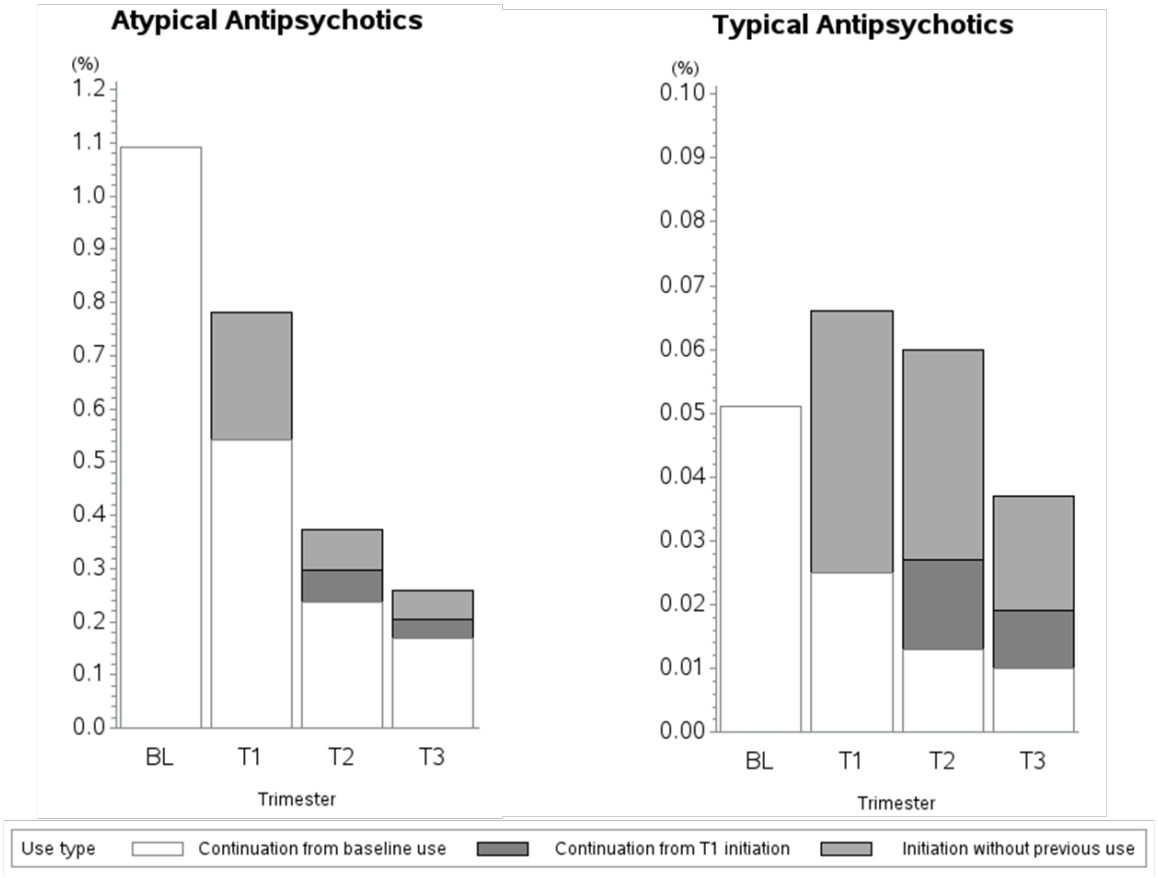


The shaded cells indicate the use of each medication during LMP to delivery. Each row represents different combinations of psychotropic drug use patterns (does not necessarily indicate concurrent use of drugs).

LMP: last menstrual period

[a] Mood stabilizers include lithium, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproate

Figure 2.4 Discontinuation and initiation of antipsychotic medication during pregnancy, by medication class



BL: baseline; T1: first trimester; T2: second trimester; T3: third trimester
Note that the y-axis scales are different between the two classes

The observed patterns at the generic level were similar to those at the class level (Appendix 2.3). Depending on the drug 49.6% to 59.6% of women exposed to individual atypical agents discontinued treatment during pregnancy, while 42.8% of women who received haloperidol in the baseline period discontinued. Switching to a different antipsychotic in the first trimester was infrequent among baseline antipsychotic users, and most women who switched did so to quetiapine in the first trimester (Appendix 2.4).

DISCUSSION

In a nationwide sample of publicly insured pregnant women in the US, we observed a 3-fold increase in the use of atypical antipsychotics from 0.4% in 2001 to 1.3% in 2010. The trend was largely driven by an increase in the use of two atypical antipsychotics, aripiprazole and quetiapine. Characteristics of antipsychotic users have changed over time with a notable increase in both diagnosis of and use for bipolar disorders. A large proportion of women are treated concomitantly with other psychotropic medications during pregnancy and 40% filled an opioid prescription, which is twice the rate observed in antipsychotic non-users. More than 50% of women who used atypical antipsychotics during the 3 months before LMP discontinued in the first trimester. Among women who switched, the majority switched to quetiapine.

The prevalence of women on antipsychotic treatment during pregnancy in our study is higher than that found in European cohorts (range 0.13% to 0.31%) or privately insured women in the US (0.7% for atypical antipsychotics) during partly overlapping periods.[23-27] This is not surprising, because Medicaid is the largest payer of mental health services in the United

States.[28] The increase in bipolar disorder diagnoses in our study population is consistent with the increase observed for the general population, including children and adolescents.[29,30] It is not entirely clear why there has been such a rapid increase in bipolar disorder diagnoses, but plausible explanations include improved classification as bipolar spectrum disorders of those previously misdiagnosed as unipolar depression or, perhaps, overdiagnosis of this condition.[30,31] We also observed a small increase in the use of antipsychotics for women with anxiety or ADHD, consistent with previous studies reporting frequent off-label use among non-pregnant populations with either disorder.[7,8] As both disorders often co-occur with other psychiatric disorders it is also possible that we did not capture other diagnoses in the claims for which the antipsychotics were truly used.[32]

The utilization trends over time were different for the different antipsychotic agents. The greater increase in the use of aripiprazole and quetiapine may be due in part to their expanded indications for treatment of MDD (2007 for aripiprazole, 2009 for quetiapine). A wide range of off-label uses for quetiapine may partly explain the increase in use observed during the years preceding the expansion of indications, in addition to the perceived relative safety based on prior evidence showing a lower rate of placental passage for quetiapine compared to the other antipsychotics.[33,34] The decrease in the use of olanzapine may be explained by the known risk of metabolic side effects including weight gain.[35] Risperidone was the first atypical antipsychotic to be approved, but its potential to cause hyperprolactinemia may be the reason why the use is less common among pregnant women.[36]

The discontinuation patterns observed in this study were similar to the results from previous studies in the UK in which close to 50% of women had discontinued atypical antipsychotics by six weeks of pregnancy and 62% to 72.3% by the third trimester.[24,27] There is a lack of evidence on clinical outcomes for those who discontinue or switch antipsychotics during pregnancy, and further studies is needed to fully understand the benefit and risk of treatment during pregnancy.

Polytherapy with other psychotropic medications was very common, as antipsychotics are often indicated as an adjunct agent.[37] Potential drug interactions between antipsychotics and other psychotropics are largely unknown, particularly in pregnancy; given the high frequency of such use, this is an important priority for future research. It is also notable that opioid use during pregnancy was remarkable high (~40%) in this population. There are potential harms such as neonatal abstinence syndrome associated with opioid use in pregnancy[38] and the risk of other negative maternal and fetal outcomes is largely unknown. More attention to appropriate use of opioid in this population is needed.

Strengths and limitations

We used a nationwide sample of more than 1.5 million pregnancies covered by Medicaid. Since Medicaid pays for close to 50% of all deliveries in the US, the results reflect the real-world utilization in a large proportion of the US population. Our population included a racially diverse, vulnerable and young population. We were able to study trends by racial groups, which can be a proxy for differential access to mental health care among Medicaid enrollees.[39]

Our study also has some limitations. The study findings about prevalence of use are not applicable to women with private insurance since the use of psychotropic medication is reported to be much higher in Medicaid[19], but some of the other trends in use may still be generalizable. Antipsychotic exposure was defined based on filling a prescription, which does not guarantee the actual intake. Although it is possible that some women did not actually take the medication or were still using prescriptions filled before LMP during pregnancy, claims from the automated dispensing records are considered to be more accurate than patient recall or medical records.[40,41] The date of LMP was not available in the data and was estimated, so some

misclassification of exposure timing is possible. But the algorithm we used estimated 75% of preterm and 99% of term deliveries within 2 weeks of the clinical gestational age at birth.[22] We defined psychiatric morbidity using ICD-9 diagnostic codes that have imperfect sensitivity[42] and as a result we could have underestimated the prevalence of each psychiatric diagnosis in the study. Since pregnant women have more frequent contact with health services than the general Medicaid population and since we required continuous coverage from 3 months before the start of pregnancy to one month after delivery, concerns about incomplete capture of diagnoses are reduced. Lastly, some of the trends in use might have been affected by changes in each state's Medicaid program at different points in time such as implementation of prior authorization or coverage expansion.[43] We were not able to disentangle the impact of changes in policies versus changes in clinician preference. Nevertheless, this study provides insight into the observed patterns of antipsychotics medication use over time at a national level.

CONCLUSION

A growing number of pregnant women in Medicaid are exposed to antipsychotic medications during pregnancy, reaching 1.3% by the year 2010, but there is still limited evidence regarding the safety of antipsychotic medication during pregnancy. The risk of pregnancy complications for mothers and any direct or indirect effect on the offspring resulting from exposure in utero requires careful examination. Polytherapy with other psychotropic medications common in this population deserves more attention with regard to fetal safety. High rate of discontinuation observed in this population suggests that clinicians and patients have concerns about the safety of the use of these medications during pregnancy. However, discontinuation of these

medications may have implications for maternal mental health. Further studies in this area are therefore urgently needed to help clinicians and patients make informed treatment decisions regarding the risks and benefits of using these medications during pregnancy.

APPENDIX

2.1 List of ICD-9 diagnostic codes and specific antipsychotics in this study

2.2 Proportion of women who were dispensed an atypical antipsychotic medication during pregnancy in Medicaid, 2001 to 2010, by age and race categories

2.3 Discontinuation and initiation of antipsychotic medication during pregnancy, by generic medication

2.4 Patterns of antipsychotic switching in the first trimester among women receiving antipsychotic during baseline

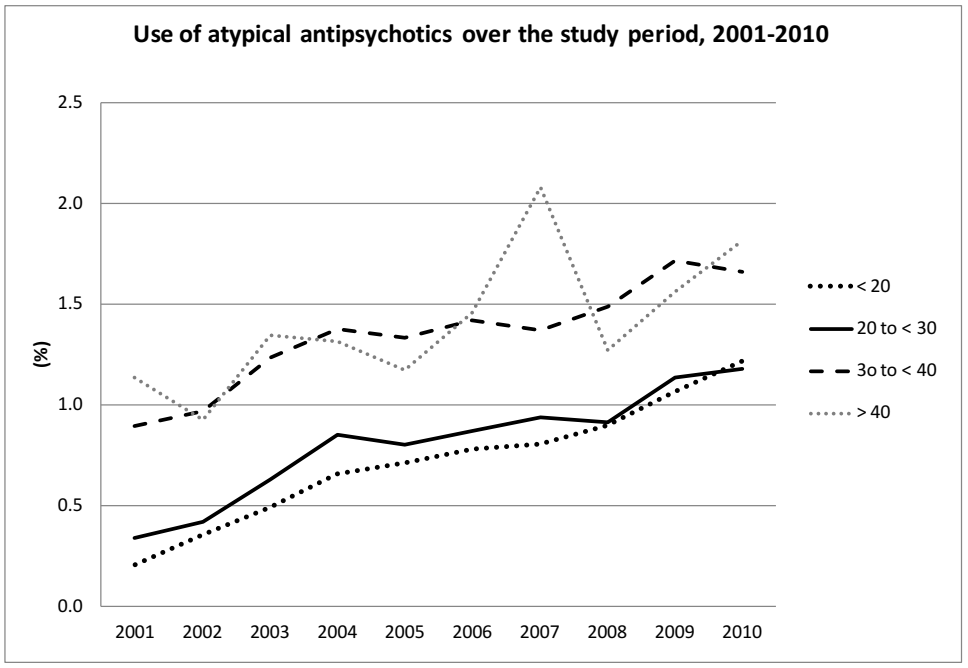
2.1 List of ICD-9 diagnostic codes and specific antipsychotics in this study

Drug class	Drug names
Atypical antipsychotic	Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
Typical antipsychotic	Chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, thioridazine, thiothixene, trifluoperazine
Disease	**ICD-9 codes**
ADHD	312.xx, 314.xx
Anxiety Disorders	293.84, 300.0x, 300.2x, 300.3, 308.0, 309.24, 309.81, 313.0x
Bipolar Disorders	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 296.99
Depression	293.83, 296.2x. 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 309.28, 311.xx
Schizophrenia or other psychotic disorders	290.8x, 290.9x, 295.xx, 297.xx, 298.xx, 299.xx, 780.1x

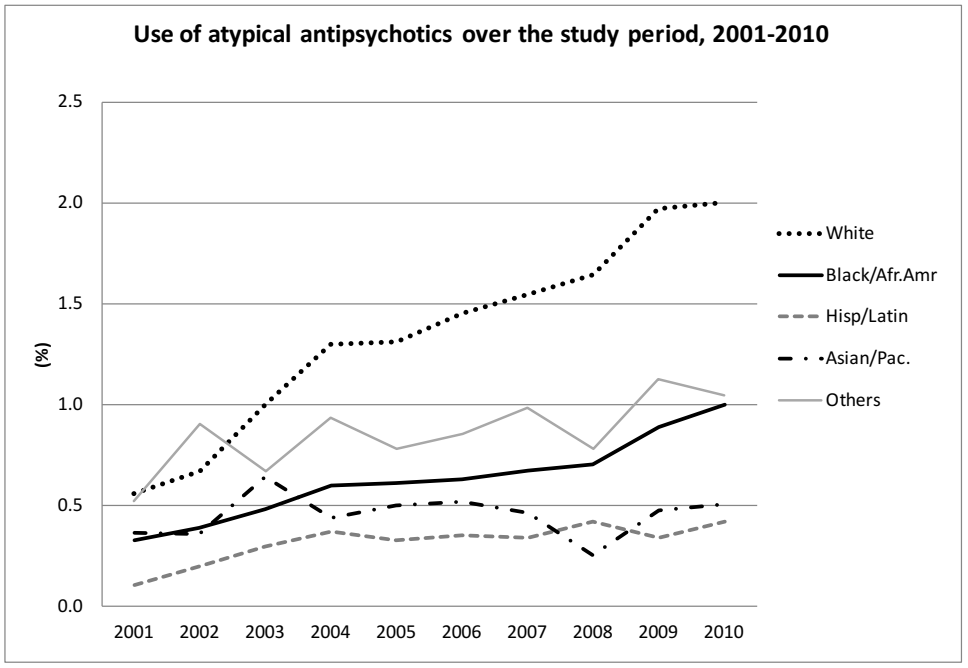
ICD-9: International Classification of Diseases, Ninth Revision; ADHD: Attention-deficithyperactivity disorder

2.2 Proportion of women who were dispensed an atypical antipsychotic medication during pregnancy in Medicaid, 2001 to 2010, by age and race categories

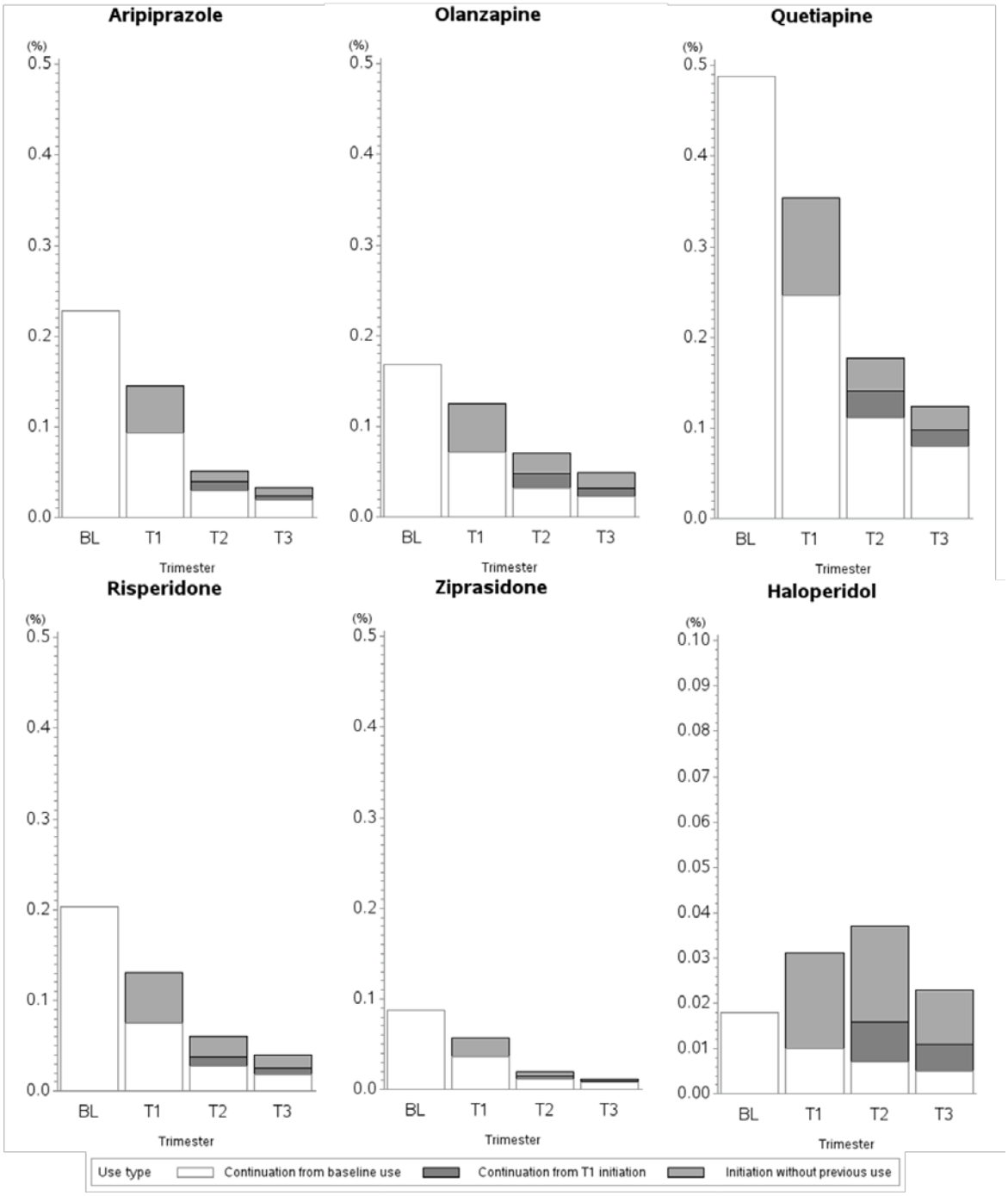
A. By age groups



B. By race groups



2.3 Discontinuation and initiation of antipsychotic medication during pregnancy, by generic medication



BL: baseline; T1: first trimester; T2: second trimester; T3: third trimester

Note that the y-axis scale is different for haloperidol

2.4 Patterns of antipsychotic switching in the first trimester among women receiving antipsychotic during baseline

	Total Switcher (n)	*Medication switched[a] to during first trimester (% of total switchers)*					
		Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Haloperidol
Baseline drug							
Aripiprazole	231	-	13.0	44.6	19.5	16.0	8.2
Olanzapine	170	19.4	-	42.4	21.8	7.6	9.4
Quetiapine	286	35.3	19.6	-	21.7	19.2	5.9
Risperidone	266	25.2	15.0	44.4	-	10.5	9.8
Ziprasidone	130	10.0	9.2	32.3	3.8	-	11.5
Haloperidol	38	10.5	39.5	39.5	13.2	13.2	-

[a] Switching defined as filling a prescription for a different antipsychotic but not for the one received during baseline

Chapter 3. Continuation of Atypical Antipsychotic Medication during Early Pregnancy and the Risk of Gestational Diabetes

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a complication of pregnancy that can lead to adverse outcomes. Some atypical antipsychotics (AAP) are associated with weight gain and insulin resistance, which are risk factors for GDM. There is lack of evidence to inform the decision about whether to discontinue AAP during pregnancy due to this concern.

Objective: To examine the risk of GDM associated with continuation of aripiprazole (ARI), ziprasidone (ZIP), quetiapine (QTP), risperidone (RSP), or olanzapine (OLZ) through the first half of pregnancy compared to discontinuation prior to pregnancy.

Methods: We conducted a cohort study using Medicaid data (2000-2010) from non-diabetic women with a live-born infant who had ≥ 1 AAP dispensing during the 3-months prior to pregnancy. For each AAP, we compared women with ≥ 2 additional dispensings (continuers) to women with no dispensing during the first half of pregnancy (discontinuers). GDM was defined using previously validated algorithm. We used a generalized linear model and propensity score stratification to obtain absolute and relative risks (RR), adjusting for confounders including psychiatric diagnoses and duration of AAP use before pregnancy.

Results: Among 1,543,334 pregnancies, the number of baseline AAP users was 1,924 for ARI, 673 for ZIP, 4,533 for QTP, 1,824 for RSP, and 1,425 for OLZ. The proportion of continuers ranged between 19.7% and 34.0%, depending on the drug. Continuers generally had higher comorbidity and longer baseline AAP use compared to discontinuers. The crude risk of GDM for continuers vs. discontinuers, respectively, was 4.8% vs.4.5% for ARI, 4.2% vs. 3.8% for ZIP, 7.1% vs. 4.1% for QTP, 6.4% vs. 4.1% for RSP, and 12.0% vs. 4.7% for OLZ. The adjusted RRs were 0.82 (0.50-1.33) for ARI, 0.76 (0.29-2.00) for ZIP, 1.28 (1.01-1.62) for QTP, 1.09 (0.70-1.70) for RSP, and 1.61 (1.13-2.29) for OLZ.

Conclusion: Our results suggest that compared to discontinuation, continued use of OLZ or QTP during the first half of pregnancy is potentially associated with an increased risk of GDM. There was no evidence of increased risk associated with continuation of ARI, ZIP or RSP. Continuing antipsychotic treatment during pregnancy should be based on a careful judgment between benefits and risk of adverse outcomes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a complication of pregnancy, defined as carbohydrate intolerance with onset or recognition during pregnancy.[44] It can lead to adverse pregnancy outcomes such as preeclampsia, cesarean delivery, neonatal hypoglycemia, and macrosomia.[45] The estimated prevalence of GDM in the United States (US) ranged between 4.6% and 9.2% in 2010.[46] Up to 50% of women with GDM develop Type 2 diabetes mellitus (T2DM) in the decades following pregnancy,[47] a risk over seven times higher than that in women without GDM.[48] GDM shares many risk factors with T2DM including older age, non-white race, and obesity.[45,49]

There is a well-recognized association between treatment with atypical antipsychotic medications and metabolic side effects including weight gain and diabetes.[35,50-53] The US Food and Drug Administration (FDA) required all manufacturers of atypical antipsychotics to add a warning for risk of hyperglycemia and diabetes to their labels in 2003. However, the metabolic safety of antipsychotics for pregnant women, whom are already predisposed to insulin resistance,[54] is not fully understood. A small number of studies and case reports suggested an increased risk of GDM for antipsychotic users during pregnancy,[16,25,26,55] but a recent large study with more than a thousand exposed women did not find any association.[56] Furthermore, while there are differences in the severity of metabolic side effects between antipsychotics, information on the risk of GDM for each specific antipsychotic is scarce.[57]

Despite limited safety information regarding their use in pregnancy, an increasing number of women of reproductive age are treated with antipsychotics in the US.[23,58] While for some women treatment continuation during pregnancy is necessary to prevent the sequelae of untreated mental illness,[47] for others clinicians must weigh the risks and benefits of continuing treatment

during pregnancy and may consider discontinuation or switch to a different antipsychotic. Understanding the potential risk of developing GDM, and how this risk may vary by the type of antipsychotic utilized, is an important consideration for patients and clinicians weighing these risks. Previous studies compared users with non-users of antipsychotics to assess the risk of GDM associated with the drug. However, most of non-users do not have psychiatric illness and the question of whether to treat or not is not very relevant in this population. Moreover, non-user comparison is susceptible to confounding bias because non-users are not very comparable with users of antipsychotics. We therefore evaluated the risk of GDM subsequent to specific antipsychotic continuation during pregnancy in a nationwide cohort of pregnant women who were treated with antipsychotics prior to the start of pregnancy.

METHODS

Data Source and Study Population

The Medicaid Analytic eXtract (MAX) is a person-level nationwide claims database, which contains information on demographics, hospitalizations, outpatient visits, and pharmacy dispensing records. We created a cohort of pregnant women linked to their live-born infants from MAX (2000-2010),[21] which has been successfully used in recent studies of medication safety in pregnancy.[17,59,60] Women were required to have continuous coverage from 3 months before the last menstrual period (LMP) to one month after delivery and not have other insurance benefits, which may lead to incomplete ascertainment of claims.

The study cohort consisted of women who filled a prescription for one of the five most frequently used atypical antipsychotics (hereafter referred to as antipsychotics) namely aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone during the 3 months before the LMP. Women who had pre-existing diabetes were excluded since they are not at risk for developing GDM. To identify these women, we modified an algorithm developed and validated by Andrade et al[61] (Appendix 3.1). Briefly, we excluded women with two or more diagnoses of any diabetes (250.x, 648.0x, or 648.8x) who received the first diagnosis, glucose tolerance test (GTT), or diabetes treatment before or on day 140 of pregnancy (i.e. the first 20 weeks). The algorithm was based on the expectation that women with known pre-existing diabetes are unlikely to receive GTT. As a modification to the algorithm, we further excluded women with only one diagnosis or who received diabetes treatment without diabetes diagnoses before the end of first trimester.

Outcome definition

Our definition of GDM was also based on the algorithm by Andrade et al.[61] We classified as GDM cases those who had two or more diagnosis codes for any diabetes between 141 days after LMP and delivery, with a GTT or at least one GDM diagnosis in the same time frame. We compared the results with or without considering metformin as an antidiabetic medication because it is sometimes used to treat polycystic ovary syndrome. The results were identical, so metformin was included as an antidiabetic medication.

Exposure definition

We defined the exposure during the first 140 days of pregnancy (Appendix 3.1). Among the cohort of women who used an antipsychotic prior to the LMP, 'continuers' were defined as women with two or more additional dispensings for the same drug during the first 140 days of pregnancy and 'discontinuers' were defined as women without any antipsychotic dispensing during the same 140 days. In dose-response analyses, we also included women with only one additional dispensing during the first 140 days to estimate the relationship at lower doses. In order to examine drug-specific effects, we excluded women with dispensings for a different drug than the one received before the start of pregnancy and also women who were dispensed more than one antipsychotic during the first 140 days of pregnancy. As a result the five exposure groups were mutually exclusive. In addition, we combined the users of individual drugs to form three 'risk-stratified groups', based on the weight gain potential and risk of diabetes outside of pregnancy.[35] Aripiprazole and ziprasidone were in the low-risk group, quetiapine and risperidone in the medium-risk group, and olanzapine constituted the high-risk group.

Covariates

Covariates for confounding adjustment were assessed during the 3 months prior to LMP and 3 months after LMP. The covariates were selected based on clinical plausibility as confounders or proxies of confounders for the association between antipsychotic continuation and GDM, and included demographics (age, race, Medicaid eligibility type), psychiatric diagnoses (anxiety disorder, attention-deficit hyperactivity disorder (ADHD), bipolar disorder, depression, schizophrenia or other psychoses, or other psychiatric disorders), comorbidity (pain disorders, hypertension, obesity, or dyslipidemia), other medication use (anticonvulsants, antidepressants, anxiolytics, benzodiazepines, mood stabilizers (other than antipsychotics), opioids, other

hypnotics, stimulants, antihypertensives), and the number of months of antipsychotic treatment received in the 3 months before the LMP. Prior record of GDM was obtained from all available data before the start of the index pregnancy. We quantified the number of different generics received and the number of emergency department visits during the 3 months prior to the LMP to capture health services utilization as a general marker of the extent of comorbid illness.

Statistical analyses

The analyses were done separately for each of the five antipsychotics. We first examined the characteristics of the continuers and discontinuers of each antipsychotic. The unadjusted risk differences per 100 subjects (RD_{100}) and relative risks (RR) with corresponding 95% confidence intervals (CI) were estimated using generalized linear regression models with identity (for RD_{100}) or log link (for RR). Propensity score (PS) stratification was used to adjust for confounding.[62] The PS was calculated as the predicted probability of continuing the treatment as opposed to discontinuing after LMP, estimated by logistic regression with all covariates mentioned above. After trimming patients in the non-overlapping parts of the PS distribution,[63] we created 50 strata based on the distribution of the PS among continuers. Weighted generalized linear models were used to estimate adjusted RD_{100} and RR along with 95% CIs, using weights based on the relative size of each strata. When the standardized difference after PS weighting was greater than 0.1, we added those covariates to the outcome model and examined if it changed the interpretation of the result from the model without additional covariates. To assess whether the variability in risk between the study drugs can be due to chance, we tested for heterogeneity using random effects meta-analysis.[64]

We explored dose-response relationships between the risk of GDM and the cumulative dose of each antipsychotic. Restricted cubic splines were used to allow for non-linear relationships,[65] adjusting for known or suspected risk factors of GDM including age, non-white race, obesity, diagnosis of schizophrenia or bipolar disorder, and the duration of antipsychotic use during the 3-month baseline period.[65] There were a small number of women with unlikely large values. In order to stabilize the dose-response curve at the extreme ranges, the maximum possible cumulative dose during the 140 days of exposure window was limited to the daily maximum dose multiplied by 140 days for each antipsychotic (mg).

Several additional analyses were conducted at the risk-stratified group level due to the small sample sizes in the drug specific analyses. First, we restricted the analyses to women with a recorded diagnosis of the approved indications for antipsychotics (schizophrenia, bipolar disorder, or depression). The rationale for this analysis is that some antipsychotics are used off-label for non-psychiatric conditions such as insomnia at different doses[66] and the different usage of these drugs may be associated with different baseline risks of GDM. Second, we extended the baseline period to 6 or 12 months before the LMP in the subsets of women who had Medicaid eligibility during this time to assess whether a longer baseline period allowed for better confounding control. Lastly we used the high-dimensional propensity score (hdPS) algorithm to empirically identify 50 additional covariates that may serve as proxies of unmeasured confounders and used them in the PS model alongside the pre-defined covariates.[67]

Because obesity is one of the most important risk factors for GDM but is incompletely captured in claims data, we conducted a bias analysis to examine the extent to which adjustment for confounding by unmeasured or poorly measured obesity would change the observed association.[68] The obesity prevalence estimate for this analysis was obtained from a registry for pregnant women with psychiatric illness.[69] Informed by the literature, we assumed that the overweight or obese women have 4 times the risk of GDM compared to non-obese women,[70]

and examined the potential bias over a range of overweight/obesity prevalence differences (0 to 25%) between continuers and discontinuers.

All analyses were performed using R (R Core Team, 2016) and SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Among 1,543,334 linked pregnancies in MAX, we identified 1,924 women who filled a prescription for aripiprazole in 3 months prior to the LMP, 673 for ziprasidone, 4,533 for quetiapine, 1,824 for risperidone, and 1,425 for olanzapine (Appendix 3.2). The proportion of women excluded with pre-existing diabetes was 4.9%, 6.5%, 4.6%, 5.3%, and 4.5%, respectively. Depending on the drug, 19.7% to 34.0% continued treatment during the first half of pregnancy. Continuers were generally older, had more psychiatric diagnoses and medication use, and were more likely to have an obesity diagnosis, and had used antipsychotics for a longer duration before the LMP (Appendix 3.3). The moderate separation in PS distribution between continuers and discontinuers reflected the patient difference measured by the covariates (Appendix 3.4). After PS weighting, most patient characteristics were balanced between continuers and discontinuers, but the prevalence of a few important covariates such as obesity or bipolar disorders remained to be higher among the continuers of olanzapine (Table 3.1, Appendix 3.5).

The absolute risk of GDM ranged from 4.2% to 12.0% in continuers and from 3.8% to 4.7% in discontinuers (Table 3.2), depending on the drug considered. The unadjusted relative risk of

GDM associated with continuing the medication during the first 140 days of pregnancy was 1.06 (95% CI 0.65-1.72) for aripiprazole, 1.12 (0.48-2.61) for ziprasidone, 1.75 (1.36-2.24) for quetiapine, 1.56 (0.98-2.49) for risperidone, and 2.55 (1.73-3.74) for olanzapine (Table 2). There was evidence for elevated risk of GDM after PS stratification for olanzapine (adjusted RR=1.61, 1.13-2.29) and quetiapine (1.28, 1.01-1.62), but not for aripiprazole (0.82, 0.50-1.33), ziprasidone (0.76, 0.29-2.00), and risperidone (1.09, 0.70-1.70). The test for heterogeneity using random effects model had a p-value of 0.18, suggesting that we cannot rule out chance as an explanation for the observed variability among these five estimates. The RRs in the low- (aripiprazole, ziprasidone), medium- (risperidone, quetiapine), and high-risk (olanzapine) group were 0.91 (0.60-1.39), 1.37 (1.12-1.69), and 1.61 (1.13-2.29), respectively. In dose-response analysis, the risk increased with increasing cumulative dose of olanzapine until about 700 mg and plateaued thereafter (Figure 3.1). No clear trend was seen for other antipsychotics considering the width of the confidence band.

Table 3.1 Selected patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score

	Aripiprazole		Ziprasidone		Quetiapine		Risperidone		Olanzapine	
Group	Cont.	Disc.	Cont.	Disc.	Cont.	Disc.	Cont.	Disc.	Cont.	Disc.
N[a]	416	1421	140	431	1542	2951	343	1449	375	978
	%	%	%	%	%	%	%	%	%	%
Age and race										
Mean age (SD)[b]	24.8 (7.2)	24.4 (6.7)	25.0 (6.4)	25.0 (5.4)	26.8 (6.4)	26.5 (6.3)	25.3 (7.4)	25.5 (7.5)	28.5 (6.9)	27.1 (6.4)
White	66.6	68.6	67.9	68.2	72.4	72.5	49.3	50.3	51.2	52.6
Black	19.7	19.2	20.7	21.0	15.4	16.0	30.3	30.9	24.5	23.4
Other race	13.7	12.3	11.4	10.8	12.1	11.5	20.4	18.8	24.3	24.1
Mental health diagnosis										
ADHD	9.4	9.2	10.7	10.0	8.3	8.3	14.9	15.0	4.5	5.3
Bipolar disorder	44.5	45.0	44.3	45.2	35.9	35.3	25.1	25.6	**31.7**	**41.9**
Schizophrenia/Other psychoses	10.1	10.7	17.1	17.8	7.4	8.2	17.8	18.7	22.9	24.1
Depression	39.2	38.0	41.4	39.8	42.9	43.7	44.3	45.6	38.7	39.3
Anxiety disorder	24.8	25.9	22.1	22.6	28.7	29.5	19.8	19.3	20.8	24.1
Comorbidity and other psychotropic use										
Prior GDM	4.8	4.7	2.1	1.6	4.9	5.2	3.2	2.8	2.9	1.5
Obesity	5.3	4.6	3.6	4.5	2.3	2.2	2.3	1.7	**2.4**	**0.7**
Antidepressants	71.6	71.8	73.6	72.4	75.6	75.5	72.6	72.2	70.7	71.2
Benzodiazepines	33.7	35.2	39.3	40.5	39.4	38.9	23.6	24.7	29.1	31.3
Mood stabilizers	29.6	28.9	31.4	35.4	31.8	31.3	28.6	32.1	**21.3**	**26.5**
Opioids	35.8	38.1	40.7	40.3	46.7	47.1	27.4	27.7	32.8	34.1
Antipsychotic use in 90 days before LMP										
Exposed ≤30 days	20.2	20.0	18.6	17.3	19.3	19.3	27.7	28.0	20.5	21.0
Exposed >30 days, ≤60 days	30.8	31.2	23.6	25.8	20.2	20.4	28.9	29.9	25.9	23.6
Exposed >60 days	49.0	48.8	57.9	56.9	60.5	60.2	43.4	42.1	53.6	55.4

Cont: Continuers; Disc: Discontinuers; SD: standard deviation; ADHD: attention-deficit hyperactivity disorder; GDM: gestational diabetes; LMP: last menstrual period

[a] Number of subject in each group after trimming and stratification

[b] Age was categorized in propensity score models but presented with the mean in this table for simplicity

Bolded cells: Absolute Standardized difference > 0.1 after propensity score weighting.

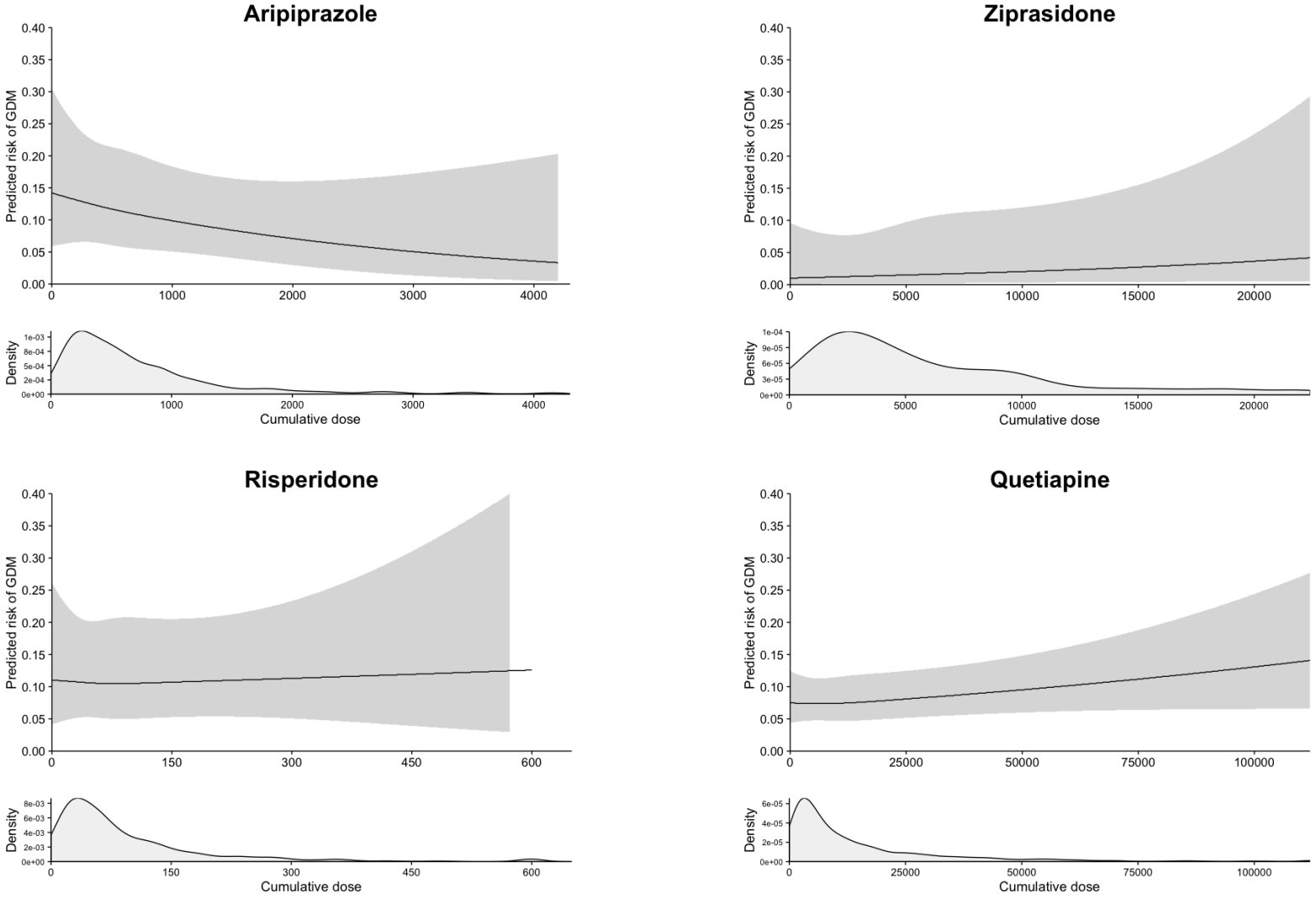
Table 3.2 Unadjusted and adjusted risk of gestational diabetes, comparing continuers to discontinuers of each antipsychotic medication or group

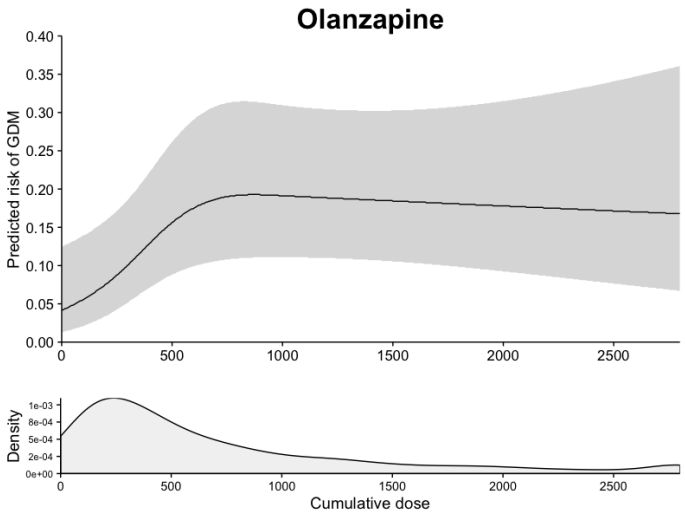
					Unadjusted				Adjusted			
		N[a]	Case	Risk	RD_{100}	(95% CI)	RR	(95% CI)	RD_{100}	(95% CI)	RR	(95% CI)
Aripiprazole	Continuer	419	20	4.8%	0.3	(-2.0, 2.6)	**1.06**	(0.65, 1.72)	-1.0	(-3.4, 1.3)	**0.82**	(0.50, 1.33)
	Discontinuer	1505	68	4.5%								
Ziprasidone	Continuer	167	*	4.2%	0.4	(-3.0, 3.9)	**1.12**	(0.48, 2.61)	-1.1	(-4.8, 2.6)	**0.76**	(0.29, 2.00)
	Discontinuer	506	19	3.8%								
Quetiapine	Continuer	1543	110	7.1%	3.1	(1.6, 4.5)	**1.75**	(1.36, 2.24)	1.6	(0.0, 3.1)	**1.28**	(1.01, 1.62)
	Discontinuer	2990	122	4.1%								
Risperidone	Continuer	359	23	6.4%	2.3	(-0.4, 5.0)	**1.56**	(0.98, 2.49)	0.6	(-2.4, 3.5)	**1.09**	(0.70, 1.70)
	Discontinuer	1465	60	4.1%								
Olanzapine	Continuer	384	46	12.0%	7.3	(3.8, 10.8)	**2.55**	(1.73, 3.74)	4.4	(0.8, 8.1)	**1.61**	(1.13, 2.29)
	Discontinuer	1041	49	4.7%								
Low risk	Continuer	586	27	4.6%	0.3	(-1.6, 2.2)	**1.07**	(0.70, 1.62)	-0.4	(-2.4, 1.5)	**0.91**	(0.60, 1.39)
	Discontinuer	2011	87	4.3%								
Median risk	Continuer	1902	133	7.0%	2.9	(1.6, 4.2)	**1.71**	(1.38, 2.13)	1.9	(0.6, 3.2)	**1.37**	(1.12, 1.69)
	Discontinuer	4455	182	4.1%								
High risk[b]	Continuer	384	46	12.0%	7.3	(3.8, 10.8)	**2.55**	(1.73, 3.74)	4.4	(0.8, 8.1)	**1.61**	(1.13, 2.29)
	Discontinuer	1041	49	4.7%								

RD_{100}: Risk difference per 100 pregnancies; RR: relative risks; CI: confidence interval

[a] Number of subject in each group before trimming and stratification
[b] High risk group is the same as the olanzapine users
* Cell size < 11

Figure 3.1 Dose-response analyses between the cumulative dose of antipsychotic exposure during the first 20 weeks of pregnancy and the risk of GDM





Upper panels: Restricted cubic spline curves [65] with 3 knots at the 25th, 50th, and 75th percentiles of the cumulative dose (mg) during the first 20 weeks of pregnancy (LMP to 140 days after LMP), adjusting for age, race, obesity, diagnosis of schizophrenia or bipolar disorder, and the duration of treatment during the 3 months prior to LMP.

Lower panels: Density curve showing the distribution of cumulative dose among the users of each antipsychotic medication who had one or more prescription dispensed during the first 20 weeks of pregnancy.

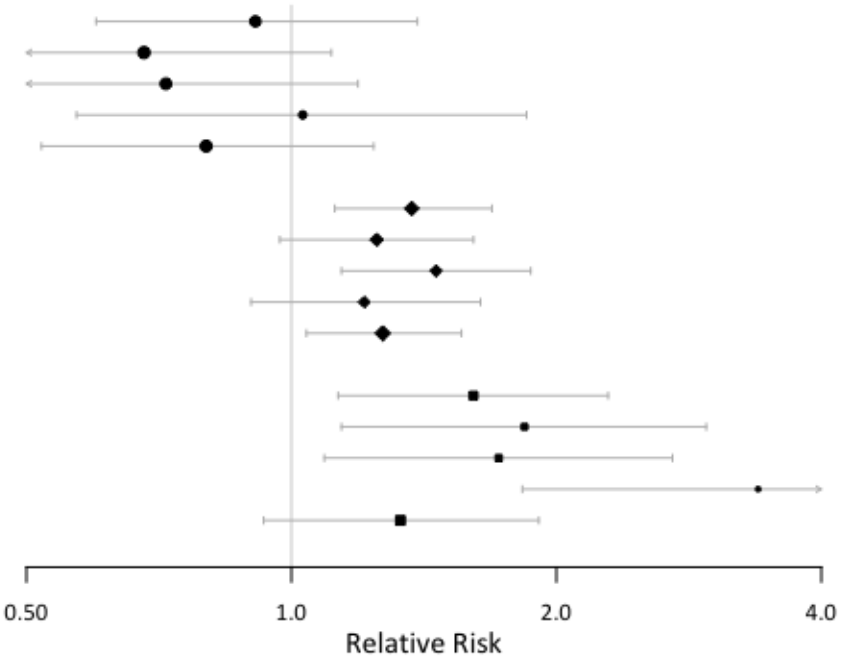
LMP: last menstrual period; GDM: gestational diabetes

Additional group-level analyses results are presented in Figure 3.2 (see also Appendix 3.6). Across the different analyses, the risk of GDM seemed to be elevated in continuers compared to discontinuers in the high- and the median-risk group, but not in the low risk group. However the effects are less precisely estimated in some of the analyses due to the reduced sample size.

The bias analyses illustrated that with an overall overweight/obesity prevalence of 62% among atypical antipsychotic users observed in the registry, the absolute difference in the prevalence of overweight/obesity between continuers and discontinuers would have to be more than 25% for the observed RR of 1.61 in olanzapine users to be completely attributable to residual confounding (solid line in Figure 3.3A, Appendix 3.7). To put this into a context, 25% difference would mean that 80% of continuers and 55% of discontinuers are overweight or obese patients. In quetiapine users with an observed RR of 1.28, the difference would have to be greater than 20% (solid line in Figure 3.3B, Appendix 3.7). If, in contrast, there were more overweight/obese women among discontinuers than among continuers, the obesity-adjusted RRs would be higher than what we observed for both drugs. If we assume the RRs to be closer to the lower bounds of each confidence interval, however, confounding due to smaller differences in obesity could explain the increased relative risk.

Figure 3.2 Forest plot of the results from additional analyses based on the risk-stratified groups

Group	Analysis	RR	95% CI
Low	PS adjusted	0.91	[0.60 , 1.39]
	Restricted	0.68	[0.41 , 1.11]
	6m Baseline	0.72	[0.44 , 1.19]
	12m Baseline	1.03	[0.57 , 1.85]
	hdPS adjusted	0.80	[0.52 , 1.24]
Median	PS adjusted	1.37	[1.12 , 1.69]
	Restricted	1.25	[0.97 , 1.61]
	6m Baseline	1.46	[1.14 , 1.87]
	12m Baseline	1.21	[0.90 , 1.64]
	hdPS adjusted	1.27	[1.04 , 1.56]
High	PS adjusted	1.61	[1.13 , 2.29]
	Restricted	1.84	[1.14 , 2.96]
	6m Baseline	1.72	[1.09 , 2.71]
	12m Baseline	3.39	[1.83 , 6.27]
	hdPS adjusted	1.33	[0.93 , 1.91]

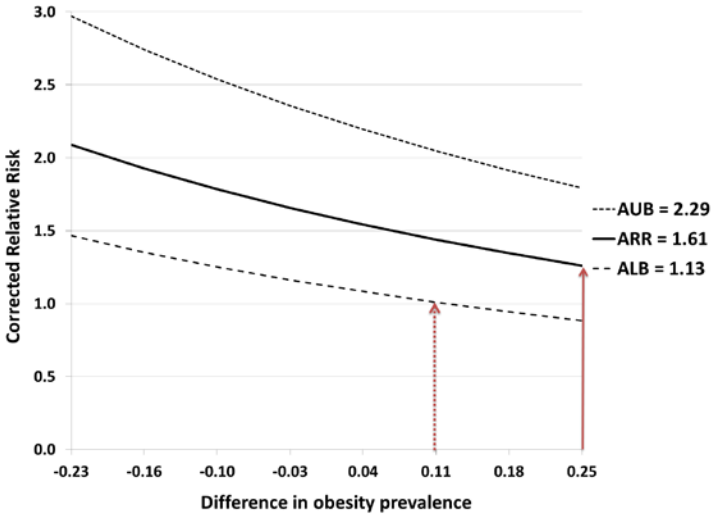


PS: Propensity score; hdPS: high-dimensional propensity score; RR: relative risk

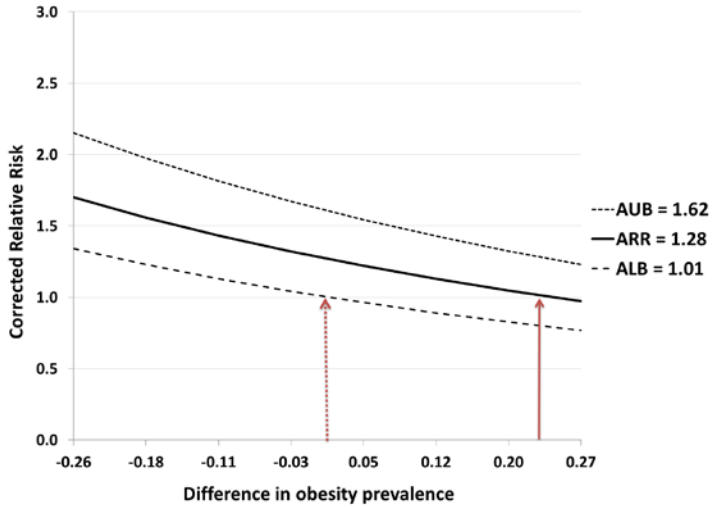
PS adjusted: adjusted RR from PS stratification in the main analysis
Restricted: analysis restricted to women with diagnosis of schizophrenia, bipolar disorder, or depression
6m or 12m baseline: results from extending 3-month baseline to either 6 months or 12 months
hdPS adjusted: stratification adjustment using 50 additional confounder proxy variables in PS estimation

Figure 3.3 The potential effect of obesity as an unmeasured confounder on the observed relative risk among the users of olanzapine or quetiapine

A. Olanzapine



B. Quetiapine



ARR = apparent RR before adjusting for obesity, ALB = apparent lower bound, AUB = apparent upper bound, P_{C1} = obesity prevalence among the exposed, P_{C0} = obesity prevalence among the unexposed, and RR_{CD} = strength of association between obesity and the risk of gestational diabetes.

Difference in the obesity prevalence (x-axis) is calculated as $P_{C1} - P_{C0}$

Assuming that obese women have 4 times the risk of GDM compared to non-obese women, the corrected or true relative risk (RR; y-axis) is obtained by dividing the ARR with the bias factor on the right side of the following formula[68]:

$$ARR = RR * \frac{P_{C1}(RR_{CD} - 1) + 1}{P_{C0}(RR_{CD} - 1) + 1}$$

Dotted lines above and below the solid line correspond to the upper and lower bound of the confidence interval for the point estimate, respectively. The solid red arrows show that > 25% difference in obesity prevalence for olanzapine users or > 20% difference in obesity prevalence for quetiapine users are required to explain the observed effect (ARR) by confounding only. The dotted red arrows show that when we take the uncertainty of the estimated ARR into account, smaller difference in obesity prevalence can account for the observed effect.

DISCUSSION

In pregnant women who were treated with an atypical antipsychotic before the start of pregnancy, continuation of treatment through the first half of pregnancy was associated with an increased risk of GDM for olanzapine and quetiapine. We did not observe evidence of increased risk for aripiprazole, ziprasidone, or risperidone continuers. While there is a chance that the heterogeneity in risks is due to random variability, multiple analyses consistently showed stronger association with olanzapine. In addition, there was evidence of a cumulative dose-response relationship for olanzapine during the first half of pregnancy. Although residual confounding by obesity is possible, the unmeasured imbalance in obesity prevalence between continuers and discontinuers, after accounting for all other covariates, would have to be very large (>20-25%) to fully explain the observed risk.

A few studies have investigated the association between antipsychotic exposure during pregnancy and the risk of gestational diabetes. Using Swedish National registries, Reis and Kallen reported an increase in the risk of GDM (OR = 1.78, 1.04-3.01) among women who self-reported any antipsychotic use in early pregnancy[25] and Boden et al concluded that mothers who used olanzapine or clozapine during pregnancy had a higher risk of GDM (OR = 1.94, 0.97-3.91) compared to those who do not.[26] Vigod et al. did not find an increased risk in an hdPS-matched cohort in Canada, either for all antipsychotics considered (RR = 1.10, 0.77-1.57) or for 166 olanzapine users only (not provided but RR close to 1 with a wide CI).[56] A direct comparison to these studies is hampered by differences in study design. Unlike our study, all three previous studies had nonusers as a reference group and these are less comparable with regard to health status or disease severity than discontinuers. The absolute risk of GDM in the reference group was 1.0% in Reis and Kallen, 1.7% in Boden et al, 6.2% in Vigod et al (non-

users) versus 4-5% in our study (discontinuers), reflecting the population heterogeneity. The difference may also be explained by the discrepancies in exposure ascertainment varying from self-report (Reis and Kallen) to two or more consecutively filled antipsychotic prescriptions (Vigod et al).

Another important distinction between this and earlier studies is that we excluded women with evidence of pre-existing diabetes. Thus our study estimates the risk of incident GDM among diabetes-free antipsychotic users whereas the previous studies estimated the risk of being diagnosed as GDM among any antipsychotic users compared to non-users during pregnancy, either regardless of or adjusting for pre-existing diabetes diagnoses. There is a possibility that our prevalent user cohort represents the women who are more resilient to metabolic side effects, since women who are more susceptible and develop diabetes before they become pregnant were excluded from our study. Thus treatment recommendations based on our findings should be applied only to women who are free of diabetes at the beginning of their pregnancy and are considering discontinuation of their specific antipsychotic drug. It appeared that women with risk factors for GDM are more likely to receive weight-neutral drugs, because the baseline users of weight-neutral aripiprazole or ziprasidone had higher prevalence of pre-existing diabetes, prior GDM, or obesity diagnosis compared to the baseline users of olanzapine. Despite having fewer risk factors, however, the continuers of olanzapine had the highest absolute risk of GDM. Based on prior knowledge that olanzapine induces the most weight gain among the five study drugs,[35,57] this result supports the hypothesis that antipsychotics may increase the risk of GDM through excessive weight gain during pregnancy. Quetiapine with moderate weight gain effect showed increased risk of GDM in this study, but available information on the association between quetiapine and diabetes or GDM is limited and not consistent.[52,57,71] Further research is needed to confirm this finding.

Our study has several strengths. The study population arises from the nation-wide Medicaid program that is representative of close to 50% of all pregnancies in the US.[20] Moreover Medicaid finances 80% of all antipsychotic prescriptions and 36% of all treatment cost for GDM in the US.[19,72] We used automated dispensing records to define exposure, which is free of recall bias, and a validated outcome definition. This study is one of the largest studies conducted in pregnant women taking antipsychotic and we were able to investigate individual drug effects rather than a drug class effect.

The study is not without limitations, however. Residual confounding is possible due to unmeasured or poorly measured factors. The estimate in Boden et al was slightly attenuated after adjusting for early pregnancy BMI, suggesting there can be residual confounding due to BMI in our study. It is likely that better measurement of confounders such as obesity or BMI and adjustment for them would attenuate the observed estimates. Comparing continuers to discontinuers rather than to non-users alleviates the concern for residual confounding because discontinuers are likely to be more similar to continuers than non-users and the impact of failing to adjust for poorly measured or unmeasured factors is likely to be smaller in our study. To address this issue we quantified the magnitude of the residual imbalance in obesity that would be required to fully explain the increased risk after all other covariates had been accounted for and found it to be very large. We also showed that adjusting for a large number of empirically identified confounders that may serve as proxies for unmeasured confounders does not change the findings. We do not have information on the reasons for discontinuation, which may be associated with the disease severity or indication for antipsychotic use not recorded in the claims. However, disease severity seems unlikely to explain the observed associations since we only observed an increased risk for selected antipsychotics. A pharmacy dispensing record does not guarantee the actual intake of the drug. By requiring at least two prescriptions during the first 20 weeks of pregnancy, we were more confident that the continuers in our study

actually took the medication. We did not have enough evidence on the comparative safety of different antipsychotics with respect to the risk of GDM, potentially due to lack of power. But this is the largest study investigating this question and we were able to estimate the relative risks for each of the five drugs, which was not possible or done in previous studies.

CONCLUSION

In a large cohort of women without pre-existing diabetes who were treated with antipsychotics before pregnancy, we observed an increased risk of GDM among women who continue to use olanzapine or quetiapine during the first 20 weeks of pregnancy compared to those who discontinue. There was a positive dose-response relationship between the use of olanzapine and GDM risk. We did not find a difference in the risk of GDM comparing continuers to discontinuers of aripiprazole, ziprasidone, and risperidone. Further studies are needed to understand the comparative risk between different antipsychotics and potential effect of switching to weight neutral antipsychotics in order to aid treatment decisions. In conclusion, the risk of GDM should be carefully weighed against the benefits of continuing specific antipsychotics in pregnant women with psychiatric illness.

APPENDIX

3.1 Study design, exposure definition, and outcome definition

3.2 Flow chart illustrating the cohort creation process for each antipsychotic exposure group

3.3 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, unadjusted

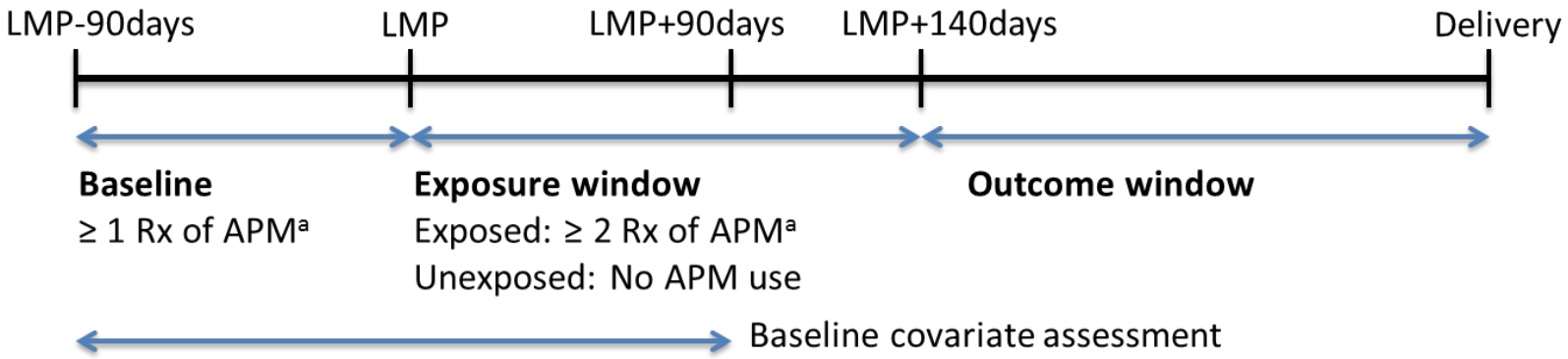
3.4 PS distribution in each antipsychotic exposure group

3.5 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score

3.6 Results from additional analyses based on the risk-stratified groups

3.7 The difference in obesity prevalence between continuers and discontinuers of olanzapine or quetiapine used in the sensitivity analysis

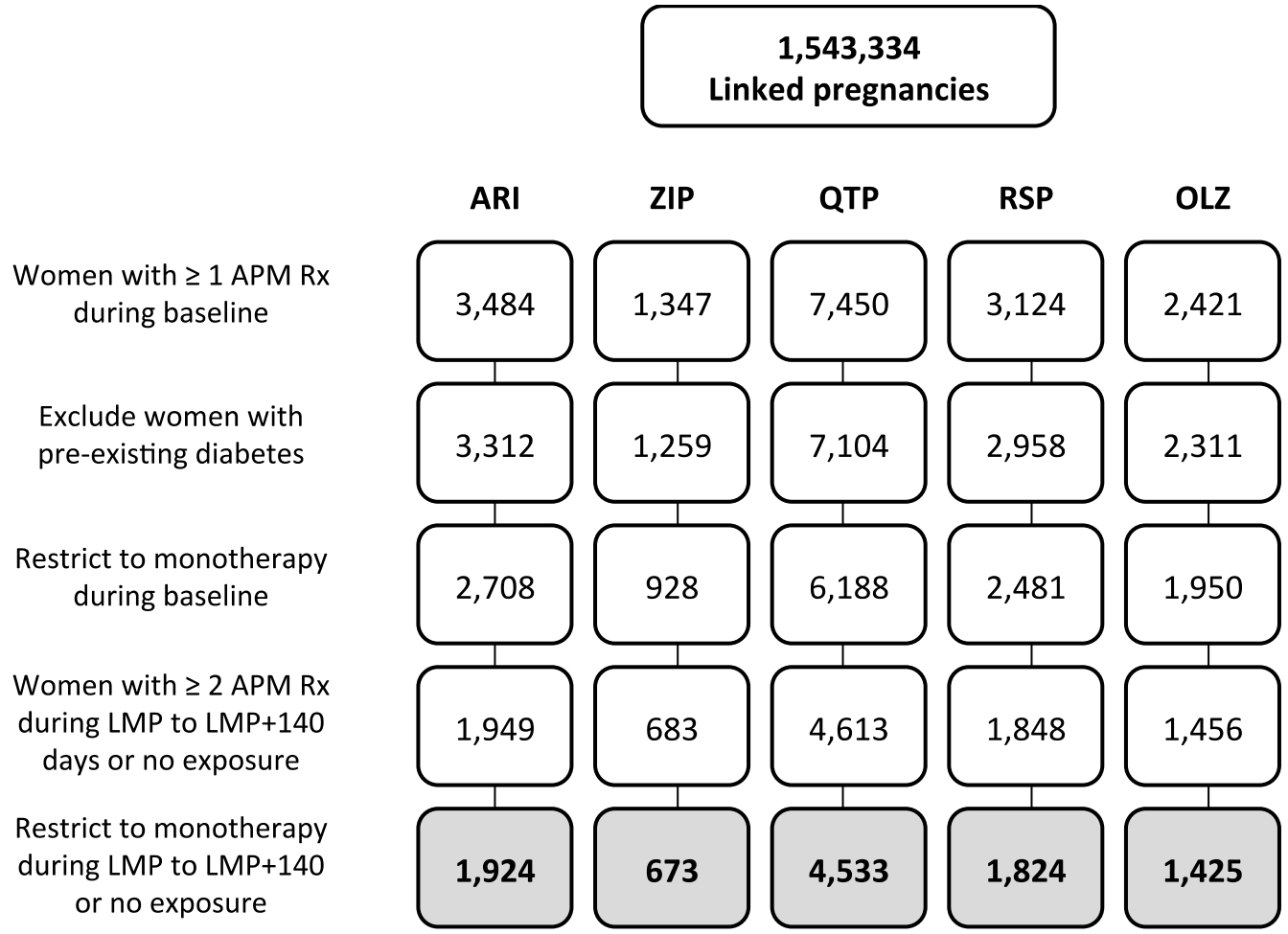
3.1 Study design, exposure definition, and outcome definition



	Gestational diabetes (case definition)	Pre-gestational diabetes (excluded)
Based on the algorithm[b]	≥ 2 diagnosis codes (250.x, 648.0x, 648.8x) on different dates from LMP+141 to delivery *and* meet the following conditions: No diabetes diagnosis, GTT, or treatment between LMP and LMP+140 and *either* 1. GTT between LMP+141 and delivery *or* 2. No GTT at any time but have at least one GDM diagnosis (648.8x) between LMP+141 and delivery	≥ 2 diagnosis codes (250.x, 648.0x, 648.8x) on different dates from LMP to delivery *and* Those who do not meet the case definition of gestational diabetes (i.e. received diagnosis, GTT, or treatment for diabetes between LMP and LMP+140 or only have diagnoses for pre-existing diabetes without a GTT)
Additional exclusion		1 diagnosis code (250.x, 648.0x, 648.8x) or diabetes treatment without a diagnosis code using the baseline covariate definitions

LMP: Last menstrual period; Rx: prescription; APM: Antipsychotic; GTT: glucose tolerance test
[a] Restricted to use of a single antipsychotic agent during baseline and exposure window
[b] In the original algorithm by Andrade et al, exclusion was based on LMP+90 days rather than LMP+140 days. It was modified to meet our exposure definition and also to make the case definition more specific

3.2 Flow chart illustrating the cohort creation process for each antipsychotic exposure group



ARI: aripiprazole; OLZ: olanzapine; QTP: quetiapine; RSP: risperidone; ZIP: ziprasidone; APM: antipsychotics; Rx: prescription; LMP: last menstrual period

3.3 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, unadjusted

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine		
Group	Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc	
N[a]	419	1505		167	506		1543	2990		359	1465		384	1041	
	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff
Demographics															
Age <20	30.1	36.0	0.13	16.2	25.5	0.23	15.6	26.0	0.26	29.2	32.4	0.07	10.2	18.1	0.23
Age 20 to <30	43.7	48.6	0.10	61.7	56.3	0.11	50.7	54.7	0.08	40.9	51.8	0.22	45.6	60.1	0.30
Age 30 to <40	22.7	14.4	0.22	18.6	17.2	0.04	30.9	18.0	0.31	27.6	14.8	0.32	40.1	20.0	0.45
Age > 40	3.6	1.0	0.17	3.6	1.0	0.18	2.8	1.3	0.10	2.2	1.0	0.10	4.2	1.8	0.14
White	66.3	65.4	0.02	69.5	67.8	0.04	72.5	68.3	0.09	49.0	54.5	0.11	50.8	61.2	0.21
Black	19.6	18.6	0.03	19.2	21.3	0.05	15.4	17.2	0.05	30.4	30.2	0.00	24.2	22.8	0.03
Other race	14.1	15.9	0.05	11.4	10.9	0.02	12.1	14.5	0.07	20.6	15.3	0.14	25.0	16.0	0.22
Eligibility[b] at baseline	15.3	18.2	0.08	7.2	16.2	0.28	9.6	12.0	0.08	9.2	13.4	0.13	3.6	8.9	0.22
Eligibility[b] before delivery	18.6	22.5	0.10	15.0	19.0	0.11	15.9	19.4	0.09	14.2	18.0	0.10	8.6	15.3	0.21
Mental health diagnosis															
ADHD	9.3	11.8	0.08	10.2	8.3	0.07	8.4	7.9	0.02	15.6	9.8	0.18	4.4	4.8	0.02
Bipolar disorder	44.6	38.4	0.13	45.5	37.7	0.16	36.0	27.5	0.18	25.1	23.8	0.03	32.0	28.9	0.07
Schizophrenia/other psychoses	10.0	7.2	0.10	19.2	9.9	0.27	7.4	5.1	0.10	18.7	10.7	0.23	24.7	9.8	0.40
Other psychiatric disorders	11.5	7.9	0.12	8.4	9.3	0.03	8.7	10.2	0.05	7.5	9.4	0.07	6.8	8.5	0.07
Depression	39.1	38.2	0.02	39.5	37.7	0.04	42.9	43.2	0.01	44.8	44.5	0.01	38.0	39.7	0.03
Anxiety disorder	24.8	20.8	0.10	21.6	22.5	0.02	28.7	22.9	0.13	20.1	20.3	0.01	20.6	20.9	0.01
Comorbidity															
Prior GDM	4.8	4.3	0.03	2.4	7.1	0.22	4.9	4.3	0.03	3.1	2.6	0.03	2.9	3.2	0.02
Any pain disorder	40.3	36.3	0.08	42.5	42.3	0.01	45.4	38.6	0.14	31.5	32.7	0.03	32.3	38.6	0.13
Hypertension	4.8	2.8	0.10	4.8	3.0	0.10	5.2	3.4	0.09	3.6	3.4	0.01	3.9	3.7	0.01
Obesity	5.3	3.7	0.07	4.8	3.4	0.07	2.3	2.6	0.02	2.2	2.5	0.02	2.3	1.4	0.07
Dyslipidemia	3.6	1.7	0.12	4.8	1.4	0.20	2.1	1.5	0.05	0.8	1.2	0.04	3.4	1.7	0.11
Other medication use															
Anticonvulsants	33.2	24.4	0.20	33.5	28.3	0.11	36.4	27.5	0.19	31.5	23.9	0.17	25.3	18.4	0.17
Antidepressants	71.8	63.2	0.19	73.7	65.8	0.17	75.6	68.0	0.17	71.9	68.4	0.08	70.1	65.6	0.10
Anxiolytics	3.3	3.5	0.01	3.6	4.7	0.06	5.1	3.6	0.07	2.8	2.8	0.00	2.1	3.7	0.10

3.3 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, unadjusted

(Continued)

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine		
Group	Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc	
N[a]	419	1505		167	506		1543	2990		359	1465		384	1041	
	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff
Benzodiazepines	34.1	20.9	0.30	41.9	24.3	0.38	39.4	23.2	0.36	24.5	17.7	0.17	29.7	22.2	0.17
Mood stabilizers	30.1	23.5	0.15	31.7	27.5	0.09	31.8	26.0	0.13	30.1	22.7	0.17	21.6	18.1	0.09
Opioids	36.0	34.3	0.04	40.1	39.1	0.02	46.7	37.9	0.18	28.4	28.9	0.01	32.6	34.4	0.04
Other hypnotics	24.1	15.3	0.22	28.1	17.4	0.26	20.6	16.3	0.11	13.6	13.9	0.01	17.7	14.5	0.09
Stimulants	15.5	12.2	0.10	15.6	7.3	0.26	11.5	8.8	0.09	18.9	9.6	0.27	4.2	3.7	0.03
Antihypertensives	10.0	6.1	0.14	10.2	3.8	0.25	10.7	6.6	0.15	8.9	7.2	0.06	5.5	6.3	0.04
Health service utilization in 90 days before LMP															
Median N generic drug	8	7	0.23	9	8	0.23	9	8	0.25	7	7	0.11	7	7	0.01
Median N ED visits	1	1	0.09	1	1	0.06	1	1	0.00	0	1	0.19	0	1	0.14
Duration of antipsychotic use during 90 days before LMP															
Exposed ≤30 days	20.0	52.6	0.72	15.6	56.7	0.95	19.2	50.1	0.68	26.7	57.0	0.64	20.1	59.2	0.87
Exposed >30 days, ≤60 days	30.5	29.2	0.03	21.6	26.5	0.12	20.2	29.9	0.23	27.9	29.9	0.05	25.3	27.2	0.04
Exposed >60 days	49.4	18.1	0.70	62.9	16.8	1.07	60.5	20.0	0.91	45.4	13.1	0.76	54.7	13.6	0.96

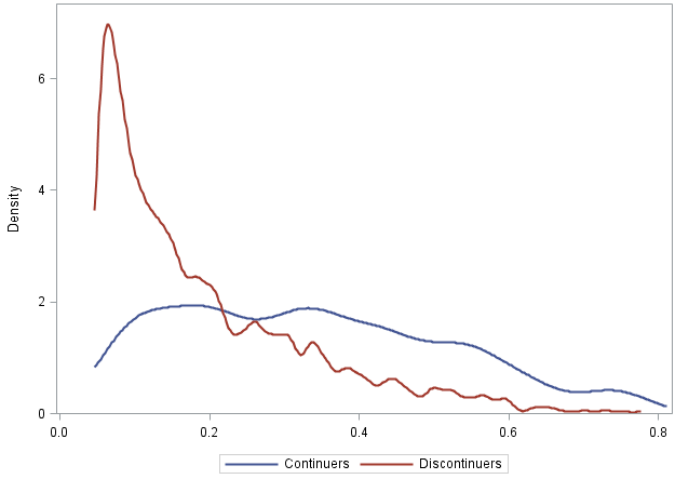
Variable formats as used in the propensity score model

Cont: Continuers; Disc: Discontinuers; SDiff: standardized difference; ADHD: attention-deficit hyperactivity disorder; GDM: gestational diabetes; ED: emergency department; LMP: last menstrual period

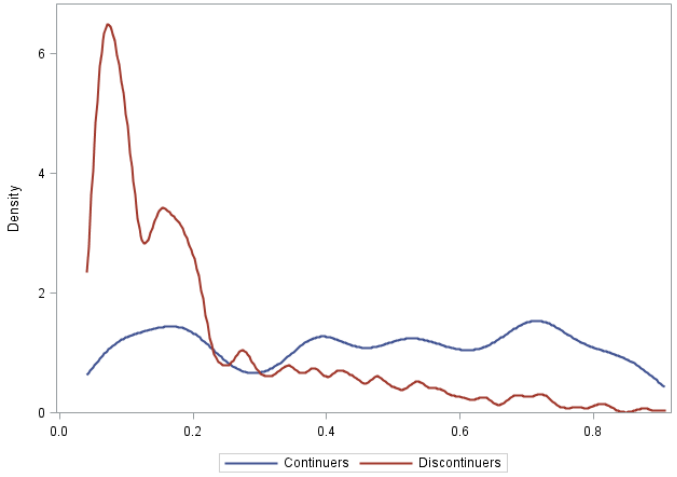
[a] Number of subject in each group before trimming and stratification
[b] Eligibility by poverty criteria in Medicaid

3.4 PS distribution in each antipsychotic exposure group

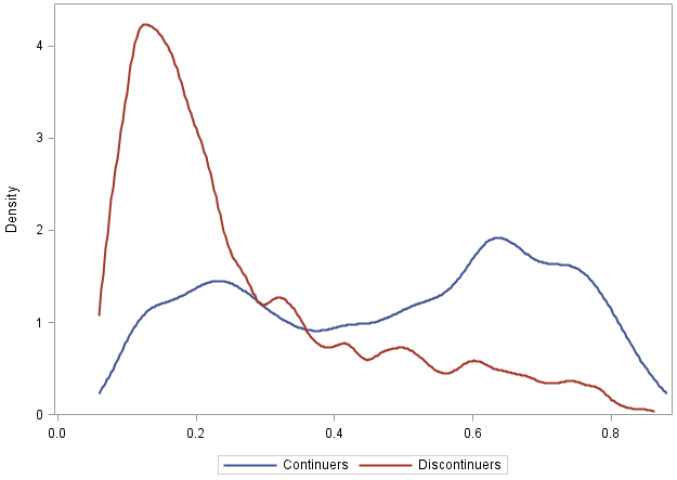
a. Aripiprazole (c-statistic: 0.76)



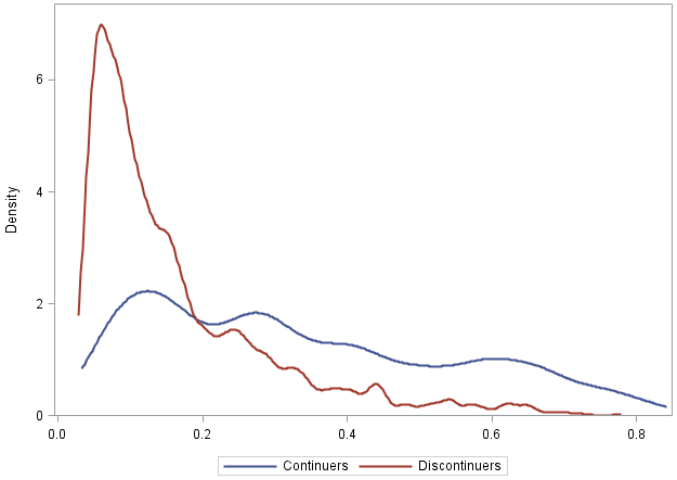
b. Ziprasidone (c-statistic: 0.84)



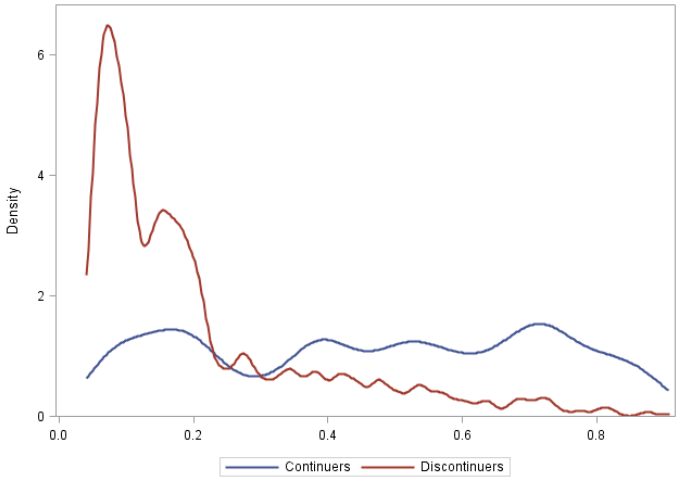
c. Quetiapine (c-statistic: 0.78)



d. Risperidone (c-statistic: 0.77)



e. Olanzapine (c-statistic: 0.81)



Distribution of propensity score (PS) for treatment continuation after trimming the non-overlapping region in each antipsychotic exposure group and the corresponding c-statistics, a measure of discrimination.

PS is a predicted probability of continuation of a specific antipsychotic as opposed to discontinuation, among the baseline users of that antipsychotic. A c-statistic close to 0.5 means the two population groups are similar in probability of being exposed (i.e. continuing antipsychotic in the context of this study).

3.5 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine		
Group	Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc	
N[a]	416	1421		140	431		1542	2951		343	1449		375	978	
	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff
Demographics															
Age <20	30.3	31.7	0.03	18.6	18.3	0.01	15.6	15.4	0.00	29.2	27.9	0.03	10.4	11.5	0.04
Age 20 to <30	44.0	44.3	0.01	58.6	61.7	0.06	50.8	51.5	0.02	42.0	40.8	0.02	**45.6**	**50.9**	**0.11**
Age 30 to <40	22.4	21.0	0.03	20.7	18.8	0.05	30.9	30.7	0.00	26.8	27.8	0.02	39.7	35.2	0.10
Age > 40	3.4	2.9	0.03	2.1	1.2	0.07	2.8	2.4	0.03	2.0	3.5	0.09	4.3	2.5	0.10
White	66.6	68.6	0.04	67.9	68.2	0.01	72.4	72.5	0.00	49.3	50.3	0.02	51.2	52.6	0.03
Black	19.7	19.2	0.01	20.7	21.0	0.01	15.4	16.0	0.01	30.3	30.9	0.01	24.5	23.4	0.03
Other race	13.7	12.3	0.04	11.4	10.8	0.02	12.1	11.5	0.02	20.4	18.8	0.04	24.3	24.1	0.01
Eligibility[b] at baseline	15.4	16.5	0.03	8.6	7.5	0.04	9.6	10.2	0.02	9.6	10.4	0.03	3.7	4.2	0.03
Eligibility[b] before delivery	18.8	19.9	0.03	15.7	17.9	0.06	16.0	15.4	0.01	14.3	13.4	0.03	8.8	8.4	0.02
Mental health diagnosis															
ADHD	9.4	9.2	0.01	10.7	10.0	0.02	8.3	8.3	0.00	14.9	15.0	0.00	4.5	5.3	0.03
Bipolar disorder	44.5	45.0	0.01	44.3	45.2	0.02	35.9	35.3	0.01	25.1	25.6	0.01	**31.7**	**41.9**	**0.21**
Schizophrenia/Other psychoses	10.1	10.7	0.02	17.1	17.8	0.02	7.4	8.2	0.03	17.8	18.7	0.02	22.9	24.1	0.03
Other psychiatric disorders	11.3	12.7	0.05	**7.9**	**10.9**	**0.11**	8.7	9.6	0.03	7.3	7.3	0.00	6.9	7.0	0.00
Depression	39.2	38.0	0.02	41.4	39.8	0.03	42.9	43.7	0.02	44.3	45.6	0.03	38.7	39.3	0.01
Anxiety disorder	24.8	25.9	0.03	22.1	22.6	0.01	28.7	29.5	0.02	19.8	19.3	0.01	20.8	24.1	0.08
Comorbidity															
Prior GDM	4.8	4.7	0.00	2.1	1.6	0.04	4.9	5.2	0.01	3.2	2.8	0.02	2.9	1.5	0.09
Any pain disorder	39.9	41.1	0.03	42.1	43.1	0.02	45.4	45.9	0.01	30.9	32.9	0.04	32.0	32.4	0.01
Hypertension	4.3	4.0	0.02	3.6	5.4	0.09	5.2	4.8	0.02	3.8	4.3	0.03	3.7	2.6	0.06
Obesity	5.3	4.6	0.03	3.6	4.5	0.05	2.3	2.2	0.01	2.3	1.7	0.05	**2.4**	**0.7**	**0.14**
Dyslipidemia	3.4	2.4	0.06	2.1	1.8	0.02	2.1	2.7	0.04	0.9	1.1	0.02	2.9	1.6	0.09
Other medication use															
Anticonvulsants	32.7	31.6	0.02	**32.1**	**37.1**	**0.11**	36.4	36.8	0.01	29.4	30.4	0.02	**25.1**	**30.1**	**0.11**
Antidepressants	71.6	71.8	0.00	73.6	72.4	0.03	75.6	75.5	0.00	72.6	72.2	0.01	70.7	71.2	0.01
Anxiolytics	3.4	3.0	0.02	**4.3**	**8.8**	**0.18**	5.0	5.3	0.02	2.6	2.7	0.00	2.1	2.1	0.01

3.5 All patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score (Continued)

	Aripiprazole			Ziprasidone			Quetiapine			Risperidone			Olanzapine		
Group	Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc		Cont	Disc	
N[a]	416	1421		140	431		1542	2951		343	1449		375	978	
	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff	%	%	SDiff
Benzodiazepines	33.7	35.2	0.03	39.3	40.5	0.02	39.4	38.9	0.01	23.6	24.7	0.03	29.1	31.3	0.05
Mood stabilizers	29.6	28.9	0.01	31.4	35.4	0.09	31.8	31.3	0.01	28.6	32.1	0.08	**21.3**	**26.5**	**0.12**
Opioids	35.8	38.1	0.05	40.7	40.3	0.01	46.7	47.1	0.01	27.4	27.7	0.01	32.8	34.1	0.03
Other hypnotics	23.8	25.2	0.03	27.9	27.3	0.01	20.6	21.0	0.01	14.0	13.7	0.01	17.6	19.7	0.06
Stimulants	15.4	14.9	0.01	14.3	13.3	0.03	11.4	11.2	0.01	17.8	17.5	0.01	4.3	3.9	0.02
Antihypertensives	9.6	12.2	0.08	**7.1**	**11.6**	**0.15**	10.7	11.5	0.02	9.0	11.0	0.07	5.3	5.6	0.01
Health service utilization in 90 days before LMP															
Median N generic drug	8	7	0.03	**7**	**8**	**0.12**	9	9	0.01	7	8	0.01	7	7	0.09
Median N ED visits	1	1	0.02	1	1	0.07	1	1	0.01	0	0	0.07	0	1	0.05
Duration of antipsychotic use during 90 days before LMP															
Exposed ≤30 days	20.2	20.0	0.01	18.6	17.3	0.03	19.3	19.3	0.00	27.7	28.0	0.01	20.5	21.0	0.01
Exposed >30 days, ≤60 days	30.8	31.2	0.01	23.6	25.8	0.05	20.2	20.4	0.01	28.9	29.9	0.02	25.9	23.6	0.05
Exposed >60 days	49.0	48.8	0.00	57.9	56.9	0.02	60.5	60.2	0.01	43.4	42.1	0.03	53.6	55.4	0.04

Bolded cells: Absolute Standardized difference > 0.1 after propensity score weighting.

Cont: Continuers; Disc: Discontinuers; SDiff: standardized difference; ADHD: attention-deficit hyperactivity disorder; GDM: gestational diabetes; ED: emergency department; LMP: last menstrual period

[a] Number of subject in each group after trimming and stratification
[b] Eligibility by poverty criteria in Medicaid

3.6 Results from additional analyses based on the risk-stratified groups

Groups	Analysis		N	Case (n)	Risk	Unadjusted RR	Unadjusted 95% CI	Adjusted RR	Adjusted 95% CI
Low risk group	Restricted	Continuer	440	19	4.3%	0.83	(0.51, 1.37)	0.68	(0.41, 1.11)
		Discontinuer	1333	69	5.2%				
	6-month baseline	Continuer	408	19	4.7%	1.03	(0.62, 1.71)	0.72	(0.44, 1.19)
		Discontinuer	1261	57	4.5%				
	12-month baseline	Continuer	306	15	4.9%	1.14	(0.64, 2.02)	1.03	(0.57, 1.85)
		Discontinuer	973	42	4.3%				
	hdPS adjusted[a]							0.80	(0.52, 1.24)
Median risk group	Restricted	Continuer	1304	91	7.0%	1.67	(1.28, 2.18)	1.25	(0.97, 1.61)
		Discontinuer	2778	116	4.2%				
	6-month baseline	Continuer	1291	93	7.2%	1.76	(1.35, 2.27)	1.46	(1.14, 1.87)
		Discontinuer	3119	128	4.1%				
	12-month baseline	Continuer	993	61	6.1%	1.44	(1.06, 1.96)	1.21	(0.90, 1.64)
		Discontinuer	2388	102	4.3%				
	hdPS adjusted							1.27	(1.04, 1.56)
High risk group	Restricted	Continuer	274	36	13.1%	2.84	(1.78, 4.53)	1.84	(1.14, 2.96)
		Discontinuer	626	29	4.6%				
	6-month baseline	Continuer	291	34	11.7%	2.47	(1.58, 3.87)	1.72	(1.09, 2.71)
		Discontinuer	762	36	4.7%				
	12-month baseline	Continuer	226	26	11.5%	2.86	(1.68, 4.88)	3.39	(1.83, 6.27)
		Discontinuer	597	24	4.0%				
	hdPS adjusted							1.33	(0.93, 1.91)

RR: relative risks; CI: confidence interval; hdPS: high-dimensional propensity score

[a] hdPS adjusted: stratification adjustment using 50 additional confounder proxy variables in propensity score estimation

3.7 The difference in obesity prevalence between continuers and discontinuers of olanzapine or quetiapine used in the sensitivity analysis

A. Olanzapine

					ALB=1.13	ARR=1.61	AUB=2.29
P_E	P_{C1}	P_{C0}	P_C	P_{diff}		RR_2	RR_3
0.27	0.45	0.68	0.62	-0.23	1.47	2.09	2.97
0.27	0.5	0.66	0.62	-0.16	1.35	1.93	2.74
0.27	0.55	0.65	0.62	-0.10	1.25	1.78	2.54
0.27	0.6	0.63	0.62	-0.03	1.16	1.66	2.36
0.27	0.65	0.61	0.62	0.04	1.08	1.54	2.19
0.27	0.7	0.59	0.62	0.11	1.01	1.44	2.05
0.27	0.75	0.57	0.62	0.18	0.94	1.35	1.91
0.27	0.8	0.55	0.62	0.25	0.88	1.26	1.79

B. Quetiapine

					ALB=1.01	ARR=1.28	AUB=1.62
P_E	P_{C1}	P_{C0}	P_C	P_{diff}	RR_1	RR_2	RR_3
0.34	0.45	0.71	0.62	-0.26	1.34	1.70	2.15
0.34	0.5	0.68	0.62	-0.18	1.23	1.56	1.97
0.34	0.55	0.66	0.62	-0.11	1.13	1.43	1.81
0.34	0.6	0.63	0.62	-0.03	1.04	1.32	1.67
0.34	0.65	0.60	0.62	0.05	0.96	1.22	1.55
0.34	0.7	0.58	0.62	0.12	0.89	1.13	1.43
0.34	0.75	0.55	0.62	0.20	0.83	1.05	1.33
0.34	0.8	0.53	0.62	0.27	0.77	0.97	1.23

RR= relative risk adjusted for obesity, ARR = apparent RR before adjusting for obesity, ALB = apparent lower bound, AUB = apparent upper bound, P_E = prevalence of continuers, P_{C1} = obesity prevalence among the exposed, P_{C0} = obesity prevalence among the unexposed, P_C = obesity prevalence in the entire population (fixed at 0.62), and $P_{diff} = P_{C1} - P_{C0}$.

The strength of association between obesity and the risk of gestational diabetes (RR_{CD}) is assumed to be 4.

Each boxed row represents the combination of parameters that corrects the ARR close to 1.00.

Chapter 4. Haloperidol versus Atypical Antipsychotics for Delirium in Patients with Myocardial Infarction: a Cohort Study

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ABSTRACT

Objective: Outpatient studies suggest a higher risk of death associated with treatment with haloperidol compared to atypical antipsychotics (AAPs) in older adults with dementia. However, little is known about the relative safety of these medications in hospitalized patients. We compared the risk of in-hospital mortality associated with haloperidol relative to AAPs in hospitalized patients with acute myocardial infarction (AMI).

Design: A cohort study

Setting: > 700 Hospitals in the United States

Participants: Hospitalized medical patients over age 18 with a primary diagnosis of AMI who initiated an oral antipsychotic drug between 2003 and 2014

Exposure: Oral haloperidol or oral AAPs (olanzapine, quetiapine, risperidone)

Main outcome measures: In-hospital mortality over 7 days of follow-up

Results: Among 6,578 patients (mean age of 75.2 years), 25.4% initiated haloperidol and 74.6% initiated AAPs. The mean time from admission to treatment initiation (5.3 vs. 5.6 days) and length of stay (12.5 vs. 13.6 days) was similar, but the mean treatment duration was shorter for haloperidol initiators than for AAP initiators (2.4 vs. 3.9 days). The unadjusted hazard ratio (HR) of death at 7 days after initiating haloperidol vs. AAP was 1.51 (95% confidence interval, 1.22-1.85) and the adjusted HR was 1.50 (1.14-1.96) in intention to treat analyses. In as-treated analyses, the unadjusted HR was 1.90 (1.43-2.53) and the adjusted HR was 1.93 (1.34-2.76).

Conclusion: Our results suggest an increased risk of death within 7 days of initiating haloperidol compared to initiating AAP in patients with AMI. Although residual confounding

cannot be excluded, this finding raises a safety concern for haloperidol when it is used for hospitalized patients with cardiac comorbidity.

INTRODUCTION

A number of studies have compared the safety of typical and atypical antipsychotics when used to treat behavioral symptoms of dementia in older adults.[73-77] While the United States Food and Drug Administration (FDA) requested inclusion of black box warnings for both classes of antipsychotics with respect to increased mortality,[78,79] FDA clearly stated that there was insufficient evidence to conclude whether typical antipsychotics have a greater risk compared to atypical antipsychotics. Since then, several studies in outpatients or nursing home residents reported a greater risk of death associated with typical antipsychotics compared with atypical antipsychotics.[73-77]

The safety of antipsychotics in the in-hospital setting, where the most frequent indication is management of delirium-related agitation,[80,81] has not been thoroughly evaluated. Currently there are no drugs approved by the FDA for treatment of delirium, and clinical guidelines for delirium vary in their recommendation on the choice of antipsychotic due to inconclusive safety evidence.[82-85] A number of randomized trials have reported similar efficacy between haloperidol and atypical antipsychotics in managing delirium symptoms in hospital.[86-90] However, these trials had insufficient power to assess potential differences in safety-related endpoints, including mortality. In nursing home residents, an increased mortality in haloperidol users compared to risperidone users has been observed within a few days after the initiation of treatment, suggesting an acute effect of haloperidol on the risk of death.[73] On the other hand, atypical antipsychotics can cause orthostatic hypotension, sedation, and anticholinergic side effects that may have adverse effect on delirious patients.[91] Furthermore, both typical and atypical antipsychotics can have adverse effects on cardiovascular system including QTc prolongation and arrhythmia.[82,92] Because of this, patients with cardiac morbidity such as those who had an

acute coronary syndrome may be more vulnerable to adverse effects of antipsychotic medication.[93]

In this study, we investigated the comparative safety of antipsychotics to treat delirium-related agitation with regard to in-hospital mortality in a cohort of hospitalized patients with acute myocardial infarction (AMI), who are expected to be at higher risk of experiencing adverse effects from antipsychotic treatment.

METHODS

Study design and population

We conducted a cohort study using the Premier Research Database from 2003 to 2014, a national hospital administrative database including more than 700 hospitals and representing 20% of all inpatient discharges in the United States (US).[94] It contains charges and date information for drugs, procedures, and diagnostic tests during hospital stays. Diagnostic codes are recorded in the discharge summary for each patient.

The source cohort consisted of hospitalized patients age 18 or older whose primary diagnosis for admission was AMI, identified by the International Classification of Diseases, 9th edition (ICD-9, 410.x0, 410.x1). Subjects were eligible for inclusion in the study if they received one of the four antipsychotics frequently used to in hospital, namely haloperidol, olanzapine, quetiapine, or risperidone. Haloperidol accounted for more than 70% of all typical antipsychotic use, and chlorpromazine was not considered because it is often used to treat nausea or

vomiting symptoms in hospitalized patients.[95] Olanzapine, quetiapine, and risperidone together comprised more than 90% of all atypical antipsychotic use in the study population. Haloperidol is frequently given as an intravenous (IV) drug but not the atypical antipsychotics, so we focused on oral treatment due to the concern of residual confounding between those who receive IV haloperidol and oral atypical antipsychotics. To assess baseline characteristics, we required a minimum 3 days of hospital stay with at least 2 days free of antipsychotic treatment following admission. We also excluded patients who received more than one antipsychotic on the treatment initiation day, as well as those who had a diagnosis for a mental disorder that is usually treated with antipsychotics (i.e., schizophrenia or bipolar disorder). This was done to ensure patients initiated antipsychotics as a treatment for delirium rather than for pre-existing psychiatric conditions. We did not require a recorded diagnosis of delirium since delirium is known to be under-recorded in medical records and the sensitivity of ICD-9 diagnosis can be as low as 3%.[96,97] Instead, we considered the initiation of antipsychotic treatment in the absence of a pre-existing psychiatric diagnosis as an indication of a delirium. We excluded patients who received coronary artery bypass graft (CABG) because perioperative delirium is a distinct clinical entity with unique risk factors and approaches to treatment. Appendix 4.1 shows how the study cohort was created.

Exposure and outcome

We defined the exposure as the class of the antipsychotic (haloperidol vs. atypical) that a patient initiated. Treatment duration was defined as the number of days from the initiation date (index date) to discontinuation or switching based on prescription information. Patients were considered discontinued if they had 2 or more days without treatment and switching was defined

as either receiving the other class of antipsychotic or receiving non-oral antipsychotics. The study outcome was defined as in-hospital death, identified from the discharge status of patients.

Other covariates

We assessed potential confounders for the planned analysis using information from admission to the day before antipsychotic initiation. The covariates included patient characteristics and conditions that were plausibly associated with both the choice of antipsychotic and the risk of in-hospital death. The list of covariates is provided in Appendix 4.2. In addition to demographic and facility characteristics, we included medication prescribed and procedures received before antipsychotic initiation. Since diagnoses are aggregated in the discharge summary without reference to when they were made, we only included chronic condition diagnoses to ensure that the conditions were present at the time of admission and did not develop after initiation of antipsychotic treatment. Lastly we adjusted for number of days from admission to the day before index date, as longer hospital stay is associated with both increased risk of developing delirium and worse prognosis.[98,99]

Statistical analysis

We compared the baseline characteristics of the haloperidol initiators and atypical antipsychotic initiators, and used Kaplan Meier survival analyses to compare the distributions of survival times. The primary analysis was an intention-to-treat (ITT) analysis with the initial exposure carried forward to the end of the follow up, based on the hypothesis that the potential effect of

antipsychotic begins with the initiation of treatment and causes a cascade of events leading to death. Follow up started on the index date and lasted until the earliest of death, discharge, or a pre-defined length of follow-up. Since the mean treatment duration was less than a week for both groups, we used as primary analyses a 7-day follow up. We also present results for a follow up of 2, 3, 5, and 30 days. The secondary analysis was an as-treated analysis in which patients were censored the day after they discontinued or on the day they switched.

The crude hazard ratio (HR) of in-hospital death for each follow-up period was estimated using Cox proportional hazard regression, and the adjusted HR was obtained using propensity score (PS) matching. In the context of this study, the PS is the probability of receiving haloperidol as opposed to one of the three atypical antipsychotics, given the baseline characteristics described above. Patients who received haloperidol were matched to patient who received an atypical antipsychotic using a 1:1 nearest neighbor matching algorithm with a caliper of 0.2 of the standard deviation of the PS on the logit scale.[100] Covariate balance between the two groups was assessed after matching and an absolute standardized difference less than 0.1 was considered evidence of balance.[100] We used robust standard errors to account for the matching in adjusted analyses.[101] The validity of the proportional hazards assumption was assessed using log of negative log of the survival plot.

Subgroup and Sensitivity Analyses

In order to examine whether there is a particular subset of patients at higher risk, we repeated the ITT analysis with 7 days of follow-up in subgroups defined by clinical characteristics that are potentially associated with risk of death. This exploratory analysis included age category (under 75, 75 to < 85, 85 or above), degree of comorbidity burden (Charlson index over 4), intensive

care unit (ICU) utilization during baseline (yes or no), and the number of antipsychotic treatment days (2 or more days) due to the fact that a large proportion of patients received antipsychotic for only one day before switching or discontinuation. We also compared haloperidol to each atypical antipsychotic separately. PSs were re-estimated in all subsets and patients were re-matched.

As a sensitivity analysis, we included the patients who initiated antipsychotics on the second day of their hospital stay and used covariates defined from admission date to examine whether our findings are applicable to a broader range of patients who might have developed delirium shortly after they were admitted. Patients who received antipsychotics on the day of admission were still excluded because we could not obtain pre-exposure characteristics. It should be acknowledged, however, that there is an increased likelihood of residual confounding in this analysis due to potentially incomplete baseline information. We repeated the main analyses with a conditional Cox model to account for differential censoring due to the shorter duration of haloperidol treatment. In this analysis, both subjects in a matched pair are censored at the same time when either one is censored. Finally, we repeated analyses controlling for correlation within each facility using random effects to adjust for differences in unmeasured facility characteristics and practice patterns.

Terminal illness in haloperidol users has been suggested as a source of potential residual confounding in outpatient studies.[102] We therefore examined medications frequently used in patients who are approaching the end-of-life stage (short- and long-acting opioids, benzodiazepines), and discontinuation of chronic disease treatments (statins, beta-blockers, angiotensin-converting-enzyme inhibitors, and angiotensin II receptor blockers).[103-105]

All analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, North Carolina) and a 2-sided p-value less than 0.05 was considered statistically significant.

RESULTS

After applying eligibility criteria, we identified 1,668 patients who received oral haloperidol and 4,910 patients who received oral atypical antipsychotic medications during their hospitalization for AMI between 2003 and 2014. The study population had an overall mean age of 75.2 years. Before PS matching, patients in the two groups were similar with regard to MI type, comorbidity, baseline treatments, time from admission to antipsychotic initiation, and the mean length of hospital stay. (Table 4.1; see Appendix 4.3 for a complete list of all patient characteristics). The patients who initiated haloperidol were older and more likely to be non-white, and received treatment for a shorter period of time than those who initiated atypical antipsychotics (mean duration 2.4 versus 3.9 days, respectively). The PSs were largely overlapping with a c-statistic of 0.65 (Appendix 4.4). 99.5% of the haloperidol initiators were matched to atypical antipsychotic initiators and all covariates included in the PS were well balanced after matching.

During the first week following treatment initiation, 129 haloperidol initiators and 92 atypical antipsychotic initiators died in the matched cohort. The cumulative probability of survival among haloperidol initiators was uniformly lower than that among atypical antipsychotic initiators during this time (Figure 4.1). In ITT analysis over 7-day follow-up, the absolute rate of death per 100 person-days was 1.7 for haloperidol initiators and 1.1 for atypical antipsychotic initiators (Table 4.2). The crude HR of death was 1.51 (1.22-1.85) and adjusted HR was 1.50 (1.14-1.96) in the matched cohort. In the as-treated analysis, the mean follow-up time was 2.8 days (standard deviation 1.7) for haloperidol initiators and 3.7 days (2.1) for atypical antipsychotic initiators. During the 7-day follow-up, the crude HR was 1.90 (1.43-2.53) and the adjusted HR was 1.93

(1.34-2.76). The HRs showed a decreasing trend as the length of follow-up increased, but there was no graphical evidence of violation of the proportionality assumption during the first 7 days where most events occurred (Appendix 4.5).

The HRs were similar across the subgroups based on age but the absolute rate of death increased as age increased (Figure 4.2, Appendix 4.6). The HR was increased only among those with at least two days of treatment but not among those with a single-day treatment. Comparison of HRs between patients who were in the ICU (HR=1.11, 0.68-1.81) on the index date and who were on the medical ward (HR=2.01, 1.44-2.82) suggested effect heterogeneity. Haloperidol was associated with increased risk of death compared to each of olanzapine (adjusted HR=1.59, 1.13-2.24), quetiapine (adjusted HR=1.79, 1.33-2.41), and risperidone (adjusted HR=1.51, 1.12-2.03).

Sensitivity analyses including patients who initiated treatment on day 2 or using different modeling assumptions did not change the results (Appendix 4.7). In addition, we did not observe different trends in discontinuation of chronic medications or in use of opioids or benzodiazepines prior to antipsychotic initiation in patients receiving haloperidol versus atypical antipsychotics (Appendix 4.8).

Table 4.1 Selected patient characteristics in the unadjusted and propensity score-matched cohorts

	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std diff	HDL N=1659 %	AAPs N=1659 %	Std diff
Demographic						
Age (mean, SD)	77.0 (11.4)	74.6 (12.8)	0.20	77.0 (11.4)	76.8 (11.8)	0.01
Female	46.6	47.2	0.01	46.6	48.3	0.04
White	68.9	73.0	0.09	69.0	69.6	0.01
ER/urgent admission	91.9	94.2	0.09	91.9	91.7	0.00
MI Type						
NSTEMI	68.8	67.2	0.02	68.8	68.1	0.01
STEMI	26.4	27.4	0.03	26.4	27.1	0.02
Unknown type	4.8	5.4	0.03	4.8	4.8	0.00
Baseline Comorbidity and Treatments						
Charlson index (mean, SD)	3.4 (1.9)	3.4 (1.9)	0.02	3.4 (1.9)	3.5 (1.9)	0.01
Heart failure	57.1	57.5	0.01	57.0	57.4	0.01
Dementia	18.9	20.1	0.03	19.0	17.5	0.04
PCI/Stent	25.5	25.3	0.01	25.4	25.0	0.01
ICU Stay ≥ 1 day	71.1	71.8	0.02	71.2	70.0	0.03
Antiplatelets[a]	90.1	86.4	0.11	90.1	90.0	0.00
Anticoagulants[b]	82.7	79.6	0.08	82.6	82.0	0.02
Heparin, intravenous	34.5	34.5	0.00	34.4	34.0	0.01
Nitrates	26.5	25.3	0.03	26.5	26.7	0.00
Antiarrhythmics	13.4	17.2	0.11	13.3	13.4	0.01
Benzodiazepines	59.7	63.9	0.09	59.7	61.5	0.04
Opioids	64.4	63.4	0.02	64.4	66.7	0.05
Antipsychotic Treatment						
Time to initiation (mean, SD)	5.3 (4.8)	5.6 (6.5)	0.05	5.3 (4.8)	5.4 (5.6)	0.02
Treatment duration (mean, SD)	2.4 (3.4)	3.9 (4.5)	0.38	2.4 (3.4)	3.7 (4.2)	0.35

Table 4.1 Selected patient characteristics in the unadjusted and propensity score-matched cohorts (Continued)

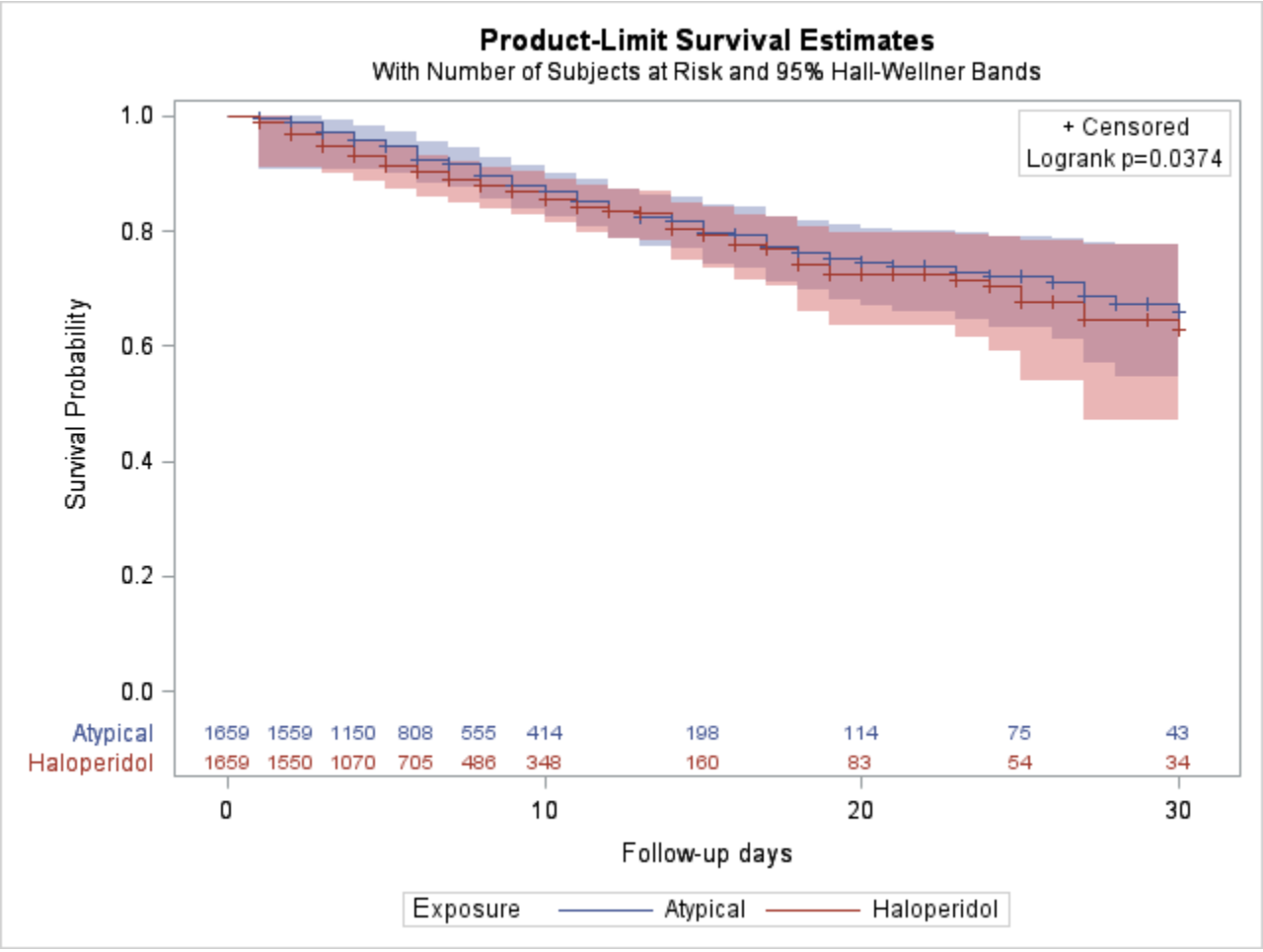
	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std diff	HDL N=1659 %	AAPs N=1659 %	Std diff
Medication switch during follow up	16.5	12.1	0.12	16.5	12.4	0.12
Discharge						
Discharged to SNF/hospice	37.6	37.3	0.01	39.2	37.7	0.03
Length of hospital stay (mean, SD)	12.5 (11.9)	13.6 (12.3)	0.09	12.5 (11.9)	13.3 (12.4)	0.06

HDL: haloperidol; AAPs: atypical antipsychotics; Std diff: standardized difference; SD: standard deviation; ER: emergency room; NSTEMI/STEMI: non/ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; ICU: intensive care unit; SNF: skilled nursing facility

[a] Antiplatelets = aspirin and other antiplatelet agents

b Anticoagulants = warfarin and other anticoagulants

Figure 4.1 Kaplan-Meier curve of in-hospital death in the matched cohort up to 30 days of follow-up, comparing haloperidol initiators to atypical antipsychotic initiators



Numbers at the bottom represents the number of remaining patients in each group over the follow-up time

Table 4.2 Hazard ratios of in-hospital death comparing haloperidol initiators to atypical antipsychotic initiators, by length of follow-up period

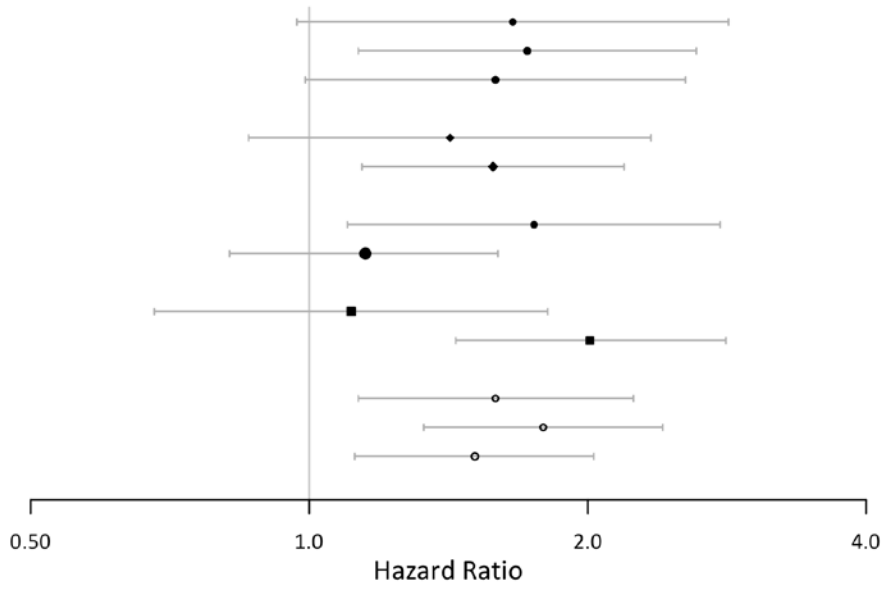
		Unadjusted							Matched						
		HDL		AAPs					HDL		AAPs				
	Follow-up	Death	Rate[a]	Death	Rate	HR	95% CI		Death	Rate	Death	Rate	HR	95% CI	
ITT	2 days	52	1.6	67	0.7	**2.30**	1.60	3.31	51	1.6	18	0.6	**2.86**	1.66	4.92
	3 days	79	1.8	127	0.9	**1.89**	1.43	2.50	78	1.7	39	0.9	**2.05**	1.39	3.02
	5 days	113	1.8	207	1.0	**1.70**	1.35	2.14	112	1.7	68	1.0	**1.73**	1.28	2.34
	7 days	131	1.7	278	1.1	**1.51**	1.22	1.85	129	1.7	92	1.1	**1.50**	1.14	1.96
	30 days	180	1.6	463	1.2	**1.31**	1.11	1.56	178	1.6	159	1.3	**1.26**	1.01	1.56
AT	2 days	48	1.6	65	0.7	**2.26**	1.55	3.28	47	1.5	18	0.6	**2.70**	1.56	4.67
	3 days	59	1.6	97	0.8	**2.12**	1.53	2.94	58	1.6	28	0.7	**2.42**	1.55	3.79
	5 days	68	1.6	128	0.8	**2.05**	1.52	2.76	67	1.6	41	0.8	**2.14**	1.46	3.14
	7 days	70	1.5	151	0.8	**1.90**	1.43	2.53	69	1.5	49	0.8	**1.93**	1.34	2.76
	30 days	75	1.5	187	0.8	**1.83**	1.40	2.41	74	1.5	62	0.9	**1.80**	1.29	2.51

ITT: Intention-to-treat; AT: as-treated; HDL: haloperidol, AAPs: atypical antipsychotics; HR: hazard ratio; CI: confidence interval

[a] Rate: number of death per 100 person-days

Figure 4.2 Subgroup analyses comparing haloperidol initiators to atypical antipsychotic initiators, based on ITT analysis with 7 days of follow-up

Subgroup		HR	95% CI
Age	75 or under	1.66	[0.97 , 2.84]
	Over 75 to 85	1.72	[1.13 , 2.62]
	Over 85	1.59	[0.99 , 2.55]
Comorbidity	CCI > 4	1.42	[0.86 , 2.34]
	CCI 4 or under	1.58	[1.14 , 2.19]
Exposure	2 or more days	1.75	[1.10 , 2.78]
	1 day	1.15	[0.82 , 1.60]
On index day	In ICU	1.11	[0.68 , 1.81]
	In Ward	2.01	[1.44 , 2.82]
Each drug	HDL vs. OLZ	1.59	[1.13 , 2.24]
	HDL vs. QTP	1.79	[1.33 , 2.41]
	HDL vs. RSP	1.51	[1.12 , 2.03]



HR: Hazard ratio; CI: confidence interval; CCI: Charlson Comorbidity index; OLZ: olanzapine; QTP: quetiapine; RSP: risperidone

For each subgroup category, propensity score was re-estimated and patients were rematched. The size of each mark represents the relative size of the number of people in each group. Analyses were based on intention-to-treat analysis with 7 days of follow-up. See Appendix 4.6 for more details.

DISCUSSION

In a large cohort of AMI patients medically treated in hospital, initiation of oral haloperidol was associated with an increase in the risk of in-hospital death compared to the initiation of oral atypical antipsychotics. The potential adverse effect of haloperidol appeared to be the strongest during the first few days following initiation, suggesting an acute harmful effect of haloperidol. Although residual confounding is a possibility, we adjusted for a large number of potential confounders and the result was consistent across a number of subgroup and sensitivity analyses. Our finding is also consistent with what has been reported from outpatient studies on the comparative safety of antipsychotic medication. Given the insufficient amount of safety evidence for delirious patients in hospital, our study adds an important piece of evidence that atypical antipsychotics with comparable efficacy to haloperidol may be a safer option with respect to mortality among patients with cardiac comorbidity.

Relation to previous studies

Due to difference in the indications for antipsychotic use, evidence from outpatient studies is not directly applicable to inpatients. Moreover, the duration of antipsychotic treatment in hospital is short and treatment is often prescribed 'as necessary',[106] unlike outpatient prescriptions that last several weeks to months.[74] According to a recent review,[107] there are 6 randomized trials that compared typical and atypical antipsychotic in hospitalized patients with delirium with regard to mortality.[87-90,108,109] The largest treatment arm among these trials included 45 patients. The authors also conducted a meta-analysis but did not find an association between any antipsychotic use and 30-day mortality (OR 0.90, 0.62-1.29). However this analysis merged

delirium prevention trials with treatment trials due to limited sample size. The heterogeneous populations and methodologies may explain this null finding. Two of the larger observational studies in hospitalized patients (n=2,453 and 244) were not able to examine comparative safety because there were no or too few deaths.[93,110]

Interpretation of results and implications

The as-treated analysis is potentially subject to informative censoring and to time-dependent confounding bias because treatment discontinuation or switching can be associated with the prognosis of the patient. It was done to examine the degree to which results from ITT analysis may be affected by exposure status misclassification. The slightly larger HRs in as-treated analyses suggests that the potential adverse effect of haloperidol is more pronounced while patients are taking the drug compared to the time after they discontinue or switch. This is supported by the fact that we observe the largest HR for a 2-day follow-up when the majority of patients is still taking the drug. In our analyses PS matching sometimes resulted in strengthened associations, in contrast to our initial expectation based on previous studies. The baseline characteristics before matching was very similar between the two groups, so it is possible that in some instances the confounding in the unmatched population was in the direction that favored haloperidol. The atypical antipsychotic initiators who were matched had a slightly lower rate of 7-day mortality (5.55%) than those who were matched (5.72%), supporting this argument.

There was evidence of effect heterogeneity with increased HR among patients who were in the medical ward on the index date compared to those who were in the ICU. Patients in the ICU are under a greater surveillance for any change in health status; so one possible explanation cuould

be that potential adverse effects of haloperidol such as arrhythmia are more quickly taken care of in the ICU and less likely to lead to death.

Cardiovascular death was suggested as the explanation for half of the excess deaths associated with typical antipsychotics in outpatients.[111] Whether the cardiac side effects also explain the increased in-hospital mortality remains unclear. The Cochrane review recommends using atypical antipsychotics rather than haloperidol if the patient is likely to develop cardiac toxicity from the use of antipsychotics.[106] While our study cannot explain the reason for potentially increased risk of death, atypical antipsychotic may be considered as a safer option if patients already have underlying cardiac comorbidity.

Strengths and weaknesses of the study

This study utilized a large nationwide hospital database, so the interpretation of the results is not limited to specific practices or hospitals. The large cohort size provided sufficient statistical power to detect a modest difference in mortality, which was not possible in earlier studies with a much smaller sample size. We were able to adjust for a large number of variables related to the treatments and procedures for each patient, reducing the concern for residual confounding.

This study is not without limitations, however. We did not have information on patients before they were admitted to hospitals, so some comorbid conditions may be misclassified depending on the completeness of coding in the hospital. The availability of confounder information is potentially associated with mortality if diagnoses are more likely to be recorded if a patient dies. But it is likely non-differential with respect to the type of antipsychotic that the patient had received, thus unlikely to cause bias from differential misclassification of confounder. The true indication for antipsychotic use is unknown, and bias can be present if the true prevalence of

delirium was differential between haloperidol and atypical antipsychotics because non-delirious patients are likely to have a lower risk of death compared to delirious patients. It should be noted, however, that the prevalence of recorded diagnoses of delirium based on ICD-9 codes was similar across the four antipsychotics examined in this study (19.6% for haloperidol, 19.6% for olanzapine, 20.5% for quetiapine, and 18.5% for risperidone). A previous validation study showed that the positive predictive value (PPV) of antipsychotic prescription among geriatric hospitalizations to predict delirium is over 80%.[81] We expect a higher PPV in this study since all patients had an AMI so the baseline mortality is probably higher. The duration of treatment was shorter for haloperidol compared to atypical antipsychotics, which may reflect a difference in usage of these drugs that is not captured by our data and can lead to differential censoring bias. However, sensitivity analyses using a conditional model to account for this difference showed consistent, even stronger, effects. Due to the short treatment duration and follow-up, we could not examine a long-term effect in hospital. Confounding due to impending death can be an alternative explanation for the observed result,[102] if haloperidol is used preferentially among terminally ill patients. However, we did not find strong evidence of confounding based on a large number of measured covariates, or based on the trend of care before antipsychotic initiation such as opioid use or discontinuation of chronic disease care. In addition, PS matching did not change the crude estimates much. This implies that either there was not much confounding before matching, or that our covariates were not good measures of the true confounders. While the latter is always a possibility, it is unlikely that close to 80 variables used in PS would fail to adjust for confounding to a large extent. Lastly the mechanism of the increased risk of death is unknown since we did not have information on cause of death.

CONCLUSION

In a large, nationwide cohort of hospitalized patients, we found an increased risk of death during the week following treatment associated with the initiation of haloperidol compared to the initiation of atypical antipsychotics. These findings are consistent with a higher risk of mortality associated with initiation of a typical versus atypical antipsychotic in the large body of evidence from outpatient studies. However, residual confounding cannot be completely excluded as a possible alternative explanation despite careful study design and adjustment for a wide range of potential confounders. In conclusion, atypical antipsychotics may be a safer therapeutic option than haloperidol for the treatment of delirium for older populations with cardiac morbidity.

APPENDIX

4.1 Flow chart of study cohort creation

4.2 Variables included in the propensity score

4.3 All patient characteristics in the unadjusted and propensity score-matched cohorts

4.4 Propensity score distribution

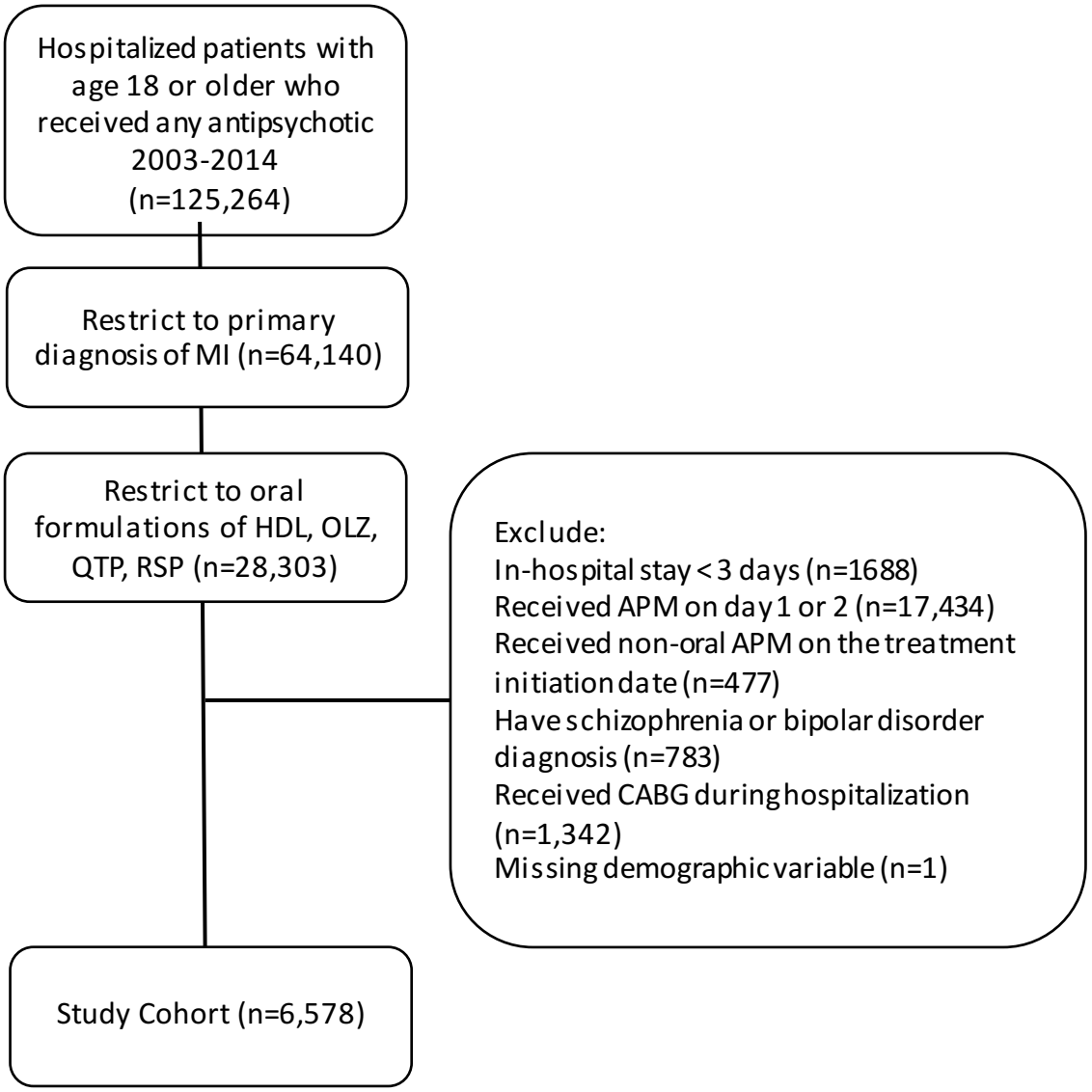
4.5 Log of negative log of estimated survivor function plot to assess proportional hazard assumption, in crude and in matched cohort

4.6 Detailed table for subgroup analyses, based on ITT analysis with 7 days of follow-up

4.7 Detailed table for sensitivity analyses, based on ITT analysis with 7 days of follow-up

4.8 Trends of medication use before initiation of antipsychotic treatment

4.1 Flow chart of study cohort creation



4.2 Variables included in the propensity score

Category	Variables
Demographics and other clinical characteristics	Age, gender, race, marital status, MI type (ST-elevation, non ST-elevation MI, or unknown), admission source (emergency/urgent admission vs. others), admission year, payer (Medicaid, Medicare, etc.)
Facility	Region (Midwest, northeast, south, west), number of beds, teaching status, location (urban vs. rural)
Chronic comorbidity	Charlson comorbidity index, chronic heart failure, chronic angina, other chronic ischemic heart diseases, diabetes, cancer, chronic obstructive pulmonary disease, dementia, depression, hypertension, atherosclerosis, chronic liver disease, chronic renal disease, epilepsy, Parkinson's disease, obesity, dyslipidemia, smoking status, alcohol or drug abuse/dependence, hemostatic disorder, endocarditis, peripheral vascular disease, records of previous coronary artery bypass graft, previous MI, previous stroke, previous valve replacement
Medications received before antipsychotic initiation	Antiplatelets (aspirin, other antiplatelets), anticoagulants (warfarin, other anticoagulants), intravenous heparin, nitrates, antiarrhythmics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, statins, fibrates, bronchodilators (beta-agonists, ipratropium, theophylline), insulin, diuretics (loop, thiazide), benzodiazepines, tricyclic antidepressants, other sedatives or hypnotics (z-drugs, barbiturates), opioids, digoxin, aldosterone agonists, fibrinolytics, antihistamines, systemic steroids, leukotriene inhibitors
Procedures received before antipsychotic initiation	Percutaneous coronary intervention/stent, intra-aortic balloon pump, mechanical ventilation, oxygen use, transfusion, intensive care unit utilization, cardiac resuscitation, cardioversion, dialysis, electrocardiogram, use of bilevel or continuous positive airway pressure
Others	Length of the baseline period (i.e., number of days from admission to the day before initiation of antipsychotics)

4.3 All patient characteristics in the unadjusted and propensity score-matched cohorts

	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std Diff	HDL N=1659 %	AAPs N=1659 %	Std Diff
Demographic						
Age (mean, SD)	77.0 (11.4)	74.6 (12.8)	0.20	77.0 (11.4)	76.8 (11.8)	0.01
Female	46.6	47.2	0.01	46.6	48.3	0.04
White	68.9	73.0	0.09	69.0	69.6	0.01
Black	10.8	9.0	0.06	10.7	9.9	0.02
Other race	20.3	18.0	0.06	20.5	20.4	0.00
MI Type						
NSTEMI	68.8	67.2	0.02	26.4	27.1	0.01
STEMI	26.4	27.4	0.03	68.8	68.1	0.02
Unknown type	4.8	5.4	0.03	4.8	4.8	0.00
ER/urgent admission	91.9	94.2	0.09	91.9	91.7	0.00
Payor						
Medicare	81.7	79.2	0.06	81.4	27.6	0.01
Medicaid	4.0	5.3	0.06	4.0	1.5	0.02
Others	14.3	15.5	0.03	14.1	4.7	0.01
Baseline Procedures						
PCI/Stent	25.5	25.3	0.01	25.4	25.0	0.01
Intraaortic balloon pump	7.3	8.8	0.05	7.3	6.8	0.02
Mechanical ventilation	4.4	4.2	0.01	4.4	4.2	0.01
Oxygen Use	53.5	52.9	0.01	53.5	54.4	0.02
Transfusion	10.5	12.4	0.06	10.5	10.8	0.01
ICU Stay ≥ 1 day	71.1	71.8	0.02	71.2	70.0	0.03
Cardiac resuscitation	2.1	3.0	0.06	2.1	1.7	0.03
Cardioversion	0.3	0.5	0.03	0.3	0.2	0.03
Dialysis	4.4	4.6	0.01	4.4	4.8	0.02

4.3 All patient characteristics in the unadjusted and propensity score-matched cohorts (Continued)

	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std Diff	HDL N=1659 %	AAPs N=1659 %	Std Diff
Electrocardiogram	1.0	0.2	0.11	0.5	0.6	0.01
BIPAP/CPAP use	10.0	10.3	0.01	9.9	9.8	0.00
Comorbidity and Disease History						
Charlson index (mean, SD)	3.4 (1.9)	3.4 (1.9)	0.02	3.4 (1.9)	3.5 (1.9)	0.01
Heart failure	57.1	57.5	0.01	57.0	57.4	0.01
Chronic angina	0.4	0.7	0.05	0.4	0.7	0.05
Other heart diseases[a]	74.7	72.0	0.06	74.6	74.6	0.00
Diabetes	38.1	40.9	0.06	38.1	39.8	0.04
Cancer	15.1	12.8	0.07	15.1	15.4	0.01
COPD	29.1	30.9	0.04	29.2	29.4	0.00
Dementia	18.9	20.1	0.03	19.0	17.5	0.04
Depression	10.1	10.8	0.02	10.1	9.8	0.01
Hypertension	73.4	71.6	0.04	73.3	74.2	0.02
Chronic liver disease	1.7	1.8	0.00	1.7	1.9	0.01
Chronic renal disease	28.2	24.9	0.07	28.0	27.9	0.00
Epilepsy	4.2	4.5	0.02	4.2	4.4	0.01
Parkinson's Disease	1.8	2.2	0.03	1.8	1.7	0.01
Obesity	6.4	8.7	0.09	6.4	5.7	0.03
Dyslipidemia	41.8	41.8	0.00	41.8	41.4	0.01
Past current smoking	29.3	28.6	0.02	29.2	28.3	0.02
Alcohol/drug abuse/dependence	6.7	6.4	0.01	6.7	6.3	0.02
Peripheral vascular disease	10.4	11.4	0.03	10.4	11.5	0.03
Previous CABG/PCI	17.6	18.6	0.03	17.6	17.1	0.01
Previous MI	11.6	11.4	0.01	11.6	11.9	0.01
Previous stroke	10.5	10.8	0.01	10.4	10.1	0.01

4.3 All patient characteristics in the unadjusted and propensity score-matched cohorts (Continued)

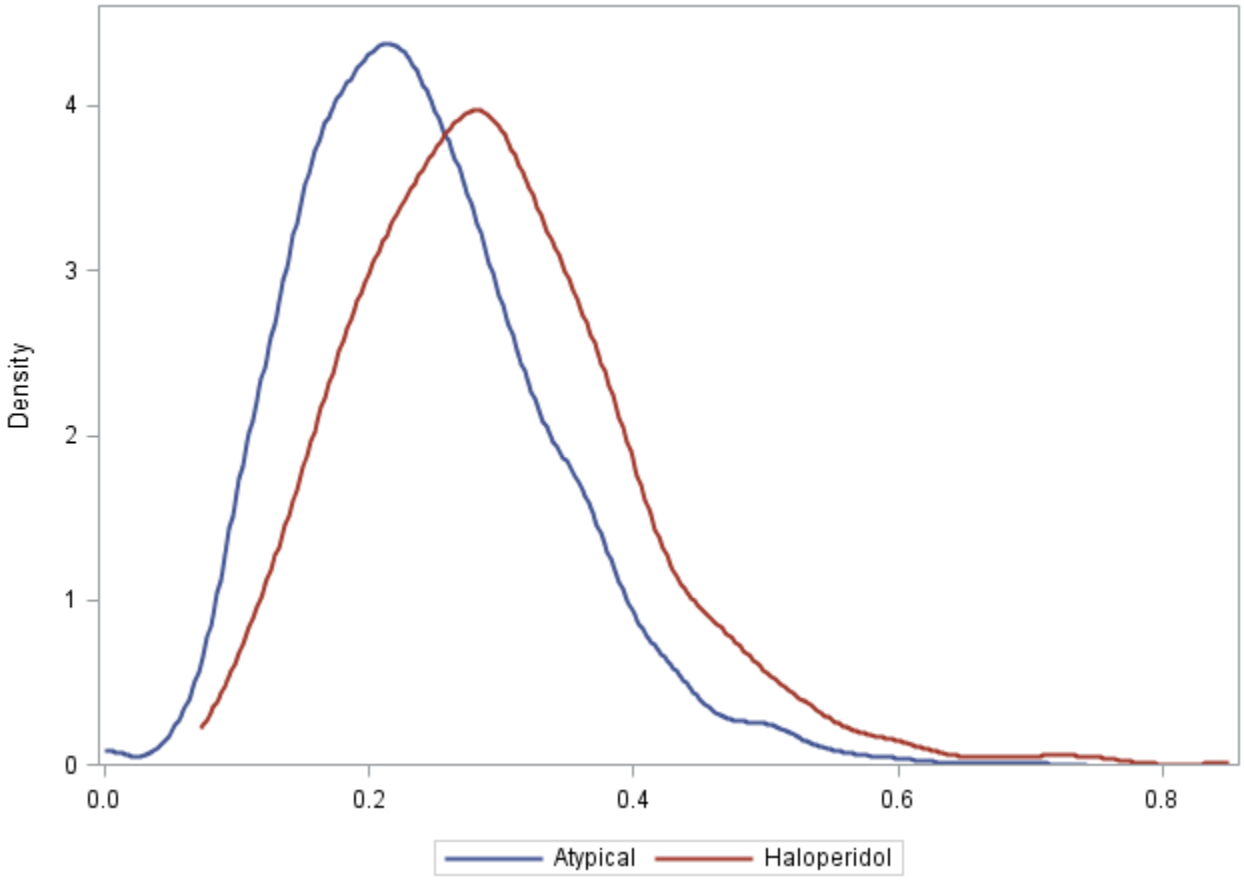
	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std Diff	HDL N=1659 %	AAPs N=1659 %	Std Diff
Previous valve replacement	0.5	0.4	0.01	0.5	0.4	0.02
Baseline Medication						
Antiplatelets[b]	90.1	86.4	0.11	90.1	90.0	0.00
Anticoagulants[c]	82.7	79.6	0.08	82.6	82.0	0.02
Heparin, IV	34.5	34.5	0.00	34.4	34.0	0.01
Nitrates	26.5	25.3	0.03	26.5	26.7	0.00
Fibrinolytics	1.8	2.3	0.03	1.8	1.7	0.01
Antiarrhythmics	13.4	17.2	0.11	13.3	13.4	0.01
ACE/ARB	53.5	46.3	0.15	53.4	54.0	0.01
Beta-blockers	84.9	79.6	0.14	84.9	85.2	0.01
Calcium channel blockers	26.9	24.2	0.06	26.8	28.8	0.05
Statins	65.3	58.8	0.14	65.3	65.3	0.00
Fibrates	2.1	1.8	0.02	2.1	2.5	0.02
Bronchodilators	37.9	38.6	0.01	37.9	38.9	0.02
Insulin	35.0	38.5	0.07	35.0	36.8	0.04
Loop Diuretics	60.0	58.0	0.04	59.9	62.0	0.04
Thiazide Diuretics	5.9	6.2	0.01	5.9	5.5	0.02
Benzodiazepines	59.7	63.9	0.09	59.7	61.5	0.04
Tricyclic antidepressants	1.7	1.8	0.01	1.7	1.7	0.00
Other sedative/hypnotics[d]	10.4	12.9	0.08	10.4	10.4	0.00
Opioids	64.4	63.4	0.02	64.4	66.7	0.05
Digoxin	14.9	14.4	0.01	14.9	14.5	0.01
Systemic steroids	19.8	22.2	0.06	19.8	20.3	0.01
Facility Characteristics						
Teaching (Y/N)	50.0	47.6	0.05	50.2	49.2	0.02

4.3 All patient characteristics in the unadjusted and propensity score-matched cohorts (Continued)

	Unadjusted			Matched		
	HDL N = 1668 %	AAPs N = 4910 %	Std Diff	HDL N=1659 %	AAPs N=1659 %	Std Diff
Urban	90.5	89.0	0.05	90.4	91.0	0.02
Antipsychotic Treatment						
Time to initiation (mean, SD)	5.3 (4.8)	5.6 (6.5)	0.05	5.3 (4.8)	5.4 (5.6)	0.02
Treatment duration (mean, SD)	2.4 (3.4)	3.9 (4.5)	0.38	2.4 (3.4)	3.7 (4.2)	0.35
Medication switch during follow up	16.5	12.1	0.12	16.5	12.4	0.12
Discharge						
Discharged to SNF/hospice	37.6	37.3	0.01	39.2	37.7	0.03
Length of stay (mean, SD)	12.5 (11.9)	13.6 (12.3)	0.09	12.5 (11.9)	13.3 (12.4)	0.06

HDL: haloperidol; AAPs: atypical antipsychotics; Std diff: standardized difference; SD: standard deviation; ER: emergency room; NSTEMI/STEMI: non/ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; ICU: intensive care unit; BIPAP/CPAP: bilevel or continuous

4.4 Propensity score distribution

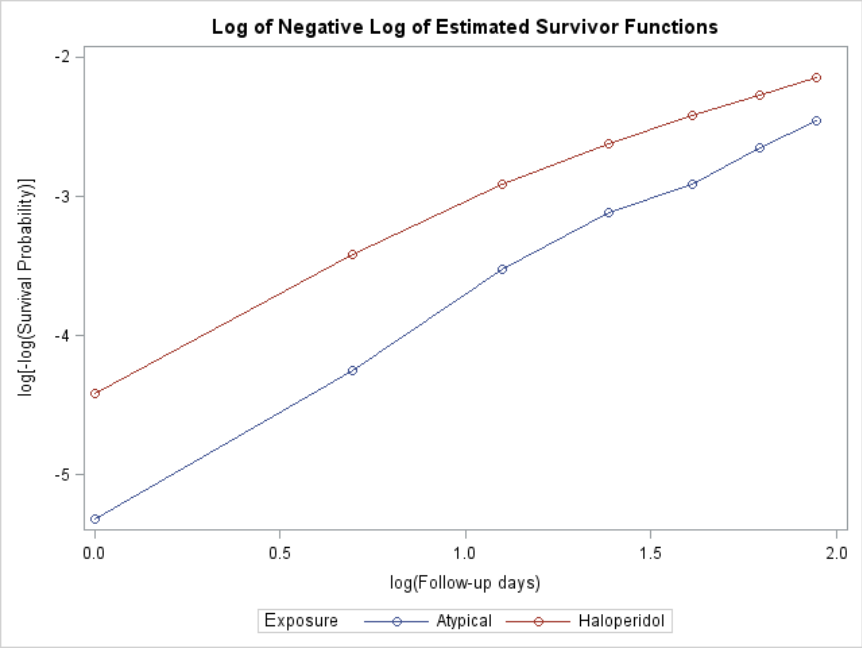


Propensity score distribution in haloperidol initiators and atypical antipsychotic initiators (reference). C-statistic was 0.65.

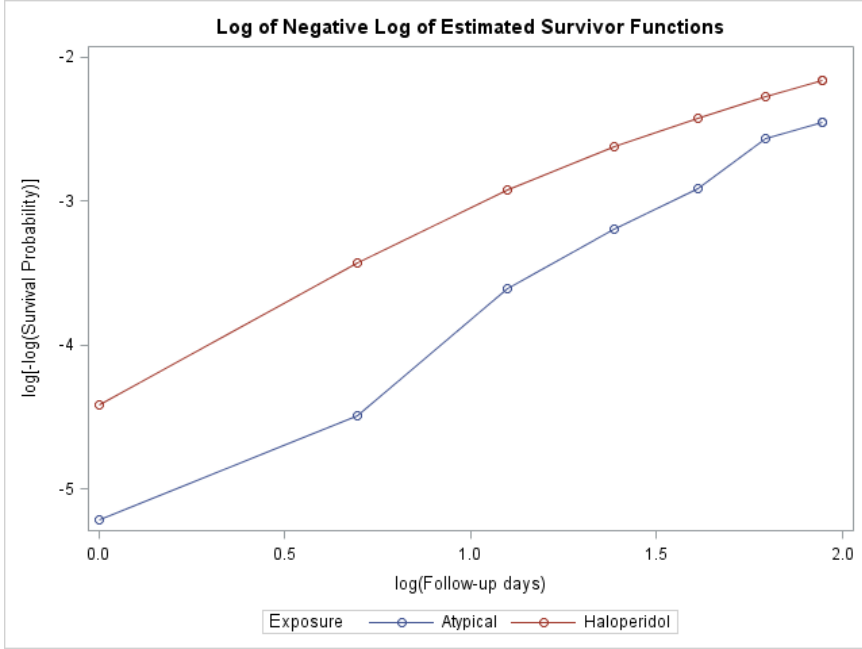
4.5 Log of negative log of estimated survivor function plot to assess proportional hazard assumption, in crude and in matched cohort

A. Intention-to-treat analyses

a. In unmatched cohorts

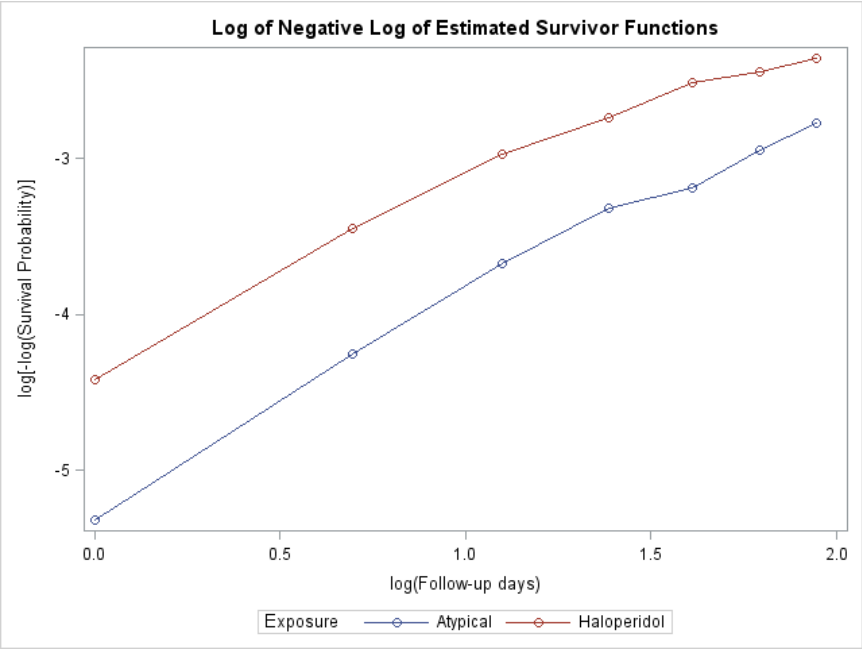


b. In matched cohorts

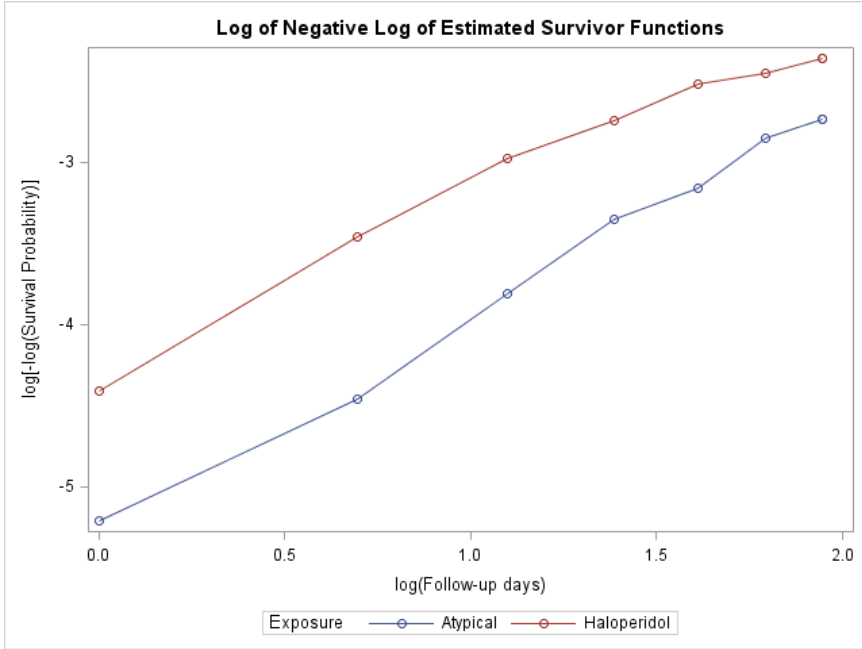


B. As-treated analyses

a. In unmatched cohorts



b. In matched cohorts



If the two lines cross each other, the proportional hazard (PH) assumption is likely violated. During the initial 7 days (i.e. up to log(Follow-up days) ≈ 2), the PH assumption does not appear to be completely violated.

4.6 Detailed table for subgroup analyses, based on ITT analysis with 7 days of follow-up

	Unadjusted									Matched								
	HDL			AAPs						HDL			AAPs					
Subgroups	N	Death	Rate[a]	N	Death	Rate	**HR**	95% CI		N	Death	Rate	N	Death	Rate	**HR**	95% CI	
Age																		
75 or under	603	33	1.1	2124	102	0.9	**1.21**	0.82	1.79	593	33	1.1	593	21	0.7	**1.66**	0.97	2.84
Over 75 to 85	582	52	2.0	1606	101	1.3	**1.57**	1.12	2.19	557	49	1.9	557	32	1.1	**1.72**	1.13	2.62
Over85	483	46	2.3	1180	75	1.5	**1.57**	1.09	2.27	450	45	2.4	450	30	1.5	**1.59**	0.99	2.55
Comorbidity level																		
CCI > 4	419	37	1.8	1189	97	1.6	**1.18**	0.81	1.72	402	36	1.8	402	27	1.3	**1.42**	0.86	2.34
CCI 4 or under	1249	94	1.7	3721	181	1.0	**1.68**	1.31	2.15	1237	90	1.6	1237	61	1.0	**1.58**	1.14	2.19
Exposure duration																		
2 or more days	667	47	1.4	3036	145	0.9	**1.62**	1.16	2.25	664	47	1.4	664	29	0.8	**1.75**	1.10	2.78
1 day	1001	84	2.0	1874	133	1.7	**1.12**	0.85	1.48	920	77	2.0	920	65	1.7	**1.15**	0.82	1.60
On index date																		
ICU	401	34	1.5	1487	129	1.5	**1.04**	0.71	1.52	381	30	1.4	381	29	1.3	**1.11**	0.68	1.81
Ward	1267	97	1.8	3423	149	1.0	**1.87**	1.45	2.41	1254	96	1.8	1254	51	0.9	**2.01**	1.44	2.82
Individual drug																		
HDL vs. OLZ	1668	131	1.7	995	63	1.2	**1.38**	1.02	1.86	866	79	1.9	866	54	1.2	**1.59**	1.13	2.24
HDL vs. QTP	1668	131	1.7	2333	123	1.1	**1.60**	1.25	2.05	1430	117	1.8	1430	69	1.0	**1.79**	1.33	2.41
HDL vs. RSP	1668	131	1.7	1582	92	1.2	**1.45**	1.11	1.89	1236	102	1.8	1236	73	1.2	**1.51**	1.12	2.03

HDL: haloperidol; AAPs: atypical antipsychotics; CCI: Charlson Comorbidity index; ICU: Intensive care unit; OLZ: olanzapine; QTP: quetiapine; RSP: risperidone

[a] Rate: number of death per 100 person-days

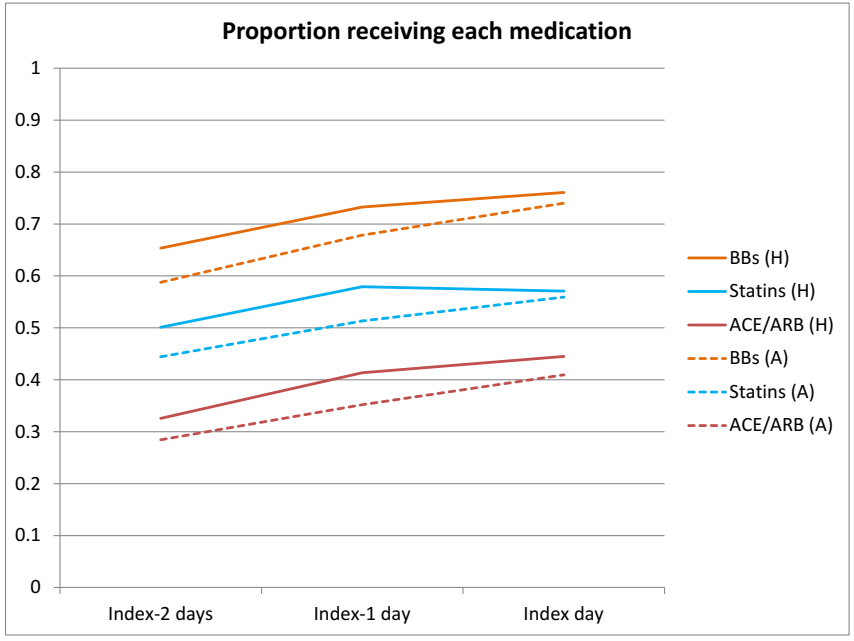
4.7 Detailed table for sensitivity analyses, based on ITT analysis with 7 days of follow-up

	Follow up	Crude result HR	95% CI		Main result HR	95% CI		Random Effects Model HR	95% CI		Conditional Cox Model HR	95% CI	
Including day 2 initiators													
ITT	7 days	**1.53**	1.30	1.80	**1.46**	1.18	1.81	**1.57**	1.22	2.02	**1.49**	1.20	1.86
AT	7 days	**1.78**	1.43	2.21	**1.96**	1.47	2.60	**2.58**	1.72	3.85	**1.97**	1.46	2.66
Different modeling assumptions													
ITT	2 days	**2.30**	1.60	3.31	**2.86**	1.66	4.92	**2.86**	1.67	4.90	**2.78**	1.62	4.76
	3 days	**1.89**	1.43	2.50	**2.05**	1.39	3.02	**2.07**	1.41	3.05	**2.25**	1.48	3.41
	5 days	**1.70**	1.35	2.14	**1.73**	1.28	2.34	**1.77**	1.30	2.40	**2.00**	1.41	2.83
	7 days	**1.51**	1.22	1.85	**1.50**	1.14	1.96	**1.54**	1.17	2.02	**1.67**	1.22	2.30
	30 days	**1.31**	1.11	1.56	**1.26**	1.01	1.56	**1.30**	1.04	1.63	**1.55**	1.15	2.10
AT	2 days	**2.26**	1.55	3.28	**2.70**	1.56	4.67	**2.70**	1.57	4.65	**2.65**	1.52	4.63
	3 days	**2.12**	1.53	2.94	**2.42**	1.55	3.79	**2.43**	1.54	3.83	**2.55**	1.52	4.28
	5 days	**2.05**	1.52	2.76	**2.14**	1.46	3.14	**2.17**	1.45	3.23	**2.62**	1.58	4.33
	7 days	**1.90**	1.43	2.53	**1.93**	1.34	2.76	**1.96**	1.34	2.85	**2.50**	1.53	4.10
	30 days	**1.83**	1.40	2.41	**1.80**	1.29	2.51	**1.83**	1.29	2.61	**2.50**	1.53	4.10

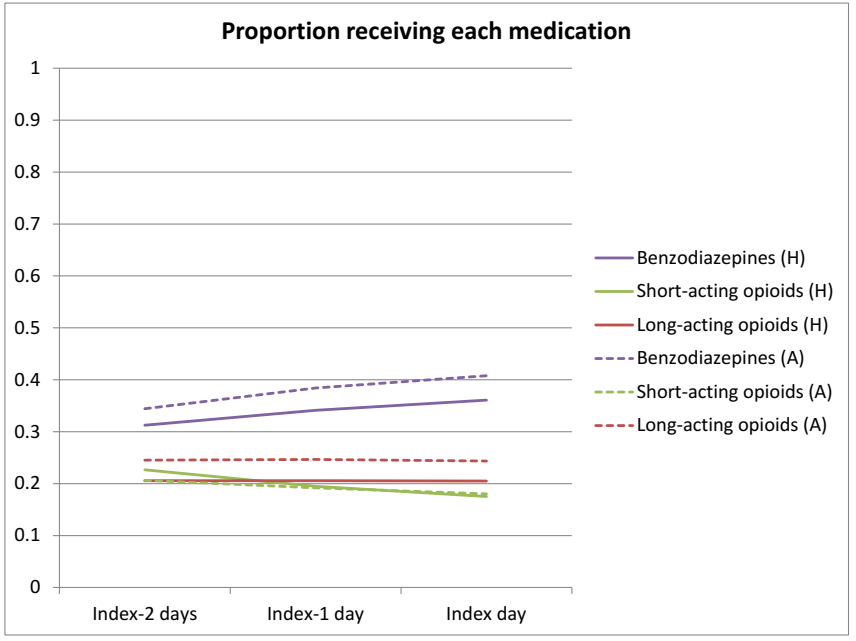
ITT: Intention-to-treat; AT: as-treated; HR: hazard ratio; CI: confidence interval

4.8 Trends of medication use before initiation of antipsychotic treatment

A. Chronic medication use



B. Opioid and benzodiazepine use



BB: beta-blockers; ACE/ARB: angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers

Each figure shows the proportion of patients before matching who received each medication from two days prior to the initiation of antipsychotic to the index date. Solid lines represent haloperidol initiators (H) and dotted lines represent atypical antipsychotic initiators (A).

Chapter 5. Conclusion

In light of the increasing use of antipsychotic medication and of its potential adverse effects on patients, the use of these drugs should be based on careful trade-offs between risks and benefits. Extrapolating safety evidence from clinical trials may not be feasible for special patient groups such as pregnant women or hospitalized elderly. This dissertation adds important pieces of scientific evidence for such patient groups. We showed how antipsychotics are utilized and how the use of antipsychotics may be associated with an increased risk of GDM in women in Medicaid. Descriptive information can help us to better understand the characteristics of patients who are using antipsychotic and also provide backgrounds for potential safety signals. We also showed that the use of haloperidol in patients with severe cardiac comorbidity could be associated with an increased risk of death in hospital compared to the use of alternative atypical antipsychotics, using a nationwide inpatient cohort. The study provides evidence to a question that had not been examined in a large inpatient cohort and borrowed information from either outpatient studies or small-scale studies. With careful interpretation and acknowledgement of limitations, these studies can help treatment decision-making in vulnerable patient groups.

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