Risk of Diabetes Hospitalization or Diabetes Drug Intensification in Patients With Depression and Diabetes Using Second-Generation Antipsychotics Compared to Other Depression Therapies

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ABSTRACT

Objective: Use of second-generation antipsychotics (SGAs) for treatment of depression has increased, and patients with depression and comorbid diabetes or cardiovascular disease are more likely to use SGAs than those without these conditions. We compared SGA and non-SGA depression pharmacotherapies on the risk of diabetes hospitalization or treatment intensification in adults with depression and preexisting diabetes.

Methods: This was a retrospective cohort study of US commercially insured adults (2009–2015 Truven MarketScan Commercial Claims and Encounters Database) aged 18–64 years old with type 2 diabetes mellitus and unipolar depression previously treated with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor. New users of SGAs versus non-SGAs, as well as specific treatments (aripiprazole, quetiapine, bupropion, mirtazapine, and tricyclic antidepressants [TCAs]) were matched on class/medication-specific high-dimensional propensity score. Cox proportional hazard models were used to compare the risk of diabetes-related hospitalization or treatment intensification.

Results: We identified 6,625 SGA (aripiprazole = 3,461; quetiapine = 1,977; other = 1,187) and 23,921 non-SGA patients for inclusion (bupropion = 15,511; mirtazapine = 1,837; TCAs = 5,989; other = 584) with a mean age of 51 years. In the matched cohort, the rate of diabetes-related hospitalization or drug intensification was 47.9 per 100 person-years in the SGA group and 43.5 per 100 person-years in the non-SGA group (adjusted hazard ratio [aHR] = 1.03; 95% CI, 0.96–1.11). When comparing treatment subgroups, the risk of events was lower for bupropion versus TCAs (aHR = 0.85; 95% CI, 0.76–0.98), quetiapine versus mirtazapine (aHR = 0.82; 95% CI, 0.67–0.99), and quetiapine versus TCAs (aHR = 0.84; 95% CI, 0.72–0.98). For other comparisons, differences were small and not statistically significant.

Conclusions: While drug-specific effects on risk of diabetes hospitalization or treatment intensification most likely guide clinical decision making, we observed only modest differences in risk. The overall impact of SGAs on diabetes control depends not only on direct effects on glucose metabolism but also on effectiveness of depression symptom relief. Future studies evaluating other diabetes outcomes (glycosylated hemoglobin, diabetes complications) are needed.

Prim Care Companion CNS Disord 2018;20(3):17m02220

To cite: Xing S, Kim S, Schumock GT, et al. Risk of diabetes hospitalization or diabetes drug intensification in patients with depression and diabetes using second-generation antipsychotics compared to other depression therapies. *Prim Care Companion CNS Disord.* 2018;20(3):17m02220.

To share: https://doi.org/10.4088/PCC.17m02220

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Use of second-generation antipsychotics (SGAs) for the treatment of depression has increased in the United States.[1] In 2009–2010, 12.5% of adult outpatient nonpsychotic depression visits included a prescription for an SGA.[1] Despite the metabolic risks previously documented with SGA use,[2,3] patients with comorbid diabetes, hyperlipidemia, or cardiovascular disease were 2 times more likely to be prescribed these medications than those without these conditions.[1] Use of SGAs in patients with comorbid diabetes may put them at higher risk for hyperglycemic events.[4]

Multiple studies[5–10] have documented the risk of new-onset diabetes associated with SGA use. However, the consequence of SGA use on diabetes control in those with preexisting diabetes is not well understood. A limited number of studies in the preexisting diabetes population have reported associations with poor diabetes outcomes[4,11–13] and improved diabetes outcomes[14,15] in SGA-treated individuals. These studies,[4,11–15] which were conducted outside the United States, primarily included patients with schizophrenia, bipolar disorder, or dementia. Two[11,12] were restricted to patients over age 64 years, and only 1 study[4] focused on SGAs exclusively (the other 5 studies compared first-generation antipsychotic [FGA] and SGA users with nonusers). Studies are needed to examine the US adult population with depression in which FGAs are not a preferred treatment option,[16] lower doses of SGAs are typically used,[16,17] and SGAs are compared to therapeutic alternatives. The objective of this study was to evaluate the comparative effects of SGAs and alternative depression pharmacotherapies on time to diabetes–related hospitalization or diabetes treatment intensification in US adults aged 18–64 years with unipolar depression and type 2 diabetes mellitus.

Clinical Points

- Use of second-generation antipsychotics (SGAs) was not associated with an increased risk of diabetes-related hospitalization or diabetes drug intensification compared to non-SGAs in patients with diabetes and depression comorbidities.
- Bupropion was associated with a 15% reduced risk of events compared to tricyclic antidepressants (TCAs).
- Quetiapine was associated with an 18% reduced risk of events compared to mirtazapine, and quetiapine was associated with a 16% reduced risk of events compared to TCAs.

METHODS

Data Source

This retrospective cohort study used the 2009–2015 Truven MarketScan Commercial Claims and Encounters Database licensed by and maintained at the University of Illinois at Chicago.[18] This administrative claims database reflects real-world treatment patterns for several million individuals who are covered by employer-sponsored private health plans across the United States.[18] The de-identified database contains information on patient demographics, medical diagnosis and procedures, and prescription drugs dispensed from outpatient pharmacies. The University of Illinois at Chicago Institutional Review Board determined that this study does meet criteria for human subject research.

Study Population

Adults aged 18–64 years who received a new prescription for an oral nonclozapine SGA (aripiprazole, asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone) or non-SGA depression medication (bupropion, mirtazapine, lithium, tricyclic antidepressants [TCAs], or thyroid hormone) between January 1, 2010, and December 30, 2015, were identified. To be included, patients must have been diagnosed with depression (any inpatient or outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 296.2x, 296.3x, 300.4, or 311 diagnoses)[19] and have received previous treatment with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor in the 365 days (ie, preindex period) before the date of first SGA or non-SGA prescription (ie, index date). Patients must also have been diagnosed with type 2 diabetes (at least 1 inpatient or 2 outpatient *ICD-9-CM* 250.x0 or 250.x2 diagnoses or at least 2 prescription fills for a diabetes drug identified by the Healthcare Effectiveness Data and Information Set[20]) during the preindex period. We required patients to have been continuously insured in the preindex period and for at least 30 days after the index date.

Patients with any previous use of a study medication and those with any prescription fill for clozapine, injectable SGA, or FGA during the preindex period were excluded. Those with any diagnosis for schizophrenia (*ICD-9-CM* 295.xx), bipolar disorder (*ICD-9-CM* 296.0x, 296.1x, 296.4x–296.8x),[21] dementia (290.xx), delusional disorder (*ICD-9-CM* 297.xx), nonorganic psychosis (*ICD-9-CM* 298.xx), autism (*ICD-9-CM* 299.0), mental retardation (*ICD-9-CM* 317.0–319.0), cerebral degeneration (*ICD-9-CM* 331.xx), Parkinson's disease (*ICD-9-CM* 332.xx), senility without mention of psychosis (*ICD-9-CM* 797.x), or thyroid disorder (*ICD-9-CM* 240.0–246.0)[22] during the preindex period were also excluded. Since inpatient medications were unavailable, patients with any hospitalizations in the 30 days prior to the index date were excluded. All *ICD-10-CM* diagnosis and procedure codes in 2015 (2.7% of all inpatient codes and 3.0% of all outpatient codes) were first mapped to *ICD-9-CM* codes using the Centers for Medicare and Medicaid Service's General Equivalence Mappings.[23]

Exposure Groups

Patients were classified as SGA or non-SGA users on the basis of their first prescription fill. We also conducted 10 pairwise contrasts directly comparing (1) quetiapine versus aripiprazole, (2) quetiapine versus mirtazapine, (3) quetiapine versus TCAs, (4) quetiapine versus bupropion, (5) bupropion versus aripiprazole, (6) bupropion versus mirtazapine, (7) bupropion versus TCAs, (8) mirtazapine versus TCAs, (9) mirtazapine versus aripiprazole, and (10) TCAs versus aripiprazole. These treatment subgroups were selected a priori on the basis of power calculations (80% power to detect a 20% difference).

Outcome

The primary outcome was time to first diabetes-related hospitalization (primary hospital discharge for diabetes [*ICD-9-CM* 250.xx]) or diabetes treatment intensification. Treatment intensification was defined as either an increase in the dose of a noninsulin diabetes medication or the addition of a new diabetes drug class. A baseline diabetes drug regimen was established for every patient on the basis of the diabetes medications patients had in possession during the preindex period. The mean daily dose (drug strength × quantity dispensed/day's supply) was calculated for each noninsulin diabetes drug. Patients were considered to have a dose increase when the mean daily dose during follow-up exceeded the baseline mean daily dose.

Follow-Up

We followed patients from the day after index drug initiation until the first occurrence of the following: (1) outcome, (2) end of continuous insurance coverage, (3) discontinuation of index drug (greater than 60-day gap in therapy), (4) addition or switch to another index drug, or (5) end of study period (December 31, 2015).

Patient and Treatment Characteristics

Baseline clinical and demographic characteristics were assessed during the preindex period, including depression and diabetes history, cardiovascular and psychiatric

comorbidities, health care utilization, and provider care team. We used the Massachusetts General Hospital-Antidepressant (MGH-AD)[24] score as a proxy for depression severity and the adapted Diabetes Complications Severity Index (aDCSI)[25] score as a proxy for diabetes severity. The MGH-AD score has been used in other depression studies[22,26,27] wherein higher scores indicate more severe depression. The score is calculated by assigning 1 point for each adequate trial (≥ 2 prescription fills for the same antidepressant) and half a point for extended duration of use (≥ 3 fills of the same antidepressant) or dose titration (prescription fill for the same antidepressant at a higher dose).[24] The aDCSI converts diagnostic codes into a single summary score on the basis of 7 categories of diabetes complications: retinopathy; nephropathy; neuropathy; cerebrovascular, cardiovascular, or peripheral vascular disease; and metabolic.[25,28] The aDCSI predicts diabetes hospitalizations and is validated against the original DCSI,[25] which was developed to model diabetes severity and where higher scores predict increased mortality, hospitalizations, and health care utilization.[28]

High-dimensional propensity score matching. We used high-dimensional propensity score (HDPS) matching to create similar exposure groups and reduce the potential for selection bias and confounding. The HDPS algorithm is designed to control for observed and unobserved confounders in large database studies[29] and has been used in previous antipsychotic safety studies.[30,31] The HDPS algorithm empirically selected the top 500 covariates across 6 data dimensions: (1) inpatient diagnoses, (2) inpatient procedures, (3) outpatient diagnoses, (4) outpatient procedures, (5) outpatient medications, and (6) facility and health care provider visit type. These covariates were combined with demographic (age, sex, geographic region, index year) and investigator-predefined variables (MGH-AD score, aDCSI score, provider care team, unique classes of diabetes drugs used, and baseline diabetes regimen) to calculate the final HDPS.

Patients taking SGAs were matched to non-SGA users by their HDPS for the between-class comparison. For the 10 subgroup contrasts, a new HDPS was generated for each pairwise comparison (eg, propensity of aripiprazole versus quetiapine treatment). Patients were matched in a 1:1 ratio without replacement by their HDPS score with the nearest neighbor matching algorithm at 0.2 caliper of the standard deviation of the logit of the HDPS.[32,33]

Statistical Analysis

Descriptive statistics characterized the patient population. To assess the balance of match, we examined propensity score distributions to ensure that there was sufficient overlap between 2 comparator groups after HDPS matching. Absolute standard differences were used to evaluate balance of potential confounders (absolute standard differences less than 0.1 indicated adequate balance between groups).[32,34] Cox proportional hazard models were used to calculate the HDPS-adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the outcome.

We conducted 5 sensitivity analyses to evaluate the impact of study design decisions on the results. Since effects of SGAs on glycemic control may continue after drug discontinuation,[35–37] we conducted 2 sensitivity analyses wherein patients who switched, added, or discontinued their index drug were followed for an additional 90 or 180 days to account for carryover effects. In the third sensitivity analysis, patients were not considered at risk for an event until 30 days after the index date. In the primary analysis, patients were considered to be at risk for an event the day after drug initiation since prior research[11,38] suggests that the effect of SGAs on glycemic control can occur rapidly, with the highest risk period during early therapy. In the fourth sensitivity analysis, we changed the definition of treatment intensification to include only the addition of a new drug class (excluding dose increases).[39–41] We evaluated diabetes-related hospitalization only (excluding treatment intensification) in the fifth sensitivity analysis.

In the post hoc analysis, we examined the mean daily doses and peak daily doses (maximum mean daily dose during follow-up) of aripiprazole, quetiapine, mirtazapine, bupropion, and specific TCAs used. SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) and Stata version 14 (StataCorp LLC, College Station, Texas) were used for data analysis. The SAS HDPS macro and the nearest neighbor matching macro were obtained from the Pharmacoepidemiology Toolbox.[42]

RESULTS

Before match, 6,625 SGA initiators and 23,921 non-SGA initiators met inclusion criteria (see Appendix 1 for study population selection). The most frequently prescribed SGAs were aripiprazole (52.4%) and quetiapine (29.8%), and the most frequently prescribed non-SGAs were bupropion (64.8%), TCAs (25.0%), and mirtazapine (7.7%). Among TCAs, amitriptyline (60.3%) and nortriptyline (21.3%) were most commonly used. See Appendix 2 for medications included at cohort entry.

Patient characteristics at baseline are shown in Table 1. Doses of aripiprazole, quetiapine, and TCAs used were low. The median mean daily doses for aripiprazole and quetiapine were 5 (interquartile range [IQR] = 2–5) and 50 (IQR = 25–100) mg/d, respectively, and median mean daily doses for specific TCAs were all less than 100 mg/d (dosing is shown in Appendix 3). The median peak mean daily doses used were similar to median mean daily doses.

After match, there were 6,465 SGA and 6,465 non-SGA initiators, of whom 1,384 (47.9 per 100 person-years) and 1,461 (43.5 per 100 person-years) developed the event, respectively (Table 2). Patient characteristics and balance of baseline variables after HDPS match are shown in Appendix 4. For subgroup comparisons, the incidence of diabetes hospitalization or drug intensification varied between 40.9 and 57.5 per 100 person-years (Table 2). Diabetes-related hospitalization only was rare and occurred in 39 SGA initiators (10.8 per 1,000 person-years) and 44 non-SGA

Table 1. Baseline Patient Demographic and Clinical Characteristics Before Match

Characteristic	SGA (n = 6,625)	Non-SGA (n = 23,921)	Specific SGAs		Specific Non-SGAs		
			Quetiapine (n = 1,977)	Aripiprazole (n = 3,461)	Mirtazapine (n = 1,837)	TCAs (n = 5,989)	Bupropion (n = 15,511)
Demographic							
Age, y							
Mean (SD)	50.6 (9.7)	50.9 (9.7)	50.4 (9.9)	51.0 (9.2)	52.4 (9.5)	51.4 (9.3)	50.6 (9.8)
Median (IQR)	53.0 (45.0, 58.0)	53.0 (45.0, 59.0)	52.0 (44.0, 58.0)	53.0 (45.0, 58.0)	55.0 (48.0, 60.0)	53.0 (46.0, 59.0)	53.0 (45.0, 58.0)
Age group, n (%)							
18–29	241 (3.6)	758 (3.2)	76 (3.8)	102 (2.9)	65 (3.5)	149 (2.5)	522 (3.4)
30–39	640 (9.7)	2,451 (10.2)	189 (9.6)	315 (9.1)	118 (6.4)	564 (9.4)	1,708 (11.0)
40–49	1,629 (24.6)	5,841 (24.4)	519 (26.3)	818 (23.6)	390 (21.2)	1,470 (24.5)	3,820 (24.6)
50–64	4,115 (62.1)	14,871 (62.2)	1,193 (60.3)	2,226 (64.3)	1,264 (68.8)	3,806 (63.5)	9,461 (61.0)
Male, n (%)	2,327 (35.1)	7,675 (32.1)	709 (35.9)	1,141 (33.0)	791 (43.1)	1,639 (27.4)	5,132 (33.1)
Index year, n (%)							
2010	1,384 (20.9)	4,268 (17.8)	419 (21.2)	692 (20.0)	355 (19.3)	1,072 (17.9)	2,709 (17.5)
2011	1,349 (20.4)	4,452 (18.6)	382 (19.3)	729 (21.1)	309 (16.8)	1,172 (19.6)	2,857 (18.4)
2012	1,283 (19.4)	4,652 (19.4)	359 (18.2)	686 (19.8)	355 (19.3)	1,163 (19.4)	3,033 (19.6)
2013	930 (14.0)	3,472 (14.5)	276 (14.0)	484 (14.0)	246 (13.4)	886 (14.8)	2,256 (14.5)
2014	901 (13.6)	3,779 (15.8)	282 (14.3)	482 (13.9)	306 (16.7)	901 (15.0)	2,488 (16.0)
2015	778 (11.7)	3,298 (13.8)	259 (13.1)	388 (11.2)	266 (14.5)	795 (13.3)	2,168 (14.0)
Depression and Psychiatric History							
Depression severity,[a] n (%)							
MGH-AD score ≤ 1	1,137 (17.2)	5,011 (20.9)	459 (23.2)	392 (11.3)	484 (26.3)	1,350 (22.5)	3,049 (19.7)
MGH-AD score 1.5–2	3,837 (57.9)	15,062 (63.0)	1,016 (51.4)	2,164 (62.5)	976 (53.1)	3,635 (60.7)	10,103 (65.1)
MGH-AD score 2.5–3	744 (11.2)	2,063 (8.6)	233 (11.8)	405 (11.7)	175 (9.5)	531 (8.9)	1,298 (8.4)
MGH-AD score ≥ 3.5	907 (13.7)	1,785 (7.5)	269 (13.6)	500 (14.4)	202 (11.0)	473 (7.9)	1,061 (6.8)
Antidepressant use, n (%)							
SSRI	4,636 (70.0)	18,671 (78.1)	1,460 (73.8)	2,297 (66.4)	1,401 (76.3)	4,458 (74.4)	12,395 (79.9)
SNRI	3,215 (48.5)	7,899 (33.0)	895 (45.3)	1,821 (52.6)	687 (37.4)	2,316 (38.7)	4,655 (30.0)
Serotonin modulator	1,259 (19.0)	2,985 (12.5)	428 (21.6)	610 (17.6)	366 (19.9)	784 (13.1)	1,763 (11.4)
Recency of antidepressant use,[b] n (%)							
Adjunctive therapy	5,246 (79.2)	14,964 (62.6)	1,500 (75.9)	2,811 (81.2)	1,151 (62.7)	3,811 (63.6)	9,594 (61.9)
Recent	1,264 (19.1)	7,802 (32.6)	428 (21.6)	610 (17.6)	608 (33.1)	1,797 (30.0)	5,247 (33.8)
Former	115 (1.7)	1,155 (4.8)	49 (2.5)	40 (1.2)	78 (4.2)	381 (6.4)	670 (4.3)
Psychiatric comorbidity,[c] n (%)							
Anxiety disorder	2,859 (43.2)	8,241 (34.5)	927 (46.9)	1,409 (40.7)	863 (47.0)	2,091 (34.9)	5,077 (32.7)
Alcohol abuse/dependence	270 (4.1)	669 (2.8)	109 (5.5)	114 (3.3)	103 (5.6)	158 (2.6)	394 (2.5)
Substance abuse/dependence	306 (4.6)	794 (3.3)	141 (7.1)	117 (3.4)	107 (5.8)	255 (4.3)	423 (2.7)
Suicide or intentional self-inflicted injury	134 (2.0)	199 (0.8)	55 (2.8)	54 (1.6)	48 (2.6)	38 (0.6)	109 (0.7)
Diabetes and Cardiovascular History							
Diabetes severity,[d] n (%)							
Mild (aDCSI score = 0)	3,634 (54.9)	13,326 (55.7)	1,098 (55.5)	1,896 (54.8)	867 (47.2)	2,771 (46.3)	9,325 (60.1)
Moderate (aDCSI score = 1–3)	2,597 (39.2)	9,171 (38.3)	747 (37.8)	1,380 (39.9)	767 (41.8)	2,751 (45.9)	5,454 (35.2)
Severe (aDCSI score ≥ 4)	394 (5.9)	1,424 (6.0)	132 (6.7)	185 (5.3)	203 (11.1)	467 (7.8)	732 (4.7)
Diabetes regimen, n (%)							
No antidiabetic drug use	2,197 (33.2)	7,233 (30.2)	708 (35.8)	1,080 (31.2)	651 (35.4)	1,886 (31.5)	4,501 (29.0)
OAD only	2,649 (40.0)	9,762 (40.8)	761 (38.5)	1,419 (41.0)	658 (35.8)	2,347 (39.2)	6,519 (42.0)
Insulin only	686 (10.4)	2,717 (11.4)	206 (10.4)	347 (10.0)	243 (13.2)	676 (11.3)	1,738 (11.2)
Non-insulin injectable only	66 (1.0)	214 (0.9)	15 (0.8)	43 (1.2)	13 (0.7)	53 (0.9)	141 (0.9)
Insulin + OAD only	683 (10.3)	2,644 (11.1)	198 (10.0)	364 (10.5)	193 (10.5)	752 (12.6)	1,650 (10.6)
OAD + non-insulin injectable	211 (3.2)	803 (3.4)	62 (3.1)	123 (3.6)	49 (2.7)	154 (2.6)	578 (3.7)
Insulin + non-insulin injectable	36 (0.5)	150 (0.6)	6 (0.3)	23 (0.7)	8 (0.4)	31 (0.5)	108 (0.7)
OAD + insulin + non-insulin injectable	97 (1.5)	398 (1.7)	21 (1.1)	62 (1.8)	22 (1.2)	90 (1.5)	276 (1.8)
Diabetes drug class, n (%)							
Metformin	2,743 (41.4)	10,649 (44.5)	795 (40.2)	1,494 (43.2)	692 (37.7)	2,567 (42.9)	7,136 (46.0)
Sulfonylurea	1,000 (15.1)	4,006 (16.7)	293 (14.8)	508 (14.7)	296 (16.1)	1,064 (17.8)	2,581 (16.6)
Thiazolidinedione	513 (7.7)	1,672 (7.0)	135 (6.8)	289 (8.4)	123 (6.7)	374 (6.2)	1,140 (7.3)
α-Glucosidase inhibitor	15 (0.2)	46 (0.2)	0 (0.0)	12 (0.3)	3 (0.2)	13 (0.2)	27 (0.2)
Meglitinide	41 (0.6)	138 (0.6)	10 (0.5)	28 (0.8)	12 (0.7)	33 (0.6)	89 (0.6)
SGLT2 inhibitor	99 (1.5)	343 (1.4)	30 (1.5)	57 (1.6)	26 (1.4)	63 (1.1)	248 (1.6)
DPP-4 inhibitor	722 (10.9)	2,468 (10.3)	199 (10.1)	405 (11.7)	181 (9.9)	623 (10.4)	1,611 (10.4)
GLP-1 agonist	396 (6.0)	1,503 (6.3)	104 (5.3)	243 (7.0)	88 (4.8)	315 (5.3)	1,062 (6.8)
Amylin analog	14 (0.2)	63 (0.3)	0 (0.0)	8 (0.2)	4 (0.2)	13 (0.2)	42 (0.3)
Insulin	1,502 (22.7)	5,909 (24.7)	431 (21.8)	796 (23.0)	466 (25.4)	1,549 (25.9)	3,772 (24.3)

(continued)

Table 1 (continued). Baseline Patient Demographic and Clinical Characteristics Before Match

Characteristic	SGA (n = 6,625)	Non-SGA (n = 23,921)	Specific SGAs		Specific Non-SGAs		
			Quetiapine (n = 1,977)	Aripiprazole (n = 3,461)	Mirtazapine (n = 1,837)	TCAs (n = 5,989)	Bupropion (n = 15,511)
Medical comorbidity,[c] n (%)							
Hypertension	4,361 (65.8)	15,725 (65.7)	1,303 (65.9)	2,285 (66.0)	1,291 (70.3)	4,153 (69.3)	9,942 (64.1)
Coronary atherosclerosis and other heart diseases	743 (11.2)	2,333 (9.8)	220 (11.1)	390 (11.3)	267 (14.5)	649 (10.8)	1,384 (8.9)
Angina pectoris	189 (2.9)	564 (2.4)	66 (3.3)	80 (2.3)	67 (3.6)	158 (2.6)	327 (2.1)
Myocardial infarction or unstable angina	156 (2.4)	532 (2.2)	57 (2.9)	78 (2.3)	85 (4.6)	141 (2.4)	299 (1.9)
Disorders of lipid metabolism	4,220 (63.7)	15,611 (65.3)	1,265 (64.0)	2,245 (64.9)	1,161 (63.2)	3,947 (65.9)	10,123 (65.3)
Congestive heart failure	259 (3.9)	832 (3.5)	76 (3.8)	125 (3.6)	140 (7.6)	244 (4.1)	435 (2.8)
Obesity diagnosis	1,437 (21.7)	5,934 (24.8)	409 (20.7)	782 (22.6)	343 (18.7)	1,608 (26.8)	3,844 (24.8)
Resource Utilization							
Outpatient depression visits							
Mean (SD)	6.0 (8.7)	4.3 (7.0)	5.2 (7.3)	6.4 (9.2)	5.0 (7.5)	3.6 (6.2)	4.5 (7.1)
Median (IQR)	3.0 (1.0, 7.0)	2.0 (1.0, 4.0)	3.0 (1.0, 6.0)	3.0 (2.0, 7.0)	3.0 (1.0, 5.0)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)
Psychiatric hospital admissions, n (%)							
0	6,347 (95.8)	23,538 (98.4)	1,863 (94.2)	3,349 (96.8)	1,777 (96.7)	5,886 (98.3)	15,298 (98.6)
1	237 (3.6)	333 (1.4)	96 (4.9)	99 (2.9)	50 (2.7)	88 (1.5)	188 (1.2)
≥ 2	41 (0.6)	50 (0.2)	18 (0.9)	13 (0.4)	10 (0.5)	15 (0.3)	25 (0.2)
Outpatient diabetes visits							
Mean (SD)	5.7 (6.3)	6.1 (6.6)	5.6 (5.9)	5.7 (6.5)	6.7 (8.4)	6.7 (7.1)	5.7 (6.2)
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 8.0)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	5.0 (2.0, 8.0)	5.0 (2.0, 9.0)	4.0 (2.0, 7.0)
Diabetes hospital admissions, n (%)							
0	6,577 (99.3)	23,711 (99.1)	1,957 (99.0)	3,443 (99.5)	1,810 (98.5)	5,913 (98.7)	15,409 (99.3)
1	35 (0.5)	185 (0.8)	15 (0.8)	12 (0.3)	20 (1.1)	65 (1.1)	95 (0.6)
≥ 2	13 (0.2)	25 (0.1)	5 (0.3)	6 (0.2)	7 (0.4)	11 (0.2)	7 (0.0)
Provider Characteristics							
Provider care team, n (%)							
PCP only	2,726 (41.1)	13,203 (55.2)	905 (45.8)	1,359 (39.3)	758 (41.3)	3,587 (59.9)	8,623 (55.6)
Psychiatry only	175 (2.6)	560 (2.3)	46 (2.3)	91 (2.6)	75 (4.1)	126 (2.1)	344 (2.2)
Endocrinology only	16 (0.2)	71 (0.3)	4 (0.2)	7 (0.2)	3 (0.2)	12 (0.2)	52 (0.3)
PCP + psychiatry	2,384 (36.0)	4,977 (20.8)	667 (33.7)	1,269 (36.7)	624 (34.0)	961 (16.0)	3,268 (21.1)
PCP + endocrinology	344 (5.2)	2,009 (8.4)	83 (4.2)	200 (5.8)	114 (6.2)	539 (9.0)	1,243 (8.0)
Psychiatry + endocrinology	38 (0.6)	103 (0.4)	5 (0.3)	27 (0.8)	6 (0.3)	15 (0.3)	76 (0.5)
PCP + psychiatry + endocrinology	489 (7.4)	1,159 (4.8)	140 (7.1)	254 (7.3)	132 (7.2)	239 (4.0)	742 (4.8)
Unspecified or other specialist	453 (6.8)	1,839 (7.7)	127 (6.4)	254 (7.3)	125 (6.8)	510 (8.5)	1,163 (7.5)

[a]The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns 1 point for each adequate antidepressant trial (at least 2 prescription fills for the same antidepressant) and half a point for each extended duration of use (at least 3 prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b]Adjunctive therapy = ≥ 30 days of overlap between index drug and other antidepressant medication (eg, selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date but less than 30 days of overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c]Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software for *ICD-9-CM* (http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp).

[d]The adapted Diabetes Complications Severity Index (aDCSI) is a claims-based measure of diabetes severity where higher scores indicate more severe disease. The aDCSI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity; higher scores predict mortality, hospitalizations, and higher health care utilization.

Abbreviations: aDCSI = adapted Diabetes Complications Severity Index, DPP-4 = dipeptidyl peptidase 4, GLP-1 = glucagon-like peptide 1, IQR = interquartile range, MGH-AD = Massachusetts General Hospital-Antidepressant version, OAD = oral antidiabetic drug, PCP = primary care provider, SGA = second-generation antipsychotic, SGLT2 = sodium-glucose cotransporter 2, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCAs = tricyclic antidepressants.

initiators (10.3 per 1,000 person-years). Appendix 5 provides the incidence of diabetes-related hospitalization for all comparisons.

Risk of diabetes-related hospitalization or drug intensification was not increased with SGA use compared to non-SGA use (aHR = 1.03; 95% CI, 0.96–1.11) (Table 3, Figure 1). The specific breakdown of diabetes-related hospitalization by *ICD-9-CM* codes is shown in Appendix 6. In the primary analysis, risk was lower comparing quetiapine versus mirtazapine (aHR = 0.82; 95% CI, 0.67–0.99), quetiapine versus TCAs (aHR = 0.84; 95% CI, 0.72–0.98), and bupropion versus TCAs (aHR = 0.85; 95% CI, 0.76–0.86). While risk of the outcome was numerically lower comparing quetiapine versus aripiprazole (aHR = 0.86; 95% CI, 0.73–1.00), results were not statistically significant. For the remaining comparisons, results were not significantly different, and any differences in effect size were small. Alteration of the at-risk window (sensitivity analyses 1 to 3) and the outcome definition to diabetes-related hospitalization or addition of new drug class only (sensitivity analysis 4) did not change our main findings. However, when the outcome was diabetes-related hospitalization only (sensitivity analysis 5), the magnitude or direction of effect did change. In particular, mirtazapine was associated with a 2.7 times higher risk of diabetes-related hospitalization compared to TCAs (aHR = 2.66; 95% CI, 1.11–6.37). For all

Table 2. Number of Events and Incidence Rate of Diabetes Hospitalization or Diabetes Drug Intensification Among Matched Groups of Patients

Match	Treatment	Number of Patients	Number of Events	Total Person-Years of Follow-Up	Incidence Rate (95% CI) per 100 Person-Years
Between SGAs and Non-SGAs					
SGAs vs Non-SGAs	SGA	6,465	1,384	2,887	47.9 (45.5–50.5)
	Non-SGA	6,465	1,461	3,359	43.5 (41.3–45.8)
Between-Treatment Subgroups					
1. QUE vs ARI	QUE	1,543	298	680	43.8 (39.1–49.1)
	ARI	1,543	350	679	51.6 (46.4–57.3)
2. QUE vs MIR	QUE	1,110	202	470	43.0 (37.5–49.4)
	MIR	1,110	233	420	55.5 (48.8–63.1)
3. QUE vs TCA	QUE	1,564	299	674	44.4 (39.6–49.1)
	TCA	1,564	342	622	55.0 (49.5–61.2)
4. QUE vs BUP	QUE	1,884	363	815	44.5 (40.2–49.4)
	BUP	1,884	430	1,004	42.8 (39.0–47.1)
5. BUP vs ARI	BUP	3,325	787	1,893	41.6 (38.8–44.6)
	ARI	3,325	786	1,584	49.6 (46.3–53.2)
6. BUP vs MIR	BUP	1,725	371	907	40.9 (36.9–45.3)
	MIR	1,725	347	658	52.8 (47.5–58.6)
7. BUP vs TCA	BUP	5,021	1,146	2,718	42.2 (39.8–44.7)
	TCA	5,021	1,133	1,969	57.5 (54.3–61.0)
8. MIR vs TCA	MIR	1,449	289	550	52.5 (46.8–59.0)
	TCA	1,449	312	584	53.4 (47.8–59.7)
9. MIR vs ARI	MIR	1,209	259	462	56.1 (49.6–63.3)
	ARI	1,209	281	561	50.1 (44.6–56.3)
10. TCA vs ARI	TCA	2,285	511	938	54.5 (49.9–59.4)
	ARI	2,285	540	1,059	51.0 (46.9–55.5)

Abbreviations: ARI = aripiprazole, BUP = bupropion, CI = confidence interval, MIR = mirtazapine, QUE = quetiapine, SGA = second-generation antipsychotic, TCA = tricyclic antidepressant.

Table 3. Adjusted Hazard Ratios (95% CI) of Diabetes Hospitalization or Diabetes Drug Intensification Comparing SGA and Non-SGA Depression Medications: Primary and Sensitivity Analyses

		Sensitivity Analysis				
Exposure vs Reference	Primary Analysis	90-Day Exposure Window Extension	180-Day Exposure Window Extension	30-Day Lag	Diabetes-Related Hospitalization or Addition of New Drug Class	Diabetes-Related Hospitalization Only
SGA vs Non-SGA	1.03 (0.96–1.11)	1.06 (0.99–1.13)	1.07 (1.01–1.14)	1.02 (0.96–1.10)	1.04 (0.96–1.13)	1.03 (0.67–1.58)
1. QUE vs ARI	0.86 (0.73–1.00)	0.92 (0.80–1.05)	0.91 (0.80–1.05)	0.94 (0.80–1.10)	0.85 (0.72–1.00)	1.03 (0.45–2.34)
2. QUE vs MIR	0.82 (0.67–0.99)	0.80 (0.68–0.95)	0.81 (0.69–0.96)	0.89 (0.73–1.08)	0.88 (0.72–1.09)	0.61 (0.23–1.57)
3. QUE vs TCA	0.84 (0.72–0.98)	0.87 (0.76–1.00)	0.85 (0.74–0.97)	0.89 (0.76–1.05)	0.88 (0.74–1.04)	1.36 (0.52–3.58)
4. QUE vs BUP	0.96 (0.84–1.11)	1.06 (0.93–1.20)	1.07 (0.95–1.22)	0.97 (0.84–1.12)	0.97 (0.84–1.13)	1.90 (0.85–4.26)
5. BUP vs ARI	0.91 (0.82–1.00)	0.88 (0.80–0.96)	0.86 (0.79–0.94)	0.93 (0.85–1.03)	0.87 (0.78–0.97)	0.64 (0.33–1.23)
6. BUP vs MIR	0.90 (0.78–1.05)	0.81 (0.70–0.92)	0.80 (0.70–0.91)	0.98 (0.85–1.14)	0.89 (0.80–1.05)	0.49 (0.24–1.00)
7. BUP vs TCA	0.85 (0.78–0.92)	0.80 (0.74–0.87)	0.76 (0.70–0.81)	0.87 (0.80–0.95)	0.86 (0.79–0.94)	0.82 (0.47–1.44)
8. MIR vs TCA	0.95 (0.81–1.12)	1.02 (0.88–1.18)	1.00 (0.87–1.15)	0.92 (0.78–1.09)	0.92 (0.78–1.10)	2.66 (1.11–6.37)
9. MIR vs ARI	1.02 (0.86–1.20)	1.08 (0.92–1.26)	1.11 (0.96–1.29)	1.00 (0.84–1.20)	0.98 (0.82–1.17)	1.70 (0.65–4.48)
10. TCA vs ARI	1.02 (0.91–1.16)	1.05 (0.94–1.18)	1.10 (0.99–1.22)	1.01 (0.89–1.15)	1.00 (0.88–1.14)	0.97 (0.43–2.17)

Abbreviations: ARI = aripiprazole, BUP = bupropion, CI = confidence interval, HR = hazard ratio, MIR = mirtazapine, QUE = quetiapine, SGA = second-generation antipsychotic, TCA = tricyclic antidepressant.

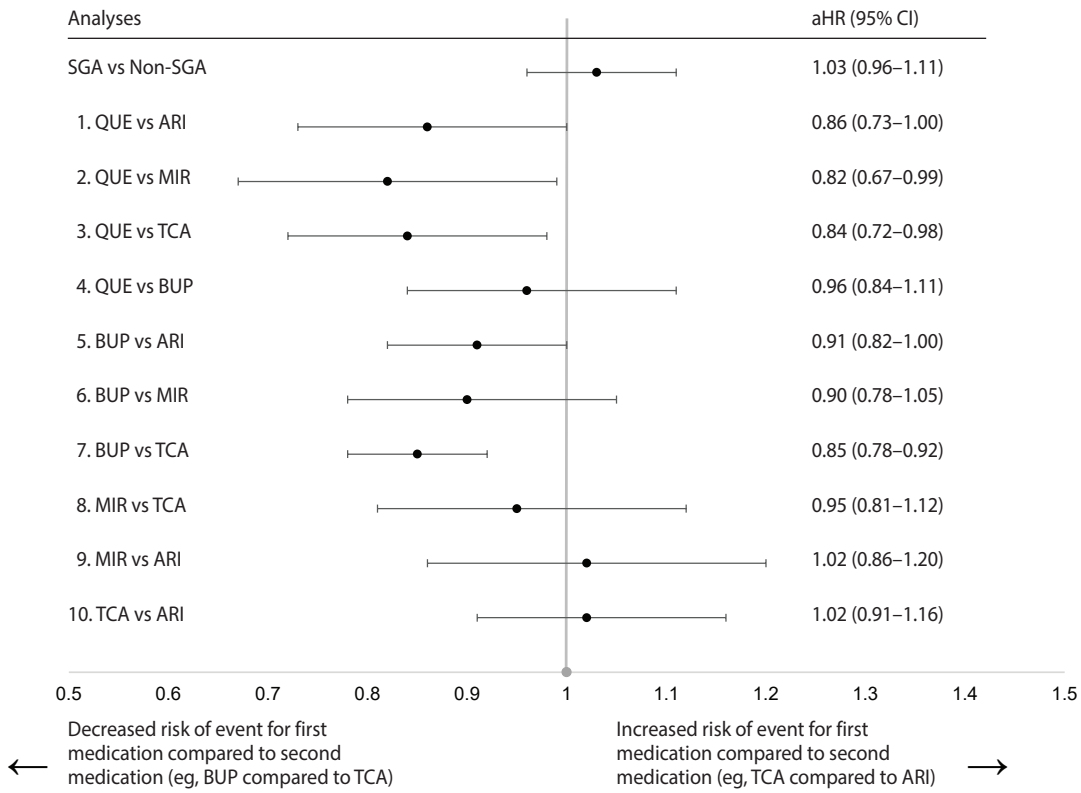
other comparisons, the CIs were wide, and results were not statistically significant.

DISCUSSION

This study is the first to directly compare SGA and non-SGA depression therapies on the risk of diabetes-related hospitalization or drug intensification in a US insured population with unipolar depression and preexisting diabetes. As a class, SGA use was not associated with an increased risk of events compared to non-SGA use. When comparing specific treatments, bupropion was associated with a small reduction (15%) in risk of the outcome compared to TCAs; quetiapine was associated with an 18% and 16% lower risk of the outcome compared to mirtazapine and TCAs, respectively. Differences between other treatments were small and not statistically significant.

The reduced risk of events comparing bupropion versus TCAs is not unexpected. In randomized studies involving patients with diabetes and depression, bupropion lowered glycosylated hemoglobin (HbA_{1c}) through improvements in depression symptoms and reductions in body weight,[43] while nortriptyline did not improve HbA_{1c} compared to placebo.[44] Path analysis revealed that nortriptyline directly

Figure 1. Hazard Ratio Plot Comparing Risk of Diabetes-Related Hospitalization or Diabetes Drug Intensification in Patients Using Second-Generation Antipsychotic and Non–Second-Generation Antipsychotic Depression Medications



Abbreviations: aHR = adjusted hazard ratio, ARI = aripiprazole, BUP = bupropion, MIR = mirtazapine, QUE = quetiapine, SGA = second-generation antipsychotic, TCA = tricyclic antidepressant.

increased HbA_{1c} but indirectly reduced HbA_{1c} through improvements in depression symptoms, and overall effects on glycemic control were similar to placebo.[44] Similarly, SGAs may negatively impact HbA_{1c} through biochemical effects and weight gain[3,45,46]; however, favorable effects on depression may mitigate these effects. The reduced risk of events observed with quetiapine compared to mirtazapine and TCAs could plausibly be related to improvements in depression symptoms. Quetiapine exhibits antidepressant properties even at the low doses observed in our study; quetiapine 50 mg/d reduces depression symptoms compared to placebo.[47] Additionally, previous studies have identified a dose-response effect with quetiapine, where doses > 150 mg are associated with higher diabetes risk[48] and > 400 mg are associated with increased HbA_{1c}.[49] Also, mirtazapine increases appetite and body weight,[50] and TCAs, although effective for depression at low doses (< 100 mg/d as seen in our study),[51] may have been used to treat diabetic neuropathy rather than depression. The direct comparative effects between quetiapine, mirtazapine, and TCAs on diabetes and depression at these doses are unknown and require future study.

When we examined the risk of diabetes-related hospitalization only, results deviated from our primary analysis. The small number of events and low incidence rate for the outcome resulted in larger effect sizes with imprecise estimates. As a class, the risk of diabetes-related hospitalization in SGA users was low (10.8 per 1,000 person-years) and comparable to a previous study.[4] In Canadian and UK patients aged 18–65 years with preexisting diabetes who used antipsychotics (FGAs or SGAs), risk of hyperglycemic emergencies was 11.5 in 1,000 person-years.[4] While we did observe a 2.7 times higher risk of diabetes-related hospitalization with mirtazapine compared to TCAs, and mirtazapine has been associated with a higher risk of weight gain,[52] these results may be related to the rareness of the event and multiple testing rather than a true causal effect.

While most studies[11–15] in patients with preexisting diabetes have compared antipsychotics (FGAs or SGAs) with nonusers, our results support the need to evaluate specific SGAs individually. In the only other study[4] that evaluated within-class comparative effects of antipsychotics on diabetes, risk of hyperglycemic emergencies was not significantly different among quetiapine, risperidone, olanzapine, or FGAs in patients aged 18–65 years with diabetes. We were unable to examine risperidone and olanzapine due to the small sample size, and there is a need for further research on the comparative impact of SGAs.

Limitations

Like other administrative claims studies, limitations include possible misclassification of exposure, diagnosis, outcome, and covariates. While patients have a diagnosis for depression, they may have been using study medications for other indications (eg, bupropion for smoking cessation, TCAs for diabetic neuropathy). There is a potential for confounding by indication wherein patients at higher risk of diabetic complications may be preferentially prescribed non-SGA over SGA therapies due to the anticipated metabolic risks associated with SGAs. In addition, confounding by disease severity may occur wherein patients who have more severe depression may be more likely to be prescribed SGA therapy[53,54] and are also at higher risk for diabetic hospitalizations.[28] Also, many variables such as HbA_{1c}, weight status, and other laboratory data are unavailable in our database. We attempted to control for unmeasured confounders, disease severity, and diabetes severity at baseline via HDPS matching.

Given that guidelines recommend that patients taking SGAs should be closely monitored for metabolic changes, there could be detection bias wherein patients taking SGAs are more closely monitored for glycemic changes and, therefore, are more likely to have therapeutic escalations compared to those not being as closely monitored. However, given that both cohorts have preexisting diabetes and should be closely monitored on glycemic control regardless of SGA use, we anticipate that this bias would be smaller than in patients without diabetes. Also, we conducted 10 pairwise comparisons but did not adjust for multiple comparisons since we were more interested in the magnitude of effect rather than statistical significance and wanted to explore potential leads that should be further explored in other research settings given the lack of information on this topic.[55] In addition, while we achieved 80% power to detect a 20% difference in the composite outcome for all treatment comparisons, diabetes hospitalizations only was a rare event for which analysis should be considered exploratory.

CONCLUSION

In summary, there is a lack of strong evidence for selection of 1 medication over another in terms of risk of diabetes-related hospitalization or diabetes drug intensification. There is strong evidence that SGAs increase the risk of diabetes[5–10]; however, our understanding on how these medications affect existing diabetes is limited. Whether these drugs should be used in this population will depend not only on their safety profile, but also on their effectiveness for depression and the ability to safely monitor patients in clinical practice. Improvement of depression may indirectly lead to improved glycemic control as patients are better able to manage their diabetes.[43,56–58] Importantly, patients with suboptimal glycemic control may not necessarily receive treatment intensification if changes in HbA_{1c} are small, if patients are nonadherent to diabetes therapy, or due to therapeutic inertia or other reasons. Physicians may also choose to discontinue SGA therapy or use low doses in patients who gain weight or have small increases in HbA_{1c}. Therefore, future studies are needed to determine the impact of these therapies on other diabetes outcomes (eg, HbA_{1c}, diabetic complications, mortality). While this study focused on diabetes, SGAs also have various other metabolic (eg, weight gain, hyperlipidemia) and nonmetabolic side effects (eg, extrapyramidal symptoms) that may vary by drug and are also important to study in the diabetes population.

Submitted: September 8, 2017; accepted December 18, 2017.

Published online: May 10, 2018.

Potential conflicts of interest: **Dr Touchette** has received research funding from Pfizer, Sunovion, and Takeda. **Drs Xing**, **Kim**, **Schumock**, **Calip**, **Leow**, and **Lee** report no conflicts of interest related to the subject of this article.

Funding/support: Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under award no. F31MH114465. The University of Illinois at Chicago provided material support for access to the Truven MarketScan Commercial Claims and Encounters Database.

Role of the sponsor: The sponsor provided no input regarding the design or conduct of the study; collection, management, analysis, or interpretation of data; or preparation, review, or approval of the manuscript.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional information: Information on the Truven MarketScan Commercial Claims and Encounters Database can be found at http://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Risk of Diabetes Hospitalization or Diabetes Drug Intensification in Patients With Depression and Diabetes Using Second-Generation Antipsychotics Compared to Other Depression Therapies

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DOI Number: https://doi.org/10.4088/PCC.17m02220

List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1. Selection of Study Population

Inclusion/Exclusion Criteria	Excluded (N)	Total (N)
1) Included patients 18-64 years with any prescription for an oral non-clozapine SGA[a] or an alternative non-SGA depression therapy (bupropion, lithium, mirtazapine, TCA[b] or thyroid hormone) between January 1, 2010 and December 30, 2015.		4,323,666
2) Excluded patients with any previous fill for a SGA or non-SGA therapy within the pre-index period (365 days prior to first SGA or non-SGA prescription fill) or who initiated both a SGA and a non-SGA medication on the same day.	656,104	3,667,562
3) Excluded patients with any gap in medical or pharmacy insurance coverage during the pre-index period or during the 30 days after the index date.	1,817,222	1,850,340
4) Excluded patients without depression diagnosis[c] or without at least one prescription for a selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor during the pre-index period.	1,418,251	432,089
5) Excluded patients without T2DM diagnosis[d] during the pre-index period.	393,348	38,741
6) Excluded patients with any diagnosis of schizophrenia-related disorders[e] or bipolar disorder[f], or who had a prescription fill for clozapine, an injectable SGA, or first generation antipsychotic[g] during the pre-index period.	3,797	34,944
7) Excluded patients with any diagnosis of dementia, delusional disorder, non-organic psychosis, autism, mental retardation, cerebral degeneration, Parkinson's, senility without mention of psychosis, or thyroid disorder during the pre-index period[h].	1,695	33,249
8) Excluded patients with any hospital admission within 30 days prior to the index date.	2,703	30,546

[a] Oral non-clozapine SGA: oral formulations of aripiprazole, asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine (including olanzapine/fluoxetine), paliperidone, quetiapine, risperidone, and ziprasidone.
[b] TCA: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, or trimipramine
[c] Depression diagnosis: any 1 inpatient or outpatient ICD-9 CM 296.2x, 296.3x, 300.4, or 311.
[d] T2DM diagnosis: ≥1 inpatient or ≥2 outpatient ICD-9-CM 250.x0 or 250.x2, or ≥2 prescription fills for a Healthcare Effectiveness Data and Information Set antidiabetic medication.
[e] Schizophrenia-related disorders diagnosis: any inpatient or outpatient ICD-9 CM 295.xx.
[f] Bipolar disorder diagnosisr: any inpatient or outpatient ICD-9 CM 296.0x, 296.1x or 296.4x-296.8x.
[g] First generation antipsychotic: oral or injectable formulations of chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine (including amitriptyline/perphenazine), pimozide, thiothixene, thioridazine, trifluoperazine (short-term (<10 days) use of prochlorperazine not included due to indication for nausea/vomiting).
[h] Any inpatient or outpatient diagnosis for dementia (ICD-9 CM 290.xx), delusional disorder (ICD-9 CM 297.xx), non-organic psychosis (ICD-9 CM 298.xx), autism (ICD-9 CM 299.0), mental retardation (ICD-9 CM 317.0-319.0), cerebral degeneration (ICD-9 CM 331.xx), Parkinson's (ICD-9 CM 332.xx), senility without mention of psychosis (ICD-9 CM 797.0), or thyroid disorder (ICD-9 CM 240.0-246.0).

Abbreviations: SGA=second generation antipsychotic, T2DM= type 2 diabetes, TCA= tricyclic antidepressant.

Appendix 2. Medications Initiated at Cohort Entry

SGA Initiators (N=6,625)	N (%)	Non-SGA Initiators (N=23,921)	N (%)
Aripiprazole	3,461 (52.4)	Bupropion	15,511 (64.8)
Quetiapine	1,977 (29.8)	TCA	5,989 (25.0)
Risperidone	613 (9.3)	Amitriptyline	3,611 (60.3)
Olanzapine	325 (4.9)	Nortriptyline	1,278 (21.3)
Ziprasidone	134 (2.0)	Doxepin	769 (12.8)
Lurasidone	60 (0.9)	Imipramine	170 (2.8)
Asenapine	42 (0.6)	Clomipramine	52 (0.9)
Paliperidone	6 (0.10)	Desipramine	91 (1.5)
Iloperidone	4 (0.10)	Protriptyline	15 (0.3)
Brexpiprazole	3 (0.10)	Amoxapine	2 (0.0)
		Trimipramine	1 (0.0)
		Mirtazapine	1,837 (7.7)
		Thyroid hormone	439 (1.8)
		Lithium	145 (0.6)

Abbreviations: SGA=second generation antipsychotic; TCA=tricyclic antidepressant

Appendix 3. Description of Average and Peak Daily Doses Used for Aripiprazole, Quetiapine, Bupropion, Mirtazapine, and Tricyclic Antidepressants

Medication	Median (IQR) average daily dose (mg/day)[a]	Median (IQR) peak daily dose (mg/day)[b]	Usual recommended dose (mg/day)
Aripiprazole	5 (2-5)	5 (2-5)	5-10[1]
Quetiapine	50 (25-100)	75 (50-150)	150-300[2]
Bupropion[c]	200 (150-300)	200 (150-300)	300-450[3]
TCAs			
Amitriptyline	30 (25-50)	30 (25-50)	100-300[3]
Nortriptyline	38.3 (25-50)	50 (25-50)	50-200[3]
Doxepin	25 (15-50)	25 (20-50)	100-300[3]
Imipramine	42.5 (25-50)	50 (25-50)	75–300[3]
Clomipramine	50 (25-80)	50 (25-80)	100-200[4]
Desipramine	40.6 (25-73.4)	50 (25-75)	100-300[3]
Protriptyline	11.7 (10-20)	15 (10-24.2)	20-60[3]
Amoxapine	45.8 (16.7-75)	62.5 (25-100)	200-300[5]
Trimipramine	25 (25-25)	25 (25-25)	75-300[3]
Mirtazapine	15 (15-30)	15 (15-30)	15–45[3]

[a]Average daily dose= strength (mg)*quantity dispensed/days' supply
[b]Peak daily dose= maximum average daily dose during follow-up
[c]Conversion of Aplenxin® (bupropion HBr) to bupropion strength used: 174 mg bupropion HBr = 150 mg bupropion HCI, 348 mg bupropion HBr= 300 bupropion, 522 mg bupropion HBr= 450 mg bupropion HCI
Abbreviations: IQR=interquartile range

Appendix 4. Baseline Characteristics and Absolute Standardized Differences after Match

Table 4.1. Baseline Characteristics after Match: Second Generation Antipsychotics (SGA) vs. Non-SGA (N=12,930)

Characteristics	SGA (N=6465)	Non-SGA (N=6465)	ASD*
Demographics			
Age (years)			
Mean (SD)	50.6 (9.7)	50.7 (9.7)	<0.01
Median (IQR)	53.0 (45.0, 58.0)	53.0 (45.0, 58.0)	
Age group, n (%)			
18-29	235 (3.6)	228 (3.5)	
30-39	628 (9.7)	669 (10.3)	
40-49	1582 (24.5)	1620 (25.1)	
50-64	4020 (62.2)	3948 (61.1)	
Male, n (%)	2269 (35.1)	2256 (34.9)	<0.01
Index year, n (%)			
2010	1337 (20.7)	1363 (21.1)	0.02
2011	1312 (20.3)	1331 (20.6)	
2012	1251 (19.4)	1222 (18.9)	
2013	910 (14.1)	906 (14.0)	
2014	888 (13.7)	911 (14.1)	
2015	767 (11.9)	732 (11.3)	

Characteristics	SGA (N=6465)	Non-SGA (N=6465)	ASD*
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	1122 (17.4)	1196 (18.5)	0.03
MGH-AD Score 1.5-2	3771 (58.3)	3705 (57.3)	
MGH-AD Score 2.5-3	717 (11.1)	729 (11.3)	
MGH-AD Score ≥ 3.5	855 (13.2)	835 (12.9)	
Antidepressant use, n (%)			
SSRI	4538 (70.2)	4557 (70.5)	0.01
SNRI	3100 (48.0)	2968 (45.9)	0.04
Serotonin modulator	1203 (18.6)	1183 (18.3)	0.01
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	5098 (78.9)	5097 (78.8)	0.01
Recent	1252 (19.4)	1246 (19.3)	
Former	115 (1.8)	122 (1.9)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	2754 (42.6)	2682 (41.5)	0.02
Alcohol abuse/dependence	255 (3.9)	242 (3.7)	0.01
Substance abuse/dependence	290 (4.5)	313 (4.8)	0.02
Suicide or intentional self-inflicted injury	125 (1.9)	94 (1.5)	0.04

Characteristics	SGA (N=6465)	Non-SGA (N=6465)	ASD*
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	3552 (54.9)	3546 (54.8)	0.01
Moderate (aDCSI score=1-3)	2539 (39.3)	2532 (39.2)	
Severe (aDCSI score ≥4)	374 (5.8)	387 (6.0)	
Diabetes regimen, n (%)			
No antidiabetic drug use	2130 (32.9)	2166 (33.5)	0.04
OAD only	2599 (40.2)	2527 (39.1)	
Insulin only	662 (10.2)	660 (10.2)	
Non-insulin injectable only	66 (1.0)	66 (1.0)	
Insulin + OAD only	671 (10.4)	714 (11.0)	
OAD + non-insulin injectable only	205 (3.2)	217 (3.4)	
Insulin + non-insulin injectable only	36 (0.6)	33 (0.5)	
OAD + insulin+ non-insulin injectable	96 (1.5)	82 (1.3)	
Diabetes drug class, n (%)			
Metformin	2694 (41.7)	2695 (41.7)	<0.01
Sulfonylurea	984 (15.2)	965 (14.9)	0.01
Thiazolidinedione	497 (7.7)	505 (7.8)	<0.01
Alpha-glucosidase inhibitor	15 (0.2)	13 (0.2)	0.01
Meglitinide	40 (0.6)	50 (0.8)	0.02

Characteristics	SGA (N=6465)	Non-SGA (N=6465)	ASD*
SGLT2 inhibitor	97 (1.5)	86 (1.3)	0.01
DPP-4 inhibitor	704 (10.9)	683 (10.6)	0.01
GLP-1 agonist	389 (6.0)	381 (5.9)	0.01
Amylin analog	14 (0.2)	17 (0.3)	0.01
Insulin	1465 (22.7)	1489 (23.0)	0.01
Medical comorbidity[c], n (%)			
Hypertension	4250 (65.7)	4221 (65.3)	0.01
Coronary atherosclerosis and other heart diseases	715 (11.1)	722 (11.2)	<0.01
Angina pectoris	180 (2.8)	189 (2.9)	0.01
Myocardial infarction or unstable angina	146 (2.3)	180 (2.8)	0.03
Disorders of lipid metabolism	4123 (63.8)	4116 (63.7)	<0.01
Congestive heart failure	248 (3.8)	249 (3.9)	<0.01
Obesity diagnosis	1402 (21.7)	1411 (21.8)	<0.01
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.9 (8.6)	5.9 (8.4)	<0.01
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	
Psychiatric hospital admissions, n (%)			
0	6210 (96.1)	6243 (96.6)	0.04
1	221 (3.4)	201 (3.1)	

Characteristics	SGA (N=6465)	Non-SGA (N=6465)	ASD*
≥2	34 (0.5)	21 (0.3)	
Outpatient diabetes visits			
Mean (SD)	5.7 (6.3)	5.8 (6.5)	0.01
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	
Diabetes hospital admissions, n (%)			
0	6419 (99.3)	6411 (99.2)	0.05
1	34 (0.5)	50 (0.8)	
≥2	12 (0.2)	4 (0.1)	
Provider Characteristics			
Provider care team, n (%)			
PCP	2705 (41.8)	2673 (41.3)	0.02
Psychiatry	172 (2.7)	168 (2.6)	
Endocrinology	16 (0.2)	13 (0.2)	
PCP + Psychiatry	2279 (35.3)	2339 (36.2)	
PCP + Endocrinology	341 (5.3)	328 (5.1)	
Psychiatry + Endocrinology	37 (0.6)	40 (0.6)	
PCP + Psychiatry + Endocrinology	470 (7.3)	467 (7.2)	
Unspecified or other specialist	445 (6.9)	437 (6.8)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.2. Baseline Characteristics after Match: Quetiapine vs. Aripiprazole (N=3,086)

Characteristics	Quetiapine (N=1543)	Aripiprazole (N=1543)	ASD*
Demographics			
Age (years)			
Mean (SD)	50.4 (9.6)	50.7 (9.3)	0.02
Median (IQR)	52.0 (44.0, 58.0)	52.0 (45.0, 58.0)	
Age group, n (%)			
18-29	54 (3.5)	49 (3.2)	
30-39	146 (9.5)	142 (9.2)	
40-49	413 (26.8)	389 (25.2)	
50-64	930 (60.3)	963 (62.4)	
Male, n (%)	550 (35.6)	549 (35.6)	<0.01
Index year, n (%)			
2010	313 (20.3)	309 (20.0)	0.02
2011	304 (19.7)	297 (19.2)	
2012	290 (18.8)	290 (18.8)	
2013	215 (13.9)	220 (14.3)	
2014	227 (14.7)	224 (14.5)	
2015	194 (12.6)	203 (13.2)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	281 (18.2)	283 (18.3)	0.02

Characteristics	Quetiapine (N=1543)	Aripiprazole (N=1543)	ASD*
MGH-AD Score 1.5-2	857 (55.5)	862 (55.9)	
MGH-AD Score 2.5-3	193 (12.5)	185 (12.0)	
MGH-AD Score ≥ 3.5	212 (13.7)	213 (13.8)	
Antidepressant use, n (%)			
SSRI	1118 (72.5)	1094 (70.9)	0.03
SNRI	724 (46.9)	743 (48.2)	0.02
Serotonin modulator	331 (21.5)	282 (18.3)	0.08
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	1195 (77.4)	1199 (77.7)	0.02
Recent	317 (20.5)	317 (20.5)	
Former	31 (2.0)	27 (1.7)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	696 (45.1)	685 (44.4)	0.01
Alcohol abuse/dependence	69 (4.5)	52 (3.4)	0.06
Substance abuse/dependence	70 (4.5)	70 (4.5)	<0.01
Suicide or intentional self-inflicted injury	35 (2.3)	38 (2.5)	0.01
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	880 (57.0)	863 (55.9)	0.02
Moderate (aDCSI score=1-3)	571 (37.0)	587 (38.0)	

Characteristics	Quetiapine (N=1543)	Aripiprazole (N=1543)	ASD*
Severe (aDCSI score≥4)	92 (6.0)	93 (6.0)	
Diabetes regimen, n (%)			
No antidiabetic drug use	551 (35.7)	523 (33.9)	0.07
OAD only	602 (39.0)	613 (39.7)	
Insulin only	156 (10.1)	167 (10.8)	
Non-insulin injectable only	14 (0.9)	9 (0.6)	
Insulin + OAD only	152 (9.9)	152 (9.9)	
OAD + non-insulin injectable only	46 (3.0)	57 (3.7)	
Insulin + non-insulin injectable only	5 (0.3)	5 (0.3)	
OAD + insulin+ non-insulin injectable	17 (1.1)	17 (1.1)	
Diabetes drug class, n (%)			
Metformin	623 (40.4)	623 (40.4)	<0.01
Sulfonylurea	227 (14.7)	223 (14.5)	0.01
Thiazolidinedione	109 (7.1)	114 (7.4)	0.01
Alpha-glucosidase inhibitor	0 (0.0)	3 (0.2)	0.06
Meglitinide	8 (0.5)	12 (0.8)	0.03
SGLT2 inhibitor	25 (1.6)	28 (1.8)	0.02
DPP-4 inhibitor	151 (9.8)	166 (10.8)	0.03
GLP-1 agonist	82 (5.3)	87 (5.6)	0.01
Amylin analog	0 (0.0)	1 (0.1)	0.04
Insulin	330 (21.4)	341 (22.1)	0.02

Characteristics	Quetiapine (N=1543)	Aripiprazole (N=1543)	ASD*
Medical comorbidity [c], n (%)			
Hypertension	1001 (64.9)	1036 (67.1)	0.05
Coronary atherosclerosis and other heart diseases	158 (10.2)	172 (11.1)	0.03
Angina pectoris	41 (2.7)	43 (2.8)	0.01
Myocardial infarction or unstable angina	38 (2.5)	40 (2.6)	0.01
Disorders of lipid metabolism	1003 (65.0)	979 (63.4)	0.03
Congestive heart failure	49 (3.2)	57 (3.7)	0.03
Obesity diagnosis	317 (20.5)	323 (20.9)	0.01
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.4 (7.4)	6.1 (9.8)	0.07
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 7.0)	
Psychiatric hospital admissions, n (%)			
0	1471 (95.3)	1483 (96.1)	0.04
1	64 (4.1)	52 (3.4)	
≥2	8 (0.5)	8 (0.5)	
Outpatient diabetes visits			
Mean (SD)	5.5 (5.8)	5.8 (6.8)	0.04
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	

Characteristics	Quetiapine (N=1543)	Aripiprazole (N=1543)	ASD*
Diabetes hospital admissions, n (%)			
0	1528 (99.0)	1531 (99.2)	0.04
1	12 (0.8)	8 (0.5)	
≥2	3 (0.2)	4 (0.3)	
Provider Characteristics			
Provider care team, n (%)			
PCP	686 (44.5)	682 (44.2)	0.03
Psychiatry	37 (2.4)	37 (2.4)	
Endocrinology	4 (0.3)	5 (0.3)	
PCP + Psychiatry	526 (34.1)	520 (33.7)	
PCP + Endocrinology	72 (4.7)	72 (4.7)	
Psychiatry + Endocrinology	4 (0.3)	6 (0.4)	
PCP + Psychiatry + Endocrinology	111 (7.2)	114 (7.4)	
Unspecified or other specialist	103 (6.7)	107 (6.9)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.3. Baseline Characteristics after Match: Quetiapine vs. Mirtazapine (N=2,220)

Characteristics	Quetiapine (N=1110)	Mirtazapine (1110)	ASD*
Demographics			
Age (years)			
Mean (SD)	51.1 (9.7)	51.3 (10.0)	0.02
Median (IQR)	53.0 (45.0, 59.0)	53.0 (46.0, 59.0)	
Age group, n (%)			
18-29	37 (3.3)	49 (4.4)	
30-39	98 (8.8)	90 (8.1)	
40-49	273 (24.6)	254 (22.9)	
50-64	702 (63.2)	717 (64.6)	
Male, n (%)	443 (39.9)	442 (39.8)	<0.01
Index year, n (%)			
2010	220 (19.8)	227 (20.5)	0.06
2011	211 (19.0)	199 (17.9)	
2012	206 (18.6)	210 (18.9)	
2013	147 (13.2)	143 (12.9)	
2014	169 (15.2)	186 (16.8)	
2015	157 (14.1)	145 (13.1)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	270 (24.3)	277 (25.0)	0.03

Characteristics	Quetiapine (N=1110)	Mirtazapine (1110)	ASD*
MGH-AD Score 1.5-2	579 (52.2)	583 (52.5)	
MGH-AD Score 2.5-3	118 (10.6)	117 (10.5)	
MGH-AD Score ≥ 3.5	143 (12.9)	133 (12.0)	
Antidepressant use, n (%)			
SSRI	849 (76.5)	816 (73.5)	0.07
SNRI	464 (41.8)	442 (39.8)	0.04
Serotonin modulator	221 (19.9)	230 (20.7)	0.02
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	785 (70.7)	789 (71.1)	0.03
Recent	294 (26.5)	285 (25.7)	
Former	31 (2.8)	36 (3.2)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	521 (46.9)	514 (46.3)	0.01
Alcohol abuse/dependence	63 (5.7)	46 (4.1)	0.07
Substance abuse/dependence	61 (5.5)	76 (6.8)	0.06
Suicide or intentional self-inflicted injury	30 (2.7)	28 (2.5)	0.01
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score =0)	588 (53.0)	577 (52.0)	0.02
Moderate (aDCSI score =1-3)	444 (40.0)	455 (41.0)	

Characteristics	Quetiapine (N=1110)	Mirtazapine (1110)	ASD*
Severe (aDCSI score ≥4)	78 (7.0)	78 (7.0)	
Diabetes regimen, n (%)			
No antidiabetic drug use	397 (35.8)	399 (35.9)	0.04
OAD only	418 (37.7)	419 (37.7)	
Insulin only	133 (12.0)	124 (11.2)	
Non-insulin injectable only	7 (0.6)	5 (0.5)	
Insulin + OAD only	105 (9.5)	108 (9.7)	
OAD + non-insulin injectable only	32 (2.9)	35 (3.2)	
Insulin + non-insulin injectable only	5 (0.5)	6 (0.5)	
OAD + insulin+ non-insulin injectable	13 (1.2)	14 (1.3)	
Diabetes drug class, n (%)			
Metformin	740 (66.7)	742 (66.8)	<0.01
Sulfonylurea	128 (11.5)	128 (11.5)	<0.01
Thiazolidinedione	38 (3.4)	34 (3.1)	0.02
Alpha-glucosidase inhibitor	32 (2.9)	46 (4.1)	0.07
Meglitinide	698 (62.9)	693 (62.4)	0.01
SGLT2 inhibitor	45 (4.1)	46 (4.1)	<0.01
DPP-4 inhibitor	227 (20.5)	218 (19.6)	0.02
GLP-1 agonist	740 (66.7)	742 (66.8)	<0.01
Amylin analog	128 (11.5)	128 (11.5)	<0.01
Insulin	38 (3.4)	34 (3.1)	0.02

Characteristics	Quetiapine (N=1110)	Mirtazapine (1110)	ASD*
Medical comorbidity [c], n (%)			
Hypertension	740 (66.7)	742 (66.8)	<0.01
Coronary atherosclerosis and other heart diseases	128 (11.5)	128 (11.5)	<0.01
Angina pectoris	38 (3.4)	34 (3.1)	0.02
Myocardial infarction or unstable angina	32 (2.9)	46 (4.1)	0.07
Disorders of lipid metabolism	698 (62.9)	693 (62.4)	0.01
Congestive heart failure	45 (4.1)	46 (4.1)	<0.01
Obesity diagnosis	227 (20.5)	218 (19.6)	0.02
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.1 (7.0)	5.1 (7.7)	0.01
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 5.0)	
Psychiatric hospital admissions, n (%)			
0	1065 (95.9)	1066 (96.0)	0.01
1	38 (3.4)	36 (3.2)	
≥2	7 (0.6)	8 (0.7)	
Outpatient diabetes visits			
Mean (SD)	5.9 (6.3)	5.8 (6.1)	0.02
Median (IQR)	4.0 (2.0, 8.0)	4.0 (2.0, 8.0)	

Characteristics	Quetiapine (N=1110)	Mirtazapine (1110)	ASD*
Diabetes hospital admissions, n (%)			
0	1100 (99.1)	1101 (99.2)	0.09
1	6 (0.5)	9 (0.8)	
≥2	4 (0.4)	0 (0.0)	
Provider Characteristics			
Provider care team, n (%)			
PCP	465 (41.9)	497 (44.8)	0.08
Psychiatry	38 (3.4)	28 (2.5)	
Endocrinology	3 (0.3)	3 (0.3)	
PCP + Psychiatry	387 (34.9)	380 (34.2)	
PCP + Endocrinology	58 (5.2)	56 (5.0)	
Psychiatry + Endocrinology	4 (0.4)	4 (0.4)	
PCP + Psychiatry + Endocrinology	73 (6.6)	69 (6.2)	
Unspecified or other specialist	82 (7.4)	73 (6.6)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.4. Baseline Characteristics after Match: Quetiapine vs. Tricyclic Antidepressant (N=3,128)

Characteristics	Quetiapine (N=1564)	TCA (N=1564)	ASD*
Demographics			
Age (years)			
Mean (SD)	50.8 (9.6)	50.9 (9.4)	0.01
Median (IQR)	53.0 (45.0, 58.0)	53.0 (45.0, 58.0)	
Age group, n (%)			
18-29	51 (3.3)	37 (2.4)	
30-39	141 (9.0)	163 (10.4)	
40-49	406 (26.0)	406 (26.0)	
50-64	966 (61.8)	958 (61.3)	
Male, n (%)	541 (34.6)	510 (32.6)	0.04
Index year, n (%)			
2010	320 (20.5)	323 (20.7)	0.04
2011	287 (18.4)	300 (19.2)	
2012	286 (18.3)	290 (18.5)	
2013	223 (14.3)	227 (14.5)	
2014	242 (15.5)	220 (14.1)	
2015	206 (13.2)	204 (13.0)	
Depression and Psychiatric History			
Depression severity [a], n (%)			

Characteristics	Quetiapine (N=1564)	TCA (N=1564)	ASD*
MGH-AD Score ≤1	364 (23.3)	354 (22.6)	0.02
MGH-AD Score 1.5-2	848 (54.2)	854 (54.6)	
MGH-AD Score 2.5-3	173 (11.1)	173 (11.1)	
MGH-AD Score ≥ 3.5	179 (11.4)	183 (11.7)	
Antidepressant use, n (%)			
SSRI	1149 (73.5)	1128 (72.1)	0.03
SNRI	682 (43.6)	694 (44.4)	0.02
Serotonin modulator	291 (18.6)	289 (18.5)	<0.01
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	1152 (73.7)	1166 (74.6)	0.02
Recent	367 (23.5)	356 (22.8)	
Former	45 (2.9)	42 (2.7)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	716 (45.8)	659 (42.1)	0.07
Alcohol abuse/dependence	69 (4.4)	57 (3.6)	0.04
Substance abuse/dependence	91 (5.8)	85 (5.4)	0.02
Suicide or intentional self-inflicted injury	35 (2.2)	19 (1.2)	0.08
Diabetes and Cardiovascular History			
Diabetes severity, n (%)			
aDCSI score [d]			

Characteristics	Quetiapine (N=1564)	TCA (N=1564)	ASD*
Mild (aDCSI score =0)	866 (55.4)	852 (54.5)	0.02
Moderate (aDCSI score =1-3)	601 (38.4)	610 (39.0)	
Severe (aDCSI score ≥4)	97 (6.2)	102 (6.5)	
Diabetes regimen, n (%)			
No antidiabetic drug use	534 (34.1)	551 (35.2)	0.03
OAD only	623 (39.8)	619 (39.6)	
Insulin only	163 (10.4)	161 (10.3)	
Non-insulin injectable only	15 (1.0)	13 (0.8)	
Insulin + OAD only	161 (10.3)	156 (10.0)	
OAD + non-insulin injectable only	46 (2.9)	41 (2.6)	
Insulin + non-insulin injectable only	5 (0.3)	5 (0.3)	
OAD + insulin+ non-insulin injectable	17 (1.1)	18 (1.2)	
Diabetes drug class, n (%)			
Metformin	657 (42.0)	636 (40.7)	0.03
Sulfonylurea	238 (15.2)	232 (14.8)	0.01
Thiazolidinedione	107 (6.8)	109 (7.0)	0.01
Alpha-glucosidase inhibitor	0 (0.0)	4 (0.3)	0.07
Meglitinide	9 (0.6)	13 (0.8)	0.03
SGLT2 inhibitor	28 (1.8)	11 (0.7)	0.10
DPP-4 inhibitor	167 (10.7)	154 (9.8)	0.03
GLP-1 agonist	83 (5.3)	76 (4.9)	0.02

Characteristics	Quetiapine (N=1564)	TCA (N=1564)	ASD*
Amylin analog	0 (0.0)	1 (0.1)	0.04
Insulin	346 (22.1)	340 (21.7)	0.01
Medical comorbidity [c], n (%)			
Hypertension	1044 (66.8)	1059 (67.7)	0.02
Coronary atherosclerosis and other heart diseases	169 (10.8)	165 (10.5)	0.01
Angina pectoris	46 (2.9)	52 (3.3)	0.02
Myocardial infarction or unstable angina	43 (2.7)	43 (2.7)	<0.01
Disorders of lipid metabolism	1006 (64.3)	1009 (64.5)	<0.01
Congestive heart failure	55 (3.5)	66 (4.2)	0.04
Obesity diagnosis	320 (20.5)	379 (24.2)	0.09
Resource Utilization			
Outpatient depression visits			
Mean (SD)	4.8 (7.0)	4.7 (7.5)	0.02
Median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	
Psychiatric hospital admissions, n (%)			
0	1500 (95.9)	1512 (96.7)	0.04
1	55 (3.5)	45 (2.9)	
≥2	9 (0.6)	7 (0.4)	

Characteristics	Quetiapine (N=1564)	TCA (N=1564)	ASD*
Outpatient diabetes visits			
Mean (SD)	5.7 (5.9)	5.8 (6.3)	0.03
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 8.0)	
Diabetes hospital admissions, n (%)			
0	1548 (99.0)	1557 (99.6)	0.07
1	11 (0.7)	6 (0.4)	
≥2	5 (0.3)	1 (0.1)	
Provider Characteristics			
Provider care team, n (%)			
PCP	810 (51.8)	812 (51.9)	0.03
Psychiatry	37 (2.4)	36 (2.3)	
Endocrinology	3 (0.2)	4 (0.3)	
PCP + Psychiatry	433 (27.7)	432 (27.6)	
PCP + Endocrinology	74 (4.7)	71 (4.5)	
Psychiatry + Endocrinology	4 (0.3)	5 (0.3)	
PCP + Psychiatry + Endocrinology	98 (6.3)	91 (5.8)	
Unspecified or other specialist	105 (6.7)	113 (7.2)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2; TCA=tricyclic antidepressant.

Table 4.5. Baseline Characteristics after Match: Quetiapine vs. Bupropion (N=3,768)

Characteristics	Quetiapine (N=1884)	Bupropion (N=1884)	ASD*
Demographics			
Age (years)			
Mean (SD)	50.4 (9.9)	50.2 (9.9)	0.01
Median (IQR)	52.0 (44.0, 58.0)	52.0 (44.0, 58.0)	
Age group, n (%)			
18-29	74 (3.9)	75 (4.0)	
30-39	177 (9.4)	210 (11.1)	
40-49	494 (26.2)	470 (24.9)	
50-64	1139 (60.5)	1129 (59.9)	
Male, n (%)	681 (36.1)	648 (34.4)	0.04
Index year, n (%)			
2010	394 (20.9)	402 (21.3)	0.03
2011	363 (19.3)	362 (19.2)	
2012	342 (18.2)	333 (17.7)	
2013	266 (14.1)	253 (13.4)	
2014	272 (14.4)	283 (15.0)	
2015	247 (13.1)	251 (13.3)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	441 (23.4)	449 (23.8)	**0.01**

Characteristics	Quetiapine (N=1884)	Bupropion (N=1884)	ASD*
MGH-AD Score 1.5-2	984 (52.2)	975 (51.8)	
MGH-AD Score 2.5-3	220 (11.7)	217 (11.5)	
MGH-AD Score ≥ 3.5	239 (12.7)	243 (12.9)	
Antidepressant use, n (%)			
SSRI	1393 (73.9)	1403 (74.5)	0.01
SNRI	836 (44.4)	759 (40.3)	0.08
Serotonin modulator	383 (20.3)	409 (21.7)	0.03
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	1422 (75.5)	1430 (75.9)	0.02
Recent	414 (22.0)	401 (21.3)	
Former	48 (2.5)	53 (2.8)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	863 (45.8)	800 (42.5)	0.07
Alcohol abuse/dependence	100 (5.3)	95 (5.0)	0.01
Substance abuse/dependence	123 (6.5)	147 (7.8)	0.05
Suicide or intentional self-inflicted injury	45 (2.4)	32 (1.7)	0.05
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score =0)	1063 (56.4)	1039 (55.1)	0.03
Moderate (aDCSI score =1-3)	698 (37.0)	714 (37.9)	

Characteristics	Quetiapine (N=1884)	Bupropion (N=1884)	ASD*
Severe (aDCSI score ≥4)	123 (6.5)	131 (7.0)	
Diabetes regimen, n (%)			
No antidiabetic drug use	666 (35.4)	673 (35.7)	0.06
OAD only	737 (39.1)	749 (39.8)	
Insulin only	194 (10.3)	174 (9.2)	
Non-insulin injectable only	14 (0.7)	11 (0.6)	
Insulin + OAD only	186 (9.9)	185 (9.8)	
OAD + non-insulin injectable only	60 (3.2)	67 (3.6)	
Insulin + non-insulin injectable only	6 (0.3)	3 (0.2)	
OAD + insulin+ non-insulin injectable	21 (1.1)	22 (1.2)	
Diabetes drug class, n (%)			
Metformin	765 (40.6)	781 (41.5)	0.02
Sulfonylurea	283 (15.0)	305 (16.2)	0.03
Thiazolidinedione	132 (7.0)	131 (7.0)	<0.01
Alpha-glucosidase inhibitor	0 (0.0)	5 (0.3)	0.07
Meglitinide	10 (0.5)	16 (0.8)	0.04
SGLT2 inhibitor	30 (1.6)	27 (1.4)	0.01
DPP-4 inhibitor	193 (10.2)	187 (9.9)	0.01
GLP-1 agonist	101 (5.4)	102 (5.4)	<0.01
Amylin analog	0 (0.0)	1 (0.1)	0.03
Insulin	407 (21.6)	384 (20.4)	0.03

Characteristics	Quetiapine (N=1884)	Bupropion (N=1884)	ASD*
Medical comorbidity [c], n (%)			
Hypertension	1233 (65.4)	1261 (66.9)	0.03
Coronary atherosclerosis and other heart diseases	200 (10.6)	203 (10.8)	0.01
Angina pectoris	60 (3.2)	55 (2.9)	0.02
Myocardial infarction or unstable angina	53 (2.8)	64 (3.4)	0.03
Disorders of lipid metabolism	1209 (64.2)	1179 (62.6)	0.03
Congestive heart failure	70 (3.7)	73 (3.9)	0.01
Obesity diagnosis	394 (20.9)	421 (22.3)	0.03
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.2 (7.2)	5.4 (7.6)	0.03
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	
Psychiatric hospital admissions, n (%)			
0	1790 (95.0)	1798 (95.4)	0.02
1	81 (4.3)	74 (3.9)	
≥2	13 (0.7)	12 (0.6)	
Outpatient diabetes visits			
Mean (SD)	5.6 (5.8)	5.8 (7.3)	0.04
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 8.0)	

Characteristics	Quetiapine (N=1884)	Bupropion (N=1884)	ASD*
Diabetes hospital admissions, n (%)			
0	1864 (98.9)	1867 (99.1)	0.04
1	15 (0.8)	15 (0.8)	
≥2	5 (0.3)	2 (0.1)	
Provider Characteristics			
Provider care team, n (%)			
PCP	875 (46.4)	860 (45.6)	0.05
Psychiatry	45 (2.4)	47 (2.5)	
Endocrinology	3 (0.2)	2 (0.1)	
PCP + Psychiatry	614 (32.6)	622 (33.0)	
PCP + Endocrinology	82 (4.4)	97 (5.1)	
Psychiatry + Endocrinology	5 (0.3)	4 (0.2)	
PCP + Psychiatry + Endocrinology	134 (7.1)	124 (6.6)	
Unspecified or other specialist	126 (6.7)	128 (6.8)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.6. Baseline Characteristics after Match: Bupropion vs. Aripiprazole (N=6,650)

Characteristics	Bupropion (N=3325)	Aripiprazole (N=3325)	ASD*
Demographics			
Age (years)			
Mean (SD)	51.0 (9.4)	51.0 (9.2)	0.01
Median (IQR)	53.0 (45.0, 58.0)	53.0 (45.0, 58.0)	
Age group, n (%)			
18-29	81 (2.4)	97 (2.9)	
30-39	352 (10.6)	301 (9.1)	
40-49	823 (24.8)	787 (23.7)	
50-64	2069 (62.2)	2140 (64.4)	
Male, n (%)	1132 (34.0)	1103 (33.2)	0.02
Index year, n (%)			
2010	655 (19.7)	657 (19.8)	0.02
2011	693 (20.8)	694 (20.9)	
2012	637 (19.2)	653 (19.6)	
2013	456 (13.7)	467 (14.0)	
2014	498 (15.0)	474 (14.3)	
2015	386 (11.6)	380 (11.4)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	401 (12.1)	387 (11.6)	0.02

Characteristics	Bupropion (N=3325)	Aripiprazole (N=3325)	ASD*
MGH-AD Score 1.5-2	2078 (62.5)	2094 (63.0)	
MGH-AD Score 2.5-3	393 (11.8)	382 (11.5)	
MGH-AD Score ≥ 3.5	453 (13.6)	462 (13.9)	
Antidepressant use, n (%)			
SSRI	2261 (68.0)	2230 (67.1)	0.02
SNRI	1650 (49.6)	1706 (51.3)	0.03
Serotonin modulator	545 (16.4)	564 (17.0)	0.02
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	2671 (80.3)	2682 (80.7)	0.01
Recent	616 (18.5)	604 (18.2)	
Former	38 (1.1)	39 (1.2)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	1298 (39.0)	1339 (40.3)	0.03
Alcohol abuse/dependence	110 (3.3)	110 (3.3)	<0.01
Substance abuse/dependence	138 (4.2)	108 (3.2)	0.05
Suicide or intentional self-inflicted injury	46 (1.4)	50 (1.5)	0.01
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	1847 (55.5)	1837 (55.2)	0.02
Moderate (aDCSI score=1-3)	1316 (39.6)	1312 (39.5)	

Characteristics	Bupropion (N=3325)	Aripiprazole (N=3325)	ASD*
Severe (aDCSI score ≥4)	162 (4.9)	176 (5.3)	
Diabetes regimen, n (%)			
No antidiabetic drug use	1018 (30.6)	1020 (30.7)	0.04
OAD only	1366 (41.1)	1370 (41.2)	
Insulin only	331 (10.0)	338 (10.2)	
Non-insulin injectable only	43 (1.3)	40 (1.2)	
Insulin + OAD only	372 (11.2)	355 (10.7)	
OAD + non-insulin injectable only	116 (3.5)	120 (3.6)	
Insulin + non-insulin injectable only	15 (0.5)	22 (0.7)	
OAD + insulin+ non-insulin injectable	64 (1.9)	60 (1.8)	
Diabetes drug class, n (%)			
Metformin	1474 (44.3)	1449 (43.6)	0.02
Sulfonylurea	485 (14.6)	494 (14.9)	0.01
Thiazolidinedione	301 (9.1)	278 (8.4)	0.02
Alpha-glucosidase inhibitor	10 (0.3)	12 (0.4)	0.01
Meglitinide	23 (0.7)	28 (0.8)	0.02
SGLT2 inhibitor	43 (1.3)	55 (1.7)	0.03
DPP-4 inhibitor	372 (11.2)	387 (11.6)	0.01
GLP-1 agonist	235 (7.1)	235 (7.1)	<0.01
Amylin analog	3 (0.1)	7 (0.2)	0.03
Insulin	782 (23.5)	775 (23.3)	0.01

Characteristics	Bupropion (N=3325)	Aripiprazole (N=3325)	ASD*
Medical comorbidity[c], n (%)			
Hypertension	2176 (65.4)	2183 (65.7)	<0.01
Coronary atherosclerosis and other heart diseases	327 (9.8)	363 (10.9)	0.04
Angina pectoris	90 (2.7)	77 (2.3)	0.03
Myocardial infarction or unstable angina	77 (2.3)	72 (2.2)	0.01
Disorders of lipid metabolism	2136 (64.2)	2157 (64.9)	0.01
Congestive heart failure	118 (3.5)	115 (3.5)	<0.01
Obesity diagnosis	761 (22.9)	749 (22.5)	0.01
Resource Utilization			
Outpatient depression visits			
Mean (SD)	6.3 (8.8)	6.3 (9.1)	<0.01
Median (IQR)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)	
Psychiatric hospital admissions, n (%)			
0	3234 (97.3)	3224 (97.0)	0.02
1	81 (2.4)	88 (2.6)	
≥2	10 (0.3)	13 (0.4)	
Outpatient diabetes visits			
Mean (SD)	5.7 (6.2)	5.7 (6.4)	<0.01
Median (IQR)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	

Characteristics	Bupropion (N=3325)	Aripiprazole (N=3325)	ASD*
Diabetes hospital admissions, n (%)			
0	3311 (99.6)	3307 (99.5)	0.05
1	13 (0.4)	12 (0.4)	
≥2	1 (0.0)	6 (0.2)	
Provider Characteristics			
Provider care team, n (%)			
PCP	1359 (40.9)	1332 (40.1)	0.03
Psychiatry	88 (2.6)	87 (2.6)	
Endocrinology	7 (0.2)	7 (0.2)	
PCP + Psychiatry	1189 (35.8)	1182 (35.5)	
PCP + Endocrinology	191 (5.7)	197 (5.9)	
Psychiatry + Endocrinology	23 (0.7)	26 (0.8)	
PCP + Psychiatry + Endocrinology	226 (6.8)	244 (7.3)	
Unspecified or other specialist	242 (7.3)	250 (7.5)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.7. Baseline Characteristics after Match: Bupropion vs. Mirtazapine (N=3,450)

Characteristics	Bupropion (N=1725)	Mirtazapine (N=1725)	ASD*
Demographics			
Age (years)			
Mean (SD)	52.1 (9.3)	52.2 (9.6)	0.01
Median (IQR)	54.0 (47.0, 59.0)	54.0 (47.0, 60.0)	
Age group, n (%)			
18-29	47 (2.7)	65 (3.8)	
30-39	133 (7.7)	113 (6.6)	
40-49	387 (22.4)	374 (21.7)	
50-64	1158 (67.1)	1173 (68.0)	
Male, n (%)	752 (43.6)	727 (42.1)	0.03
Index year, n (%)			
2010	339 (19.7)	331 (19.2)	0.07
2011	300 (17.4)	296 (17.2)	
2012	345 (20.0)	337 (19.5)	
2013	202 (11.7)	231 (13.4)	
2014	307 (17.8)	282 (16.3)	
2015	232 (13.4)	248 (14.4)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	436 (25.3)	452 (26.2)	0.03

Characteristics	Bupropion (N=1725)	Mirtazapine (N=1725)	ASD*
MGH-AD Score 1.5-2	947 (54.9)	926 (53.7)	
MGH-AD Score 2.5-3	154 (8.9)	158 (9.2)	
MGH-AD Score ≥ 3.5	188 (10.9)	189 (11.0)	
Antidepressant use, n (%)			
SSRI	1347 (78.1)	1311 (76.0)	0.05
SNRI	599 (34.7)	646 (37.4)	0.06
Serotonin modulator	340 (19.7)	340 (19.7)	<0.01
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	1082 (62.7)	1078 (62.5)	0.01
Recent	574 (33.3)	576 (33.4)	
Former	69 (4.0)	71 (4.1)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	736 (42.7)	794 (46.0)	0.07
Alcohol abuse/dependence	92 (5.3)	82 (4.8)	0.03
Substance abuse/dependence	89 (5.2)	88 (5.1)	<0.01
Suicide or intentional self-inflicted injury	26 (1.5)	46 (2.7)	0.08
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	852 (49.4)	842 (48.8)	0.02
Moderate (aDCSI score=1-3)	724 (42.0)	724 (42.0)	

Characteristics	Bupropion (N=1725)	Mirtazapine (N=1725)	ASD*
Severe (aDCSI score ≥4)	149 (8.6)	159 (9.2)	
Diabetes regimen, n (%)			
No antidiabetic drug use	620 (35.9)	600 (34.8)	0.07
OAD only	628 (36.4)	630 (36.5)	
Insulin only	220 (12.8)	222 (12.9)	
Non-insulin injectable only	7 (0.4)	11 (0.6)	
Insulin + OAD only	179 (10.4)	183 (10.6)	
OAD + non-insulin injectable only	36 (2.1)	49 (2.8)	
Insulin + non-insulin injectable only	10 (0.6)	8 (0.5)	
OAD + insulin+ non-insulin injectable	25 (1.4)	22 (1.3)	
Diabetes drug class, n (%)			
Metformin	684 (39.7)	669 (38.8)	0.02
Sulfonylurea	301 (17.4)	283 (16.4)	0.03
Thiazolidinedione	122 (7.1)	115 (6.7)	0.02
Alpha-glucosidase inhibitor	1 (0.1)	3 (0.2)	0.03
Meglitinide	6 (0.3)	10 (0.6)	0.03
SGLT2 inhibitor	19 (1.1)	26 (1.5)	0.04
DPP-4 inhibitor	168 (9.7)	174 (10.1)	0.01
GLP-1 agonist	72 (4.2)	86 (5.0)	0.04
Amylin analog	6 (0.3)	4 (0.2)	0.02
Insulin	434 (25.2)	435 (25.2)	<0.01

Characteristics	Bupropion (N=1725)	Mirtazapine (N=1725)	ASD*
Medical comorbidity[c], n (%)			
Hypertension	1178 (68.3)	1197 (69.4)	0.02
Coronary atherosclerosis and other heart diseases	233 (13.5)	235 (13.6)	<0.01
Angina pectoris	68 (3.9)	61 (3.5)	0.02
Myocardial infarction or unstable angina	61 (3.5)	73 (4.2)	0.04
Disorders of lipid metabolism	1090 (63.2)	1096 (63.5)	0.01
Congestive heart failure	113 (6.6)	104 (6.0)	0.02
Obesity diagnosis	311 (18.0)	324 (18.8)	0.02
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.0 (7.7)	5.1 (7.6)	0.01
Median (IQR)	2.0 (1.0, 5.0)	3.0 (1.0, 5.0)	
Psychiatric hospital admissions, n (%)			
0	1679 (97.3)	1676 (97.2)	0.03
1	40 (2.3)	40 (2.3)	
≥2	6 (0.3)	9 (0.5)	
Outpatient diabetes visits			
Mean (SD)	6.5 (8.8)	6.4 (7.6)	<0.01
Median (IQR)	4.0 (2.0, 8.0)	4.0 (2.0, 8.0)	

Characteristics	Bupropion (N=1725)	Mirtazapine (N=1725)	ASD*
Diabetes hospital admissions, n (%)			
0	1701 (98.6)	1704 (98.8)	0.07
1	23 (1.3)	16 (0.9)	
≥2	1 (0.1)	5 (0.3)	
Provider Characteristics			
Provider care team, n (%)			
PCP	734 (42.6)	718 (41.6)	0.04
Psychiatry	72 (4.2)	75 (4.3)	
Endocrinology	4 (0.2)	3 (0.2)	
PCP + Psychiatry	570 (33.0)	574 (33.3)	
PCP + Endocrinology	98 (5.7)	106 (6.1)	
Psychiatry + Endocrinology	5 (0.3)	6 (0.3)	
PCP + Psychiatry + Endocrinology	113 (6.6)	123 (7.1)	
Unspecified or other specialist	129 (7.5)	120 (7.0)	

*ASDs≥0.1 indicates imbalance in baseline characteristics

[a]The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b]Adjunctive therapy: at least 30 days overlap between index drug and antidepressant therapy; recent = end of supply for last antidepressant medication within 180 days of index date, but less than 30 day overlap with index drug, former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c]Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d]The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.8. Baseline Characteristics after Match: Bupropion vs. Tricyclic Antidepressant (N=10,042)

Characteristics	Bupropion (N=5021)	TCA (N=5021)	ASD*
Demographics			
Age (years)			
Mean (SD)	51.6 (9.3)	51.4 (9.4)	0.02
Median (IQR)	53.0 (46.0, 59.0)	53.0 (46.0, 59.0)	
Age group, n (%)			
18-29	112 (2.2)	130 (2.6)	
30-39	504 (10.0)	472 (9.4)	
40-49	1167 (23.2)	1225 (24.4)	
50-64	3238 (64.5)	3194 (63.6)	
Male, n (%)	1412 (28.1)	1421 (28.3)	<0.01
Index year, n (%)			
2010	883 (17.6)	904 (18.0)	0.03
2011	966 (19.2)	974 (19.4)	
2012	1039 (20.7)	982 (19.6)	
2013	736 (14.7)	748 (14.9)	
2014	734 (14.6)	761 (15.2)	
2015	663 (13.2)	652 (13.0)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	1111 (22.1)	1097 (21.8)	0.03

Characteristics	Bupropion (N=5021)	TCA (N=5021)	ASD*
MGH-AD Score 1.5-2	3079 (61.3)	3101 (61.8)	
MGH-AD Score 2.5-3	413 (8.2)	433 (8.6)	
MGH-AD Score ≥ 3.5	418 (8.3)	390 (7.8)	
Antidepressant use, n (%)			
SSRI	3762 (74.9)	3805 (75.8)	0.02
SNRI	1867 (37.2)	1847 (36.8)	0.01
Serotonin modulator	625 (12.4)	641 (12.8)	0.01
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	3187 (63.5)	3207 (63.9)	0.01
Recent	1536 (30.6)	1517 (30.2)	
Former	298 (5.9)	297 (5.9)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	1731 (34.5)	1700 (33.9)	0.01
Alcohol abuse/dependence	139 (2.8)	136 (2.7)	<0.01
Substance abuse/dependence	225 (4.5)	186 (3.7)	0.04
Suicide or intentional self-inflicted injury	41 (0.8)	30 (0.6)	0.03
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	2459 (49.0)	2493 (49.7)	0.02

Characteristics	Bupropion (N=5021)	TCA (N=5021)	ASD*
Moderate (aDCSI score=1-3)	2195 (43.7)	2180 (43.4)	
Severe (aDCSI score≥4)	367 (7.3)	348 (6.9)	
Diabetes regimen, n (%)			
No antidiabetic drug use	1583 (31.5)	1547 (30.8)	0.02
OAD only	2019 (40.2)	2022 (40.3)	
Insulin only	550 (11.0)	554 (11.0)	
Non-insulin injectable only	41 (0.8)	47 (0.9)	
Insulin + OAD only	591 (11.8)	610 (12.1)	
OAD + non-insulin injectable only	140 (2.8)	138 (2.7)	
Insulin + non-insulin injectable only	26 (0.5)	28 (0.6)	
OAD + insulin+ non-insulin injectable	71 (1.4)	75 (1.5)	
Diabetes drug class, n (%)			
Metformin	2202 (43.9)	2199 (43.8)	<0.01
Sulfonylurea	839 (16.7)	896 (17.8)	0.03
Thiazolidinedione	331 (6.6)	326 (6.5)	<0.01
Alpha-glucosidase inhibitor	11 (0.2)	10 (0.2)	<0.01
Meglitinide	19 (0.4)	24 (0.5)	0.02
SGLT2 inhibitor	59 (1.2)	55 (1.1)	0.01
DPP-4 inhibitor	473 (9.4)	521 (10.4)	0.03
GLP-1 agonist	265 (5.3)	278 (5.5)	0.01
Amylin analog	13 (0.3)	10 (0.2)	0.01

Characteristics	Bupropion (N=5021)	TCA (N=5021)	ASD*
Insulin	1238 (24.7)	1267 (25.2)	0.01
Medical comorbidity [c], n (%)			
Hypertension	3478 (69.3)	3422 (68.2)	0.02
Coronary atherosclerosis and other heart diseases	552 (11.0)	510 (10.2)	0.03
Angina pectoris	144 (2.9)	115 (2.3)	0.04
Myocardial infarction or unstable angina	128 (2.5)	104 (2.1)	0.03
Disorders of lipid metabolism	3384 (67.4)	3270 (65.1)	0.05
Congestive heart failure	207 (4.1)	186 (3.7)	0.02
Obesity diagnosis	1370 (27.3)	1279 (25.5)	0.04
Resource Utilization			
Outpatient depression visits			
Mean (SD)	4.0 (6.3)	3.7 (6.3)	0.05
Median (IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	
Psychiatric hospital admissions, n (%)			0.01
0	4940 (98.4)	4936 (98.3)	
1	73 (1.5)	74 (1.5)	
≥2	8 (0.2)	11 (0.2)	
Outpatient diabetes visits			
Mean (SD)	6.4 (7.8)	6.3 (6.5)	0.01

Characteristics	Bupropion (N=5021)	TCA (N=5021)	ASD*
Median (IQR)	5.0 (2.0, 8.0)	5.0 (2.0, 8.0)	
Diabetes hospital admissions, n (%)			
0	4974 (99.1)	4967 (98.9)	0.02
1	43 (0.9)	48 (1.0)	
≥2	4 (0.1)	6 (0.1)	
Provider Characteristics			
Provider care team, n (%)			
PCP	3012 (60.0)	3002 (59.8)	0.03
Psychiatry	102 (2.0)	112 (2.2)	
Endocrinology	7 (0.1)	11 (0.2)	
PCP + Psychiatry	862 (17.2)	844 (16.8)	
PCP + Endocrinology	408 (8.1)	419 (8.3)	
Psychiatry + Endocrinology	19 (0.4)	13 (0.3)	
PCP + Psychiatry + Endocrinology	198 (3.9)	199 (4.0)	
Unspecified or other specialist	413 (8.2)	421 (8.4)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2; TCA=tricyclic antidepressant.

Table 4.9. Baseline Characteristics after Match: Mirtazapine vs. Tricyclic Antidepressant (N=2,898)

Characteristics	Mirtazapine (N=1449)	TCA (N=1449)	ASD*
Demographics			
Age (years)			
Mean (SD)	52.1 (9.6)	52.1 (9.2)	<0.01
Median (IQR)	54.0 (47.0, 59.0)	54.0 (46.0, 59.0)	
Age group, n (%)			
18-29	55 (3.8)	30 (2.1)	
30-39	100 (6.9)	123 (8.5)	
40-49	316 (21.8)	335 (23.1)	
50-64	978 (67.5)	961 (66.3)	
Male, n (%)	573 (39.5)	582 (40.2)	0.01
Index year, n (%)			
2010	281 (19.4)	288 (19.9)	0.03
2011	259 (17.9)	255 (17.6)	
2012	283 (19.5)	293 (20.2)	
2013	189 (13.0)	182 (12.6)	
2014	229 (15.8)	232 (16.0)	
2015	208 (14.4)	199 (13.7)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	368 (25.4)	377 (26.0)	0.03

Characteristics	Mirtazapine (N=1449)	TCA (N=1449)	ASD*
MGH-AD Score 1.5-2	795 (54.9)	777 (53.6)	
MGH-AD Score 2.5-3	137 (9.5)	139 (9.6)	
MGH-AD Score ≥ 3.5	149 (10.3)	156 (10.8)	
Antidepressant use, n (%)			
SSRI	1087 (75.0)	1070 (73.8)	0.03
SNRI	556 (38.4)	569 (39.3)	0.02
Serotonin modulator	268 (18.5)	277 (19.1)	0.02
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	920 (63.5)	943 (65.1)	0.04
Recent	466 (32.2)	441 (30.4)	
Former	63 (4.3)	65 (4.5)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	645 (44.5)	632 (43.6)	0.02
Alcohol abuse/dependence	61 (4.2)	69 (4.8)	0.03
Substance abuse/dependence	75 (5.2)	87 (6.0)	0.04
Suicide or intentional self-inflicted injury	31 (2.1)	15 (1.0)	0.09
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	702 (48.4)	719 (49.6)	0.02

Characteristics	Mirtazapine (N=1449)	TCA (N=1449)	ASD*
Moderate (aDCSI score =1-3)	599 (41.3)	588 (40.6)	
Severe (aDCSI score ≥4)	148 (10.2)	142 (9.8)	
Diabetes regimen, n (%)			
No antidiabetic drug use	508 (35.1)	482 (33.3)	0.05
OAD only	533 (36.8)	543 (37.5)	
Insulin only	183 (12.6)	187 (12.9)	
Non-insulin injectable only	12 (0.8)	11 (0.8)	
Insulin + OAD only	152 (10.5)	162 (11.2)	
OAD + non-insulin injectable only	33 (2.3)	39 (2.7)	
Insulin + non-insulin injectable only	8 (0.6)	6 (0.4)	
OAD + insulin+ non-insulin injectable	20 (1.4)	19 (1.3)	
Diabetes drug class, n (%)			
Metformin	560 (38.6)	575 (39.7)	0.02
Sulfonylurea	241 (16.6)	245 (16.9)	0.01
Thiazolidinedione	95 (6.6)	100 (6.9)	0.01
Alpha-glucosidase inhibitor	3 (0.2)	2 (0.1)	0.02
Meglitinide	8 (0.6)	8 (0.6)	<0.01
SGLT2 inhibitor	22 (1.5)	15 (1.0)	0.04
DPP-4 inhibitor	145 (10.0)	172 (11.9)	0.06
GLP-1 agonist	69 (4.8)	74 (5.1)	0.02
Amylin analog	4 (0.3)	1 (0.1)	0.05

Characteristics	Mirtazapine (N=1449)	TCA (N=1449)	ASD*
Insulin	363 (25.1)	374 (25.8)	0.02
Medical comorbidity [c], n (%)			
Hypertension	1017 (70.2)	999 (68.9)	0.03
Coronary atherosclerosis and other heart diseases	196 (13.5)	175 (12.1)	0.04
Angina pectoris	54 (3.7)	39 (2.7)	0.06
Myocardial infarction or unstable angina	64 (4.4)	42 (2.9)	0.08
Disorders of lipid metabolism	926 (63.9)	906 (62.5)	0.03
Congestive heart failure	92 (6.3)	69 (4.8)	0.07
Obesity diagnosis	282 (19.5)	310 (21.4)	0.05
Resource Utilization			
Outpatient depression visits			
Mean (SD)	4.8 (7.5)	4.6 (6.5)	0.03
Median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	
Psychiatric hospital admissions, n (%)			0.03
0	1409 (97.2)	1407 (97.1)	
1	33 (2.3)	37 (2.6)	
≥2	7 (0.5)	5 (0.3)	
Outpatient diabetes visits			
Mean (SD)	6.5 (7.8)	6.7 (7.4)	0.02

Characteristics	Mirtazapine (N=1449)	TCA (N=1449)	ASD*
Median (IQR)	4.0 (2.0, 8.0)	5.0 (2.0, 9.0)	
Diabetes hospital admissions, n (%)			
0	1430 (98.7)	1430 (98.7)	0.01
1	14 (1.0)	15 (1.0)	
≥2	5 (0.3)	4 (0.3)	
Provider Characteristics			
Provider care team, n (%)			
PCP	662 (45.7)	665 (45.9)	0.05
Psychiatry	45 (3.1)	47 (3.2)	
Endocrinology	2 (0.1)	2 (0.1)	
PCP + Psychiatry	426 (29.4)	448 (30.9)	
PCP + Endocrinology	98 (6.8)	93 (6.4)	
Psychiatry + Endocrinology	6 (0.4)	5 (0.3)	
PCP + Psychiatry + Endocrinology	100 (6.9)	86 (5.9)	
Unspecified or other specialist	110 (7.6)	103 (7.1)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2; TCA=tricyclic antidepressant.

Table 4.10. Baseline Characteristics after Match: Mirtazapine vs. Aripiprazole (N=2,418)

Characteristics	Mirtazapine (N=1209)	Aripiprazole (N=1209)	ASD*
Demographics			
Age (years)			
Mean (SD)	51.5 (9.7)	51.6 (9.0)	0.01
Median (IQR)	54.0 (46.0, 59.0)	54.0 (46.0, 58.0)	
Age group, n (%)			
18-29	47 (3.9)	27 (2.2)	
30-39	92 (7.6)	107 (8.9)	
40-49	280 (23.2)	277 (22.9)	
50-64	790 (65.3)	798 (66.0)	
Male, n (%)	461 (38.1)	469 (38.8)	0.01
Index year, n (%)			
2010	227 (18.8)	219 (18.1)	0.04
2011	215 (17.8)	218 (18.0)	
2012	235 (19.4)	237 (19.6)	
2013	177 (14.6)	179 (14.8)	
2014	182 (15.1)	194 (16.0)	
2015	173 (14.3)	162 (13.4)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	235 (19.4)	229 (18.9)	0.02

Characteristics	Mirtazapine (N=1209)	Aripiprazole (N=1209)	ASD*
MGH-AD Score 1.5-2	696 (57.6)	705 (58.3)	
MGH-AD Score 2.5-3	129 (10.7)	126 (10.4)	
MGH-AD Score ≥ 3.5	149 (12.3)	149 (12.3)	
Antidepressant use, n (%)			
SSRI	865 (71.5)	859 (71.1)	0.01
SNRI	530 (43.8)	543 (44.9)	0.02
Serotonin modulator	241 (19.9)	221 (18.3)	0.04
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	857 (70.9)	845 (69.9)	0.02
Recent	324 (26.8)	335 (27.7)	
Former	28 (2.3)	29 (2.4)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	542 (44.8)	537 (44.4)	0.01
Alcohol abuse/dependence	45 (3.7)	46 (3.8)	<0.01
Substance abuse/dependence	63 (5.2)	54 (4.5)	0.03
Suicide or intentional self-inflicted injury	29 (2.4)	25 (2.1)	0.02
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	635 (52.5)	615 (50.9)	0.06
Moderate (aDCSI score=1-3)	503 (41.6)	507 (41.9)	

Characteristics	Mirtazapine (N=1209)	Aripiprazole (N=1209)	ASD*
Severe (aDCSI score ≥4)	71 (5.9)	87 (7.2)	
Diabetes regimen, n (%)			
No antidiabetic drug use	410 (33.9)	413 (34.2)	0.07
OAD only	459 (38.0)	449 (37.1)	
Insulin only	143 (11.8)	143 (11.8)	
Non-insulin injectable only	10 (0.8)	5 (0.4)	
Insulin + OAD only	124 (10.3)	134 (11.1)	
OAD + non-insulin injectable only	42 (3.5)	39 (3.2)	
Insulin + non-insulin injectable only	6 (0.5)	7 (0.6)	
OAD + insulin+ non-insulin injectable	15 (1.2)	19 (1.6)	
Diabetes drug class, n (%)			
Metformin	487 (40.3)	478 (39.5)	0.02
Sulfonylurea	185 (15.3)	194 (16.0)	0.02
Thiazolidinedione	80 (6.6)	85 (7.0)	0.02
Alpha-glucosidase inhibitor	2 (0.2)	3 (0.2)	0.02
Meglitinide	8 (0.7)	10 (0.8)	0.02
SGLT2 inhibitor	14 (1.2)	24 (2.0)	0.07
DPP-4 inhibitor	136 (11.2)	134 (11.1)	0.01
GLP-1 agonist	71 (5.9)	67 (5.5)	0.01
Amylin analog	2 (0.2)	3 (0.2)	0.02
Insulin	288 (23.8)	303 (25.1)	0.03

Characteristics	Mirtazapine (N=1209)	Aripiprazole (N=1209)	ASD*
Medical comorbidity [c], n (%)			
Hypertension	819 (67.7)	837 (69.2)	0.03
Coronary atherosclerosis and other heart diseases	138 (11.4)	157 (13.0)	0.05
Angina pectoris	37 (3.1)	41 (3.4)	0.02
Myocardial infarction or unstable angina	39 (3.2)	32 (2.6)	0.03
Disorders of lipid metabolism	759 (62.8)	787 (65.1)	0.05
Congestive heart failure	53 (4.4)	50 (4.1)	0.01
Obesity diagnosis	242 (20.0)	278 (23.0)	0.07
Resource Utilization			
Outpatient depression visits			
Mean (SD)	5.3 (7.9)	5.7 (8.1)	0.05
Median (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	
Psychiatric hospital admissions, n (%)			
0	1173 (97.0)	1167 (96.5)	0.05
1	28 (2.3)	36 (3.0)	
≥2	8 (0.7)	6 (0.5)	
Outpatient diabetes visits			
Mean (SD)	5.9 (6.5)	6.5 (8.7)	0.07
Median (IQR)	4.0 (2.0, 8.0)	5.0 (2.0, 8.0)	

Characteristics	Mirtazapine (N=1209)	Aripiprazole (N=1209)	ASD*
Diabetes hospital admissions, n (%)			
0	1197 (99.0)	1200 (99.3)	0.07
1	12 (1.0)	7 (0.6)	
≥2	0 (0.0)	2 (0.2)	
Provider Characteristics			
Provider care team, n (%)			
PCP	491 (40.6)	497 (41.1)	0.05
Psychiatry	45 (3.7)	39 (3.2)	
Endocrinology	3 (0.2)	1 (0.1)	
PCP + Psychiatry	415 (34.3)	421 (34.8)	
PCP + Endocrinology	77 (6.4)	74 (6.1)	
Psychiatry + Endocrinology	3 (0.2)	4 (0.3)	
PCP + Psychiatry + Endocrinology	87 (7.2)	87 (7.2)	
Unspecified or other specialist	88 (7.3)	86 (7.1)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2.

Table 4.11. Baseline Characteristics after Match: Tricyclic Antidepressant vs. Aripiprazole (N=4,570)

Characteristics	TCA (N=2285)	Aripiprazole (N=2285)	ASD*
Demographics			
Age (years)			
Mean (SD)	51.1 (9.5)	51.1 (9.2)	<0.01
Median (IQR)	53.0 (45.0, 59.0)	53.0 (45.0, 58.0)	
Age group, n (%)			
18-29	60 (2.6)	61 (2.7)	
30-39	233 (10.2)	219 (9.6)	
40-49	561 (24.6)	533 (23.3)	
50-64	1431 (62.6)	1472 (64.4)	
Male, n (%)	700 (30.6)	699 (30.6)	<0.01
Index year, n (%)			
2010	432 (18.9)	414 (18.1)	0.05
2011	458 (20.0)	474 (20.7)	
2012	438 (19.2)	453 (19.8)	
2013	319 (14.0)	332 (14.5)	
2014	364 (15.9)	333 (14.6)	
2015	274 (12.0)	279 (12.2)	
Depression and Psychiatric History			
Depression severity [a], n (%)			
MGH-AD Score ≤1	304 (13.3)	316 (13.8)	0.04

Characteristics	TCA (N=2285)	Aripiprazole (N=2285)	ASD*
MGH-AD Score 1.5-2	1461 (63.9)	1448 (63.4)	
MGH-AD Score 2.5-3	258 (11.3)	240 (10.5)	
MGH-AD Score ≥ 3.5	262 (11.5)	281 (12.3)	
Antidepressant use, n (%)			
SSRI	1613 (70.6)	1560 (68.3)	0.05
SNRI	1046 (45.8)	1130 (49.5)	0.07
Serotonin modulator	364 (15.9)	379 (16.6)	0.02
Recency of antidepressant use [b], n (%)			
Adjunctive therapy	1751 (76.6)	1746 (76.4)	0.01
Recent	498 (21.8)	500 (21.9)	
Former	36 (1.6)	39 (1.7)	
Psychiatric comorbidity [c], n (%)			
Anxiety Disorder	853 (37.3)	883 (38.6)	0.03
Alcohol abuse/dependence	73 (3.2)	62 (2.7)	0.03
Substance abuse/dependence	86 (3.8)	85 (3.7)	<0.01
Suicide or intentional self-inflicted injury	19 (0.8)	33 (1.4)	0.06
Diabetes and Cardiovascular History			
Diabetes severity [d], n (%)			
Mild (aDCSI score=0)	1221 (53.4)	1197 (52.4)	0.02
Moderate (aDCSI score=1-3)	924 (40.4)	948 (41.5)	

Characteristics	TCA (N=2285)	Aripiprazole (N=2285)	ASD*
Severe (aDCSI score≥4)	140 (6.1)	140 (6.1)	
Diabetes regimen, n (%)			
No antidiabetic drug use	714 (31.2)	693 (30.3)	0.04
OAD only	920 (40.3)	926 (40.5)	
Insulin only	250 (10.9)	240 (10.5)	
Non-insulin injectable only	29 (1.3)	27 (1.2)	
Insulin + OAD only	252 (11.0)	268 (11.7)	
OAD + non-insulin injectable only	71 (3.1)	76 (3.3)	
Insulin + non-insulin injectable only	11 (0.5)	14 (0.6)	
OAD + insulin+ non-insulin injectable	38 (1.7)	41 (1.8)	
Diabetes drug class, n (%)			
Metformin	989 (43.3)	1002 (43.9)	0.01
Sulfonylurea	353 (15.4)	359 (15.7)	0.01
Thiazolidinedione	168 (7.4)	190 (8.3)	0.04
Alpha-glucosidase inhibitor	5 (0.2)	10 (0.4)	0.04
Meglitinide	18 (0.8)	12 (0.5)	0.03
SGLT2 inhibitor	29 (1.3)	41 (1.8)	0.04
DPP-4 inhibitor	252 (11.0)	259 (11.3)	0.01
GLP-1 agonist	145 (6.3)	152 (6.7)	0.01
Amylin analog	4 (0.2)	6 (0.3)	0.02
Insulin	551 (24.1)	563 (24.6)	0.01

Characteristics	TCA (N=2285)	Aripiprazole (N=2285)	ASD*
Medical comorbidity [c], n (%)			
Hypertension	1561 (68.3%)	1550 (67.8%)	0.01
Coronary atherosclerosis and other heart diseases	240 (10.5%)	257 (11.2%)	0.02
Angina pectoris	51 (2.2%)	49 (2.1%)	0.01
Myocardial infarction or unstable angina	50 (2.2%)	51 (2.2%)	<0.01
Disorders of lipid metabolism	1474 (64.5%)	1486 (65.0%)	0.01
Congestive heart failure	78 (3.4%)	86 (3.8%)	0.02
Obesity diagnosis	548 (24.0%)	535 (23.4%)	0.01
Resource Utilization			
Outpatient depression visits			
Mean (SD)	4.9 (7.4)	5.4 (8.7)	0.06
Median (IQR)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	
Psychiatric hospital admissions, n (%)			
0	2225 (97.4)	2229 (97.5)	0.02
1	54 (2.4)	49 (2.1)	
≥2	6 (0.3)	7 (0.3)	
Outpatient diabetes visits			
Mean (SD)	6.0 (6.6)	6.1 (7.1)	0.01
Median (IQR)	4.0 (2.0, 8.0)	4.0 (2.0, 8.0)	

Characteristics	TCA (N=2285)	Aripiprazole (N=2285)	ASD*
Diabetes hospital admissions, n (%)			
0	2272 (99.4)	2270 (99.3)	0.01
1	9 (0.4)	10 (0.4)	
≥2	4 (0.2)	5 (0.2)	
Provider Characteristics			
Provider care team, n (%)			
PCP	6 (0.3)	5 (0.2)	0.03
Psychiatry	152 (6.7)	144 (6.3)	
Endocrinology	1105 (48.4)	1115 (48.8)	
PCP + Psychiatry	164 (7.2)	159 (7.0)	
PCP + Endocrinology	596 (26.1)	611 (26.7)	
Psychiatry + Endocrinology	204 (8.9)	191 (8.4)	
PCP + Psychiatry + Endocrinology	11 (0.5)	13 (0.6)	
Unspecified or other specialist	47 (2.1)	47 (2.1)	

*ASDs≥0.1 indicates imbalance in baseline characteristics.

[a] The Massachusetts General Hospital-Antidepressant (MGH-AD) score assigns one point for each adequate antidepressant trial (at least two prescription fills for the same antidepressant) and half a point for each extended duration of use (at least three prescription fills for the same antidepressant) or dose titration (increase in dose for the same antidepressant); higher scores indicate more severe depression.

[b] Adjunctive therapy= ≥30 days overlap between index drug and other antidepressant medication (e.g. selective serotonin reuptake inhibitor); recent = end of supply for last antidepressant medication used was within 180 days of index date, but less than 30 day overlap with index drug; former = end of supply for last antidepressant medication was greater than 180 days but within 365 days of index date.

[c] Psychiatric and medical comorbidities were identified based on the Agency for Healthcare Research and Quality Clinical Classifications Software.[6]

[d] The adopted diabetes complications severity index (aDCSI) is a claims based measure of diabetes severity where higher scores indicate more severe disease. The aDSCI has been shown to predict diabetes hospitalizations and has been validated against the original DCSI, which was developed to model diabetes severity, and where higher scores predict mortality, hospitalizations and higher healthcare utilization.

Abbreviations: aDCSI =adopted diabetes complications severity index; ASDs=absolute standardized differences; DPP-4= dipeptidyl peptidase 4; GLP-1=glucagon-like peptide 1; IQR= interquartile range; MGH-AD= Massachusetts General Hospital- Antidepressant version; PCP=primary care provider; OAD= oral antidiabetic drug; SGLT2=sodium-glucose co-transporter 2; TCA=tricyclic antidepressant.

Appendix 5. Number of Events and Incidence Rate of Diabetes-Related Hospitalizations among Matched Groups of Patients

Match	Treatment	Number of Patients (n)	Number of Events (n)	Total Person-Years of Follow-up	Incidence Rate (95% CI) per 1000 Person-Years
Between SGAs and Non-SGAs					
SGAs vs. Non-SGAs	SGA	6465	39	3602	10.8 (7.9-18.8)
	Non-SGA	6465	44	4267	10.3 (7.7-13.9)
Between Treatment Subgroups					
1) QUE vs. ARI	QUE	1543	12	844	14.2 (8.1-25.0)
	ARI	1543	11	849	13.0 (7.2-23.4)
2) QUE vs. MIR	QUE	1110	7	564	12.4 (5.9-26.1)
	MIR	1110	11	542	20.3 (11.3-36.7)
3) QUE vs. TCA	QUE	1564	10	826	12.1 (6.5-22.5)
	TCA	1564	7	790	8.9 (4.2-18.6)
4) QUE vs. BUP	QUE	1884	15	1007	14.9 (9.0-24.7)
	BUP	1884	10	1309	7.6 (4.1-14.2)
5) BUP vs. ARI	BUP	3325	16	2463	6.5 (4.0-10.6)
	ARI	3325	20	1983	10.1 (6.5-15.6)

Match	Treatment	Number of Patients (n)	Number of Events (n)	Total Person-Years of Follow-up	Incidence Rate (95% CI) per 1000 Person-Years
6) BUP vs. MIR	BUP	1725	12	1145	10.5 (6.0-18.5)
	MIR	1725	21	826	25.4 (16.6-39.0)
7) BUP vs. TCA	BUP	5021	25	3396	7.4 (5.0-10.9)
	TCA	5021	24	2495	9.6 (6.4-14.4)
8) MIR vs. TCA	MIR	1449	25	874	28.6 (19.3-42.3)
	TCA	1449	21	2068	10.2 (6.6-15.6)
9) MIR vs. ARI	MIR	1209	18	659	27.3 (17.2-43.4)
	ARI	1209	7	691	10.1 (4.8-21.3)
10) TCA vs. ARI	TCA	2285	38	2964	12.8 (9.3-17.6)
	ARI	2285	21	2068	10.2 (6.6-15.6)

Abbreviations: ARI=aripiprazole, BUP=bupropion; CI=confidence interval, HR=hazard ratio, MIR=Mirtazapine, QUE=quetiapine, SGA=second generation antipsychotic; TCA=tricyclic antidepressant.

Appendix 6. Type of Diabetes-Related Hospitalization by ICD-9 CM Codes

Exposure group	All diabetes-related hospitalizations (ICD-9 CM 250.xx), n (%)[a]	Specific type of diabetes-related hospitalization*, n (%)[b]				p-value[c]
		DKA (ICD-9 CM 250.1x)	HHS (ICD-9 CM 250.2x)	Diabetes hospitalization without complications (ICD-9 CM 250.0x)	Diabetes hospitalization with complications (ICD-9 CM 250.4x-250.9x)	
SGA	39 (53.0%)	16 (41.0%)	1 (2.3%)	5 (12.8%)	17 (43.6%)	0.976
Non-SGA	44 (47.0%)	16 (36.4%)	1 (2.6%)	6 (13.6 %)	21 (47.7%)	
Total (n)	83	32	2	11	38	

[a]Any patient who had a hospitalization during follow-up with a primary diagnosis for diabetes mellitus (ICD-9 CM 250.xx) was deemed to have a diabetes-related hospitalization.

[b]No patients had a primary diagnoses ICD-9 CM 250.3x (diabetic coma)

[c]X^2 test

Abbreviations: DKA= Diabetes ketoacidosis; HHS= Hyperosmolar hyperglycemic state; ICD-9=International Classification of Diseases, Ninth Revision, Clinical Modification

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