Supplementary Material

List of Supplementary Material for the article

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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 HCl, 348 mg bupropion HBr= 300 bupropion, 522 mg bupropion HBr= 450 mg bupropion HCl
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]

^dThe 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.

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^dThe 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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