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The Impact of Depression Medications on Oral Antidiabetic Drug Adherence in Patients with Diabetes and Depression

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Abstract

Aims—To compare adherence and persistence to oral antidiabetic drugs (OAD) between patients who are new users of second generation antipsychotics (SGA) versus new users of other depression therapies in adults with type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD).

Methods—Adults 18-64 years with previously-treated T2DM and MDD (past OAD and SSRI/SNRI use) who are new users of SGA or non-SGA therapies (bupropion, lithium, mirtazapine, thyroid hormone, tricyclic antidepressant) were identified in the 2009-2015 MarketScan® Commercial Claims and Encounters database. Multivariate regression models were used to determine the odds of a 10% decline in OAD adherence over 180- and 365-days, and time to OAD discontinuation, adjusting for differences between groups.

Results—A total of 8,664 (21.5% SGA), 8,311 (22.1% SGA), and 17,524 (21.3% SGA) patients met inclusion criteria for the 180-day adherence, 365-day adherence, and persistence cohorts, respectively. Over 180-days, 16.6% of SGA and 13.3% of non-SGA initiators had a 10% decline

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Duality of Interest

The other authors have no conflicts of interest to declare.

Author Contributions

All authors contributed to study design, interpretation of results, and manuscript revisions, as well as provided final approval for the manuscript. S.X. also analyzed the data and wrote the first draft of the manuscript. As the guarantor of this work, S.X. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

in OAD adherence (adjusted odds ratio [OR]=1.41, 95% CI 1.21-1.63). Over 365-days, 22.3% of SGA and 18.9% of non-SGA initiators had a 10% decline (OR=1.34, 95% CI 1.17-1.53). Time to OAD discontinuation was similar between groups (adjusted hazard ratio=1.03, 95% CI 0.94-1.12).

Conclusion—Use of SGA was associated with a 1.3-1.4 times higher odds of a 10% decline in OAD adherence. Adherence to OAD is critical for optimal diabetes control and reductions in this magnitude may impact A1C. Close monitoring of OAD adherence after SGA initiation is warranted.

Keywords

medication adherence; depression; type 2 diabetes mellitus; healthcare administration claims; antidepressants; antipsychotics

1. Introduction

Comorbid depression affects one in five patients with type 2 diabetes and is associated with poor diabetes self-care, suboptimal medication adherence, worse clinical outcomes, reduced survival, and higher healthcare costs (Egede, Walker, Bishu, & Dismuke, 2016; Fisher, Chan, Nan, Sartorius, & Oldenburg, 2012; Jeffrey S Gonzalez et al., 2008; Petrak, Baumeister, Skinner, Brown, & G Holt, 2015; Roy & Lloyd, 2012). Because of the adverse bidirectional interaction between depression and diabetes, where depression is associated with poor glycemic control and poor glycemic control is associated with poor response to depression treatment, treatment goals should focus on both improvement of depression symptoms and maintenance of diabetes control (Fisher et al., 2012; Petrak et al., 2015). In recent years, the use of second generation antipsychotics (SGA) for unipolar depression has increased in the United States, with SGAs being prescribed for one in eight adult outpatient nonpsychotic depression visits in 2009-2010 (Gerhard et al., 2014). Notably, rates of SGA use was two times higher among patients with comorbid diabetes, hyperlipidemia or cardiovascular disease (Gerhard et al., 2014) despite their well-documented cardiometabolic risks (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity, 2004).

Physicians and patients with comorbid depression and diabetes must carefully weigh the metabolic risks of SGAs against the potential benefit of depression control. Compared to other adjunctive treatments, SGAs have the most consistent clinical trial evidence for major depressive disorder (MDD) after inadequate or non-response to antidepressants (Kennedy et al., 2016; Komossa, Depping, Gaudchau, Kissling, & Leucht, 2010) and is the only class of drugs approved by the Food and Drug Administration for this indication. Better control of depression symptoms may result in improved adherence to diabetes medications and self-care behaviors (Jeffrey S Gonzalez et al., 2008; Markowitz, Gonzalez, Wilkinson, & Safren, 2011), possibly negating any direct negative impact on glycemic control with SGAs. Similarly, while antidepressants have been implicated as a risk factor for developing diabetes (Barnard, Peveler, & Holt, 2013), preliminary research suggest that antidepressants have a positive impact on glycemic control among patients with pre-existing diabetes (Baumeister, Hutter, & Bengel, 2012; Brieler, Lustman, Scherrer, Salas, & Schneider, 2016), which is

thought to be related to improved self-care behaviors and adherence to medications after alleviation of depressive symptoms (J. S. Gonzalez et al., 2008; Jeffrey S Gonzalez et al., 2008).

Although adherence to diabetes medications may be an important pathway between depression and glycemic control (J. S. Gonzalez et al., 2008; Jeffrey S Gonzalez et al., 2008) and is also a significant predictor of diabetes hospitalizations, healthcare costs, and patient survival (Balkrishnan et al., 2003; Ho et al., 2006; Rozenfeld, Hunt, Plauschinat, & Wong, 2008), there is a paucity of research evaluating the effect of depression therapies on diabetes medication adherence (Baumeister et al., 2012; Markowitz et al., 2011). The objective of this study is to compare adherence and persistence to oral antidiabetic drugs (OAD) between patients who are new users of SGAs and those who are new users of non-SGA depression medications. Based on previous research (Desai et al., 2014; Kennedy et al., 2016; Spielmans et al., 2013; Zhou et al., 2015), we hypothesized that SGA users would have better adherence to OAD compared to non-SGA users. This study is restricted to adults 18-64 years with previously-treated MDD [past use of a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI)] and pre-existing type 2 diabetes.

2. Methods

2.1 Study design and data source

This retrospective cohort study used data from the MarketScan® Commercial Claims and Encounters databases from January 1, 2009 to December 31, 2015. The databases contained patient-level health care utilization and enrollment information across inpatient, outpatient, and prescription claims from a selection of large employer-sponsored commercial plans (Hansen, Leigh G; Chang, 2011). The inpatient and outpatient databases included diagnoses information (e.g., International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes) and dates of service while the pharmacy database provided the National Drug Code (NDC) of the drug dispensed, date dispensed, quantity, days' supply, and copayments. Due to the transition from ICD-9 to ICD-10 in 2015, ICD-10 codes in 2015 were mapped to ICD-9CM codes using the General Equivalence Mappings provided by the Center for Medicare and Medicaid Services (Centers for Medicare and Medicaid Services (CMS), 2014).

2.2 Subjects

Adults 18-64 years with a new prescription for a cohort drug - either an oral non-clozapine SGA or a non-SGA depression medication [bupropion, lithium, mirtazapine, thyroid hormone, or tricyclic antidepressant (TCA)] - between January 1, 2010 and December 30, 2015 were eligible for inclusion. The date of the first dispensing of the cohort drug was assigned as the index date. To maintain a new user cohort, patients could not have had any dispensing of a cohort drug during the one year pre-index period (i.e., 365 days prior to index date).

To be included, patients were required to have been diagnosed with type 2 diabetes and have had filled at least one prescription for an OAD in the one year pre-index period. To meet criteria for type 2 diabetes diagnosis, patients must have had at least one inpatient or two outpatient ICD-9CM 250.x0 or 250.x2, or two prescription fills for a non-metformin diabetes drug identified by Healthcare Effectiveness Data and Information Set (Leong et al., 2013). Patients must also have had a diagnosis for MDD [any inpatient or outpatient ICD-9CM 296.2x, 296.3x, 300.4, or 311 (Fiest et al., 2014)] and have had filled at least one SSRI or SNRI during the pre-index period. Those with any diagnosis of schizophrenia (295.xx), bipolar disorder (296.0x, 296.1x, 296.4x-296.8x) (Hartung et al., 2013), dementia (290.xx), delusional disorder (297.xx), non-organic psychosis (298.xx), autism (299.0), mental retardation (317.0-319.0), cerebral degeneration (331.xx), Parkinson's disease (332.xx), senility without mention of psychosis (797.0) (Hassan, Farmer, Brahm, & Neas, 2016a), or thyroid disorder (240.0-246.0) during the pre-index period were excluded. Patients who have had a prescription filled for clozapine, a first generation antipsychotic, or an injectable SGA during the pre-index period were also excluded, since use of these medications typically represents underlying psychosis.

2.3 Outcome definitions

The outcomes of interest were adherence and persistence to OAD therapy. For the primary adherence outcome, we evaluated the proportion of SGA and non-SGA initiators with a 10% or greater decline in adherence to OAD during the 180 days after versus the 180 days before cohort drug initiation. Adherence was estimated using the proportion of days' covered (PDC), which measures the total amount of medication available to a patient over a given time period. Specifically, PDC was calculated as the sum of the days' supply of each medication divided the number of days between the first and last dispensing plus the days' supply from the last dispensing (Choudhry et al., 2009). This measure was chosen *a priori* because PDC measured over 6 months is more strongly correlated with hemoglobin A1C (A1C) levels compared with other claims-based measures (Zhu, Tu, Rosenman, & Overhage, 2014), and a 10% decline in OAD adherence is associated with a 0.1% increase in A1C (Rozenfeld et al., 2008), a 4% higher odds of hospitalization or emergency department visit (Jha, Aubert, Yao, Teagarden, & Epstein, 2012), and a 8.6-28.9% increase in annual healthcare expenditures (Balkrishnan et al., 2003). As patients often take more than one OAD concurrently, we calculated the average PDC for patients taking multiple OAD classes (Choudhry et al., 2009). Analysis was restricted to patients who had a minimum of two OAD fills and continuous insurance coverage during each measurement period, since estimating adherence using pharmacy claims is only meaningful when patients have at least two prescription fills in a closed pharmacy system.

Persistence to OAD was measured from the index date to date of discontinuation, where we allowed patients to have a gap of twice the days' supply for the last OAD prescription. Gaps between prescriptions were calculated as the number of days between the end of one prescription supply and the start of the next. Unlike for adherence, we did not require a minimum of two OAD prescriptions and 180 (or 365 days) of follow-up, however, analysis was restricted to patients who were current users of an OAD at the time of cohort drug initiation (i.e., patients who had a gap of twice the last days' supply between the end of last

OAD fill and the index date were excluded). Follow-up ended at the first occurrence of discontinuation of OAD therapy, switch or addition of a medication from the alternative cohort drug class (e.g., SGA to non-SGA or vice versa), any gap in insurance coverage, or end of the study period (December 31, 2015).

2.4 Study variables

Patient characteristics were assessed during the pre-index period. Potential confounders were identified based on previous studies (Krass, Schieback, & Dhippayom, 2015; Mhatre et al., 2016). Depression severity was approximated using the Massachusetts General Hospital scale-Antidepressant version (MGH-AD) score (Gibson et al., 2010), and by counting depression hospitalizations and outpatient visits. The MGH-AD is a claims-based measure which assigns one point for each adequate antidepressant trial (minimum two fills) and 0.5 points for each optimization strategy (extended duration or dose titration) using the number of antidepressant fills, duration of use, and increase in dose from pharmacy claims (Gibson et al., 2010). The MGH-AD score has been used in other studies as a proxy for depression severity (Hassan et al., 2015, 2016a; Jing et al., 2011) and higher scores indicate more severe depression (Gibson et al., 2010). Diabetes severity was assessed using the adopted Diabetes Complications Severity Index (aDSCI) (Chang, Weiner, Richards, Bleich, & Segal, 2012), diabetes medication use, and health care resource use in the pre-index period. The DSCI was developed to model the severity of diabetes, and higher scores predict mortality, hospitalizations and higher healthcare utilization (Young et al., 2008). The aDSCI is a claims-based measure that has been validated against the DCSI and shown to predict diabetes hospitalizations (Chang et al., 2012). We also distinguished patients who initiated a cohort drug as adjunctive therapy (minimum 30-day overlap between cohort drug and SSRI/SNRI) versus monotherapy (less than 30-day overlap). Other variables assessed included medical and psychiatric comorbidities, concomitant medications, pill burden, polypharmacy, copayment, and predictors of future OAD adherence including total number of OAD fills, number of OAD classes filled, and days' supply of last filled OAD (Mhatre et al., 2016).

2.5 Statistical Analyses

We used the Pearson's Chi-square test or the Fisher's exact test to assess baseline differences between the SGA and the non-SGA initiator cohorts for categorical variables. The student t-test was used to evaluate continuous and normally distributed variables, and the Wilcoxon rank sum test for ordinal or non-normally distributed continuous variables. Multivariable logistic regression was used to compare the odds of a 10% and 20% decline in adherence and the odds of non-adherence to OAD between SGA and non-SGA initiators. Kaplan Meier curves were used to estimate time to OAD discontinuation and the log-rank test was used to determine whether survivor functions differed across groups. We used the Cox proportional hazards models to compare risk of non-persistence to OAD therapy, adjusting for selected confounders. Demographic and clinical covariates were evaluated for inclusion in multivariate regression by first assessing each in single-factor stratified analyses. Variables that met a cut-off of $p < 0.10$ were further tested for inclusion in multivariate regression using manual backwards selection, and variables that met a 10% change in estimate criterion were included in the final regression models.

We conducted several sensitivity analyses to test the robustness of our findings. We also measured adherence 1) over 365 days compared to 180 days in the main analysis; 2) using a 80% PDC cut-off where non-adherence was defined as $PDC < 0.8$ compared to a 10% decline in the main analysis; 3) using the “Diabetes All Class Rate” (Alliance, 2014) instead of the average PDC for patients using multiple diabetes drug classes in the main analysis; 4) measuring a 20% decline compared to 10% decline in the main analysis; and 5) excluding patients with an inpatient admission since inpatient prescription claims are not included in the database. For the persistence outcome, sensitivity analyses with 45, 60, and 90-day permissible gaps were conducted compared to a gap of two times the last days’ supply in the main analysis. SAS version 9.4 (NC, Cary) and Stata version 14 (College Station, TX) were used for data management and analyses. The University of Illinois at Chicago institutional review board approved this study as exempt from review.

3. Results

3.1. Clinical and demographic characteristics of study subjects

A total of 3,734 SGA and 13,790 non-SGA initiators met the inclusion criteria for the persistence cohort (see Supplemental Fig S1 for patient selection criteria). The median age was 54 years in both groups and a higher proportion of SGA initiators were male (Table 1). At baseline, SGA users had more severe depression and psychiatric comorbidities and used more antidepressants and psychotropic medications. Adherence to SSRI or SNRI at baseline was high, with 80% of patients being adherent to therapy in both groups. About 80% of SGA initiators were using a SSRI/SNRI concurrently compared to 64% of non-SGA initiators. Diabetes severity and treatment history were not significantly different, and about 70% of patients used OAD only. A higher proportion of SGA initiators had a diagnosis of coronary atherosclerosis or other heart diseases while non-SGA initiators were more frequently diagnosed with hyperlipidemia and obesity, although cardiovascular drug use was similar. In general, SGA initiators utilized more inpatient, outpatient, and pharmacy resources, although pill burden and polypharmacy use were high in both groups.

3.2. Adherence to oral antidiabetic drugs

For the 180-day adherence cohort, 1,865 and 6,799 SGA and non-SGA initiators met inclusion criteria. Patient characteristics were generally similar in the persistence cohort, although the adherence cohort appeared to be slightly older, had used OAD longer, had higher pill burden and polypharmacy use, and spent more on diabetes medication copayments in the past year. Additional patient characteristics for the 365-day adherence cohort are shown in Supplemental Table S1. In all cohorts, the majority of SGA initiators used aripiprazole (54-57%) or quetiapine (27-29%) while the majority of non-SGA initiators used bupropion (63-68%) or a TCA (24%) (Supplemental Table S2 shows the specific cohort drugs used).

Adherence to OAD was high in the pre-index period and similar between SGA and non-SGA initiators (Table 2). In the 180-days pre-index, 20.9% of SGA and 21.0% of non-SGA initiators were non-adherent ($PDC < 0.8$) to therapy ($p=0.953$). In the 180-days post-index, 21.3% and 18.7% of SGA and non-SGA initiators were non-adherent to OAD ($p=0.012$). A

total of 16.6% of SGA and 13.3% of non-SGA initiators had a 10% or greater decline in adherence to OAD therapy comparing the 180 days before and after the index date ($p < 0.001$). When adherence was measured over the 365 days post-index, a greater proportion of SGA initiators were non-adherent (33.4% versus 30.6%, $p = 0.025$) and had a 10% or greater decline in OAD adherence compared to non-SGA initiators (22.3% versus 18.9%, $p = 0.001$).

In crude analyses, SGA initiators had a 1.31 (95% confidence interval (CI) 1.13-1.50) and 1.23 (95% CI 1.09-1.40) times higher odds of having a 10% decline in adherence to OAD when evaluated over 180 and 365 days respectively (Table 2). After adjustment for age, gender, depression and diabetes severity, polypharmacy, pill burden, days' supply of last OAD prescription filled pre-index, adjunctive vs monotherapy, and baseline adherence to OAD, odds of 10% decline in OAD adherence was 1.4 times higher in SGA initiators over 180 days (adjusted odds ratio (OR) = 1.41, 95% CI 1.21-1.63) and 1.3 times higher in SGA initiators over 365 days (adjusted OR = 1.34, 95% CI 1.17-1.53). Sensitivity analyses did not alter the direction or significance of results (Figure 1, Supplemental Table S3).

3.3. Persistence to oral antidiabetic drugs

Persistence to OAD was similar between groups and Kaplan Meier survival curves were not significantly different (log rank test, $p = 0.134$) (Supplemental Figure S2). In primary analysis, median time to discontinuation was 118 and 123 days for SGA and non-SGA initiators respectively (Table 3). Hazards of discontinuation was similar between groups in both crude (hazard ratio (HR) = 1.07, 95% CI 0.98-1.16) and adjusted analyses (adjusted HR = 1.03, 95% CI 0.94-1.12). Altering the permissible gap to 45, 60, and 90 days did not appreciably change the adjusted HR, although median times to non-persistence were longer with less restrictive gaps.

4. Discussion

The goal of this study was to examine adherence and persistence to OAD therapy comparing new users of SGAs and new users of non-SGA depression therapies with previously treated MDD and type 2 diabetes. SGA initiators had a 1.3-1.4 times higher odds of having a 10% or greater decline in OAD adherence, while persistence to OAD was not different between groups. Sensitivity analysis using different measures of adherence and persistence were consistent with the primary analysis. This finding was surprising as we had originally expected that SGA initiators would have better adherence to OAD given preliminary evidence that antipsychotics use is associated with improved adherence to OAD (Desai, Adeyemi, Richards, & Lawson, 2014), guideline recommendations of close metabolic monitoring with SGA use (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, 2004) resulting in potentially closer follow-up and attention to diabetes therapy, and consistent clinical trial evidence demonstrating SGAs' efficacy in depression relief (Kennedy et al., 2016; Spielmans et al., 2013; Zhou et al., 2015).

The only other study that has evaluated the effect of antipsychotic use on OAD adherence found that antipsychotic users were two times *more* likely to be adherent to OAD therapy

compared to non-users (Desai et al., 2014). However, this study was different from ours in terms of the exposure, the comparison group, and the study population. Desai and colleagues compared first generation antipsychotic or SGA users versus non-users who initiated an OAD among a Texas Medicaid-insured, antipsychotic treatment-experienced (at least 2 antipsychotic prescriptions before and after OAD initiation) population, while we compared initiators of SGA versus non-SGA depression treatments in an OAD treatment-experienced, commercially-insured population. The Medicaid cohort likely had poorer diabetes control given that only 37.2% and 24.0% of antipsychotic users and non-users were adherent to OAD therapy over one year whereas in our study, 67.8% SGA and 67.9% non-SGA initiators were adherent to OAD in the year prior to SGA initiation. Study differences also highlight the need to understand SGA effects in a pre-existing diabetic population. Patients who initiate diabetes therapy after antipsychotic exposure may have developed diabetes or started an OAD as a consequence of SGA use and may be managed differently from patients with pre-existing diabetes. Additionally, while the current study focused on patients with MDD, the diagnoses were unspecified in Desai's study and thus it is probable that a proportion of these patients were prescribed antipsychotics for schizophrenia, bipolar disorder or other off-label indications. It may be necessary to separately evaluate the impact of SGAs on OAD adherence in patients with depression. While studies have consistently shown that patients with depression were *less* adherent to OAD than patients without depression (Krass et al., 2015), several Veterans Affairs (VA) studies have found that patients with schizophrenia or severe mental illness (SMI) were *more* adherent to OAD and antihyperlipidemic medications compared to patients without mental illness (Kreyenbuhl et al., 2010, 2011; Nelson, Graham, Lindsey, & Rasu, 2011). The authors postulated that this may have been related to increased healthcare contacts in persons with SMI, or that the experience from managing a SMI confers advantages in the management of other conditions. These studies were all conducted in the VA, and it remains uncertain whether results might differ in a community setting.

It is worth noting that our study population was relatively young (majority 40-64 years) and probably fairly healthy compared to an uninsured or older population with type 2 diabetes and comorbid MDD. The SGA initiators had more severe depression than the non-SGA initiators; however, patients with the most severe depression were likely excluded given that this was a commercially-insured population, only 3.3% of SGA initiators had a psychiatric hospitalization in the past year, and patients who previously filled a non-SGA cohort drug were excluded. In contrast, diabetes severity and adherence to OAD were similar between groups at baseline. Adherence to OAD was high and 79% of patients in both groups were adherent to OAD in the 180 days pre-index. Part of this may be due to the high use of 90-day prescription fills (>40% in both groups), indicating that diabetes regimens may be relatively stable at baseline.

Examining crude estimates, about 1 in 6 SGA initiators and 1 in 8 non-SGA initiators had a 10% or greater decline in OAD adherence over 6 months, and 1 in 14 and 1 in 20 SGA and non-SGA initiators experienced a 20% or greater decline in adherence to OAD respectively. Numerous studies have documented that poor adherence to OAD is associated with poor diabetes outcomes, and declines of this magnitude may impact glycemic control (Balkrishnan et al., 2003; Jha et al., 2012; Rozenfeld et al., 2008); therefore, clinicians may

need to more closely monitor patients' adherence to OAD after initiation of antidepressant medications, in particular among SGA initiators.

Although our study was unable to determine the reasons behind the higher decline in OAD adherence observed among SGA initiators, there are several plausible explanations. One potential reason for the increased odds of a 10% or greater decline in OAD adherence in the SGA group could be that their glycemic control deteriorated and they were switched from OAD to insulin therapy. While we were unable to conclusively measure insulin intensification in the insulin-experienced group, we evaluated whether there was differential insulin initiation in insulin naïve patients. However, none of the insulin naïve patients (i.e. OAD-only users who did not have any prescription claim for insulin therapy in the 365 days prior to initiation of SGA (76.7%, n=1,426) or non-SGA (77.0%, n=5,232) in the 180-day adherence cohort had started insulin during the 180-days when adherence to OAD therapy was accessed. Therefore, the greater odds of a 10% decline in OAD adherence in the SGA group could not be explained by switching to insulin treatment in these patients. In addition, adverse effects of SGAs could have led to premature discontinuation of these therapies, and these patients may have had unresolved or worsening depressive symptoms, which led to the decline in adherence to OAD. While discontinuation of SGAs is already high in clinical trials (Chen, Gao, & Kemp, 2011), it may be magnified in patients with diabetes, who are perhaps more vulnerable to the harmful consequences of weight gain and hyperglycemia. It is also possible that SGA initiators felt better in general due to SGA response and were able to improve other aspects of diabetes self-care (e.g. lifestyle modification), leading to a reduction in the perceived need for OAD therapy. Also, the impact of SGA use on perceptions towards food, appetite, weight, and body image may be complicated. Despite the typical negative connotations surrounding SGA-induced weight gain, anecdotally, we know of patients who are actually appreciative of weight gain because they feel better. The perceived need for OAD treatment may be reduced in these patients, affecting their adherence to therapy. All these reasons are speculative and outside the scope of the current study, but may be important avenues for future research.

Despite having the most clinical trial evidence for MDD over other adjunctive treatments, several systematic reviews have concluded that SGAs are only modestly more efficacious than placebo, but at the risk of increased adverse events (Komossa et al., 2010; Rummel-Kluge et al., 2010; Spielmans et al., 2013; Wright, Eiland, & Lorenz, 2013). In a US Veterans Health Administration randomized controlled trial (RCT), aripiprazole augmentation and switching to bupropion monotherapy resulted in only a modest increased likelihood of remission compared with switching to bupropion monotherapy after 12 weeks (Mohamed et al., 2017). Two small 6-week RCTs involving 65 and 103 Korean patients have directly evaluated SGAs against active comparators for MDD (Cheon et al., 2017; Han et al., 2015). One found that adjunctive aripiprazole resulted in greater improvement of depressive symptoms compared to switching antidepressants (Han et al., 2015) and the other concluded that adjunctive aripiprazole and bupropion were equally efficacious, although patients on aripiprazole experienced faster remission (Cheon et al., 2017). To date, "real-world" studies have failed to demonstrate the effectiveness of SGAs over other depression therapies for MDD in terms of quality of life, hospitalizations, or healthcare costs (Al-Ruthia, Hong, & Solomon, n.d.; Hassan et al., 2015; Hassan, Farmer, Brahm, & Neas, 2016b; Wade,

Kindermann, Hou, & Thase, 2014). We reiterate what other authors have previously stated, that there is limited knowledge on proper and effective use of SGAs for MDD outside of clinical trials and more research on practical clinical issues in routine practice is warranted (Han et al., 2013; Pae & Patkar, 2013).

The greater decline in adherence observed among SGA initiators may also be related to unmeasured confounding. To address the potential for confounding by indication where SGA initiators had more severe depression and therefore were more likely to have a greater decline in OAD adherence, we tested and controlled for a number of factors at baseline that may be proxies for depression severity (e.g., MGH-AD score, baseline adherence to OAD, prior antidepressant treatment). However, since administrative claims are primarily used for billing instead of clinical or research purposes, the clinical granularity and ability to discern specific depression subtypes (e.g. depression with psychotic features) and severity is limited. In addition, other factors such as race and socioeconomic status may also be confounders that are unmeasured in our database. One may expect that physicians would preferentially prescribe SGAs to depressed patients who appeared to have additional or comorbid psychiatric diagnosis (for example, some may exhibit signs of possible mild cognitive impairment or early dementia that were misinterpreted to be psychotic in nature) that are not documented or coded. Since baseline adherence to OAD was similar between groups and diabetes severity was similar at baseline despite higher depression severity, it is possible that cognitive dysfunction did not impact adherence to OAD or that physicians selectively avoided prescribing SGAs to patients at higher risk for poor glycemic control or who were non-adherent to OAD. Although we adjusted for disease severity using MGH-AD and aDCSI scores, these are proxies but not actual disease severity measures. A limitation common to administrative database studies is misclassification of diagnosis, since ICD-9 codes are intended for billing and not clinical or research purposes. In addition, pharmacy dispensing data only serves as a proxy for adherence but does not ensure that patients have actually taken the medication. Without laboratory data, we were also unable to directly examine the impact of SGA use on glycemic control.

This study is the first to evaluate change in adherence and persistence to OAD comparing SGA versus non-SGA initiators with MDD and type 2 diabetes. We used a clinically meaningful endpoint of 10% decline in OAD, which corresponds with poor glycemic control, diabetes hospitalizations and healthcare costs (Balkrishnan et al., 2003; Jha et al., 2012; Rozenfeld et al., 2008). The reasons, predictors, and clinical implications for the decline in OAD adherence in both groups deserve further study. For physicians treating patients with depression and diabetes, close monitoring of OAD adherence may be warranted, particularly in patients' initiating a SGA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Al-Ruthia YS, Hong SH, Solomon D. Do depressed patients on adjunctive atypical antipsychotics demonstrate a better quality of life compared to those on antidepressants only? A comparative cross-sectional study of a nationally representative sample of the US population. *Research in Social & Administrative Pharmacy: RSAP*. 11(2):228–40. (n.d.). <https://doi.org/10.1016/j.sapharm.2014.06.001>.
- Pharmacy Quality Alliance. Technical Specifications for PQA Approved Measures. 2014. Retrieved February 28, 2017 from http://www.nbch.org/nbch/files/ccLibraryFiles/Filename/000000003537/1_July2014_PQA_Measure_Manual.pdf
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Society of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity. *J Clin Psychiatry*. 2004; 65(2):267–272. <https://doi.org/10.2337/diacare.27.2.596>. [PubMed: 15003083]
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004; 27(2):596–601. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14747245>. [PubMed: 14747245]
- Balkrishnan R, Rajagopalan R, Camacho FT, Huston SA, Murray FT, Anderson RT. Predictors of Medication Adherence and Associated Health Care Costs in an Older Population with Type 2 Diabetes Mellitus: A Longitudinal Cohort Study. *Clinical Therapeutics*. 2003; 25(11):2958–2971. [https://doi.org/10.1016/S0149-2918\(03\)80347-8](https://doi.org/10.1016/S0149-2918(03)80347-8). [PubMed: 14693318]
- Barnard K, Peveler RC, Holt RIG. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. *Diabetes Care*. 2013; 36(10):3337–45. <https://doi.org/10.2337/dc13-0560>. [PubMed: 24065841]
- Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *The Cochrane Database of Systematic Reviews*. 2012; 12(12):CD008381. <https://doi.org/10.1002/14651858.CD008381.pub2>. [PubMed: 23235661]
- Brieler, Ja, Lustman, PJ., Scherrer, JF., Salas, J., Schneider, FD. Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression. *Family Practice*. 2016; 33(1):30–36. <https://doi.org/10.1093/fampra/cmz100>. [PubMed: 26743722]
- Centers for Medicare and Medicaid Services (CMS). 2015 ICD-10-CM and General Equivalence Mappings. 2014. Retrieved March 14, 2017, from <https://www.cms.gov/medicare/coding/icd10/2015-icd-10-cm-and-gems.html>
- Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. *The American Journal of Managed Care*. 2012; 18(11):721–6. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23198714>. [PubMed: 23198714]
- Chen J, Gao K, Kemp DE. Second-generation antipsychotics in major depressive disorder: update and clinical perspective. *Current Opinion in Psychiatry*. 2011; 24(1):10–7. <https://doi.org/10.1097/YCO.0b013e3283413505>. [PubMed: 21088586]
- Cheon EJ, Lee KH, Park YW, Lee JH, Koo BH, Lee SJ, Sung HM. Comparison of the Efficacy and Safety of Aripiprazole Versus Bupropion Augmentation in Patients With Major Depressive Disorder Unresponsive to Selective Serotonin Reuptake Inhibitors: A Randomized, Prospective, Open-Label Study. *Journal of Clinical Psychopharmacology*. 2017; 37(2):193–199. <https://doi.org/10.1097/JCP.0000000000000663>. [PubMed: 28129308]

- Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, Solomon DH. Measuring concurrent adherence to multiple related medications. *American Journal of Managed Care*. 2009; 15(7):457–464. <https://doi.org/10.1021/ac901991x>. [PubMed: 19589013]
- Desai PR, Adeyemi AO, Richards KM, Lawson KA. Adherence to oral diabetes medications among users and nonusers of antipsychotic medication. *Psychiatric Services (Washington, D.C.)*. 2014; 65(2):215–20. <https://doi.org/10.1176/appi.ps.201300118>.
- Egede LE, Walker RJ, Bishu K, Dismuke CE. Trends in Costs of Depression in Adults with Diabetes in the United States: Medical Expenditure Panel Survey, 2004–2011. *Journal of General Internal Medicine*. 2016; 31(6):615–622. <https://doi.org/10.1007/s11606-016-3650-1>. [PubMed: 26969312]
- Fiest KM, Jette N, Quan H, St Germaine-Smith C, Metcalfe A, Patten SB, Beck CA. Systematic review and assessment of validated case definitions for depression in administrative data. *BMC Psychiatry*. 2014; 14(1):289. <https://doi.org/10.1186/s12888-014-0289-5>. [PubMed: 25322690]
- Fisher EB, Chan JCN, Nan H, Sartorius N, Oldenburg B. Cooccurrence of diabetes and depression: conceptual considerations for an emerging global health challenge. *Journal of Affective Disorders*. 2012; 142(Suppl):S56–66. [https://doi.org/10.1016/S0165-0327\(12\)70009-5](https://doi.org/10.1016/S0165-0327(12)70009-5). [PubMed: 23062858]
- Gerhard T, Akincigil A, Correlli CU, Foglio NJ, Crystal S, Olfson M. National trends in second-generation antipsychotic augmentation for nonpsychotic depression. *Journal of Clinical Psychiatry*. 2014; 75(5):490–497. <https://doi.org/10.4088/JCP.13m08675>. [PubMed: 24500284]
- Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, Burton WN, Goetzel RZ. Cost burden of depression resistance in patients with depression. *The American Journal of Managed Care*. 2010; 16(5):370–377. [https://doi.org/10.1016/S1098-3015\(10\)73947-4](https://doi.org/10.1016/S1098-3015(10)73947-4). [PubMed: 20469957]
- Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, Safren SA. Depression and diabetes treatment nonadherence: a metaanalysis. *Diabetes Care*. 2008; 31(12):2398–403. <https://doi.org/10.2337/dc08-1341>. [PubMed: 19033420]
- Gonzalez JS, Safren SA, Delahanty LM, Cagliero E, Wexler DJ, Meigs JB, Grant RW. Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes. *Diabetic Medicine*. 2008; 25(9):1102–1107. <https://doi.org/10.1111/j.1464-5491.2008.02535.x>. [PubMed: 19183315]
- Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, Pae CU. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. *Expert Review of Neurotherapeutics*. 2013; 13(7):851–70. <https://doi.org/10.1586/14737175.2013.811901>. [PubMed: 23898855]
- Han C, Wang SM, Kwak KP, Won WY, Lee HY, Chang CM, Pae CU. Aripiprazole augmentation versus antidepressant switching for patients with major depressive disorder: A 6-week, randomized, rater-blinded, prospective study. *Journal of Psychiatric Research*. 2015; 66–67:84–94. <https://doi.org/10.1016/j.jpsychires.2015.04.020>.
- Hansen, Leigh G., Chang, S. White Paper. Health research data for the real world: The MarketScan databases. 2011. Retrieved from http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf
- Hartung DM, Middleton L, McFarland BH, Haxby DG, McDonagh MS, McConnell KJ. Use of Administrative Data to Identify Off-Label Use of Second-Generation Antipsychotics in a Medicaid Population. *Psychiatric Services*. 2013; 64(12):1236–1242. <https://doi.org/10.1176/appi.ps.005482012>. [PubMed: 23999754]
- Hassan AK, Farmer KC, Brahm NC, Keast S, Nesser N, Neas BR. Does the use of atypical antipsychotics as adjunctive therapy in depression result in cost savings? Comparing healthcare costs and utilization between second-line treatment options. *Journal of Mental Health*. 2015 May. 8237:1–6. 2016. <https://doi.org/10.3109/09638237.2015.1078879>.
- Hassan AK, Farmer KC, Brahm NC, Neas BR. Evaluating antidepressant treatment prior to adding second-line therapies among patients with treatment-resistant depression. *International Journal of Clinical Pharmacy*. 2016a; 38(2):429–437. <https://doi.org/10.1007/s11096-016-0272-y>. [PubMed: 26935957]
- Hassan, AK., Farmer, KC., Brahm, NC., Neas, BR. Evaluating antidepressant treatment prior to adding second-line therapies among patients with treatment-resistant depression. *International Journal of Clinical Pharmacy*. 2016b. <https://doi.org/10.1007/s11096-016-0272-y>

- Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, Magid DJ. Effect of Medication Nonadherence on Hospitalization and Mortality Among Patients With Diabetes Mellitus. *Archives of Internal Medicine*. 2006; 166(17):1836. <https://doi.org/10.1001/archinte.166.17.1836>. [PubMed: 17000939]
- Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly \$5 billion annually. *Health Affairs (Project Hope)*. 2012; 31(8):1836–46. <https://doi.org/10.1377/hlthaff.2011.1198>. [PubMed: 22869663]
- Jing Y, Kalsekar I, Curkendall SM, Carls GS, Bagalman E, Forbes RA, Thase ME. Intent-to-Treat Analysis of Health Care Expenditures of Patients Treated With Atypical Antipsychotics as Adjunctive Therapy in Depression. *Clinical Therapeutics*. 2011; 33(9):1246–1257. <https://doi.org/10.1016/j.clinthera.2011.07.015>. [PubMed: 21840058]
- Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 5. Complementary and Alternative Medicine Treatments. *Canadian Journal of Psychiatry*. 2016; 61(9):1–12. *Revue Canadienne de Psychiatrie*. <https://doi.org/10.1177/0706743716659417>.
- Komossa, K., Depping, AM., Gaudchau, A., Kissling, W., Leucht, S. Second-generation antipsychotics for major depressive disorder and dysthymia; *Cochrane Database Syst Rev* (1469-493X (Electronic)). 2010. p. CD008121 <https://doi.org/10.1002/14651858.CD008121.pub2>
- Krass, I., Schieback, P., Dhippayom, T. Adherence to diabetes medication: A systematic review. *Diabetic Medicine*. 2015 Jun. <https://doi.org/10.1111/dme.12651>
- Kreyenbuhl J, Dixon LB, McCarthy JF, Soliman S, Ignacio RV, Valenstein M. Does adherence to medications for type 2 diabetes differ between individuals with vs without schizophrenia? *Schizophrenia Bulletin*. 2010; 36(2):428–35. <https://doi.org/10.1093/schbul/sbn106>. [PubMed: 18718883]
- Kreyenbuhl J, Leith J, Medoff DR, Fang L, Dickerson FB, Brown CH, Dixon LB. A comparison of adherence to hypoglycemic medications between Type 2 diabetes patients with and without serious mental illness. *Psychiatry Research*. 2011; 188(1):109–114. <https://doi.org/10.1016/j.psychres.2011.03.013>. [PubMed: 21459458]
- Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic Review and Meta-Analysis of Validation Studies on a Diabetes Case Definition from Health Administrative Records. *PLoS ONE*. 2013; 8(10) <https://doi.org/10.1371/journal.pone.0075256>.
- Markowitz S, Gonzalez JS, Wilkinson JL, Safren SA. Treating Depression in Diabetes: Emerging findings. *Psychosomatics*. 2011; 52(1):1–18. <https://doi.org/10.1016/j.psych.2010.11.007>. [PubMed: 21300190]
- Mhatre SK, Serna O, Sansgiry S, Fleming ML, Essien EJ, Sansgiry SS. Risk of Nondherence to Diabetes Medications Among Medicare Advantage Enrollees: Development of a Validated Risk Prediction Tool. *Journal of Managed Care & Specialty Pharmacy*. 2016; 22(11):1293–1301. <https://doi.org/10.18553/jmcp.2016.22.11.1293>. [PubMed: 27783546]
- Mohamed S, Johnson GR, Chen P, Hicks PB, Davis LL, Yoon J, Little JT. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *JAMA*. 2017; 318(2):132–145. <https://doi.org/10.1001/jama.2017.8036>. [PubMed: 28697253]
- Nelson LA, Graham MR, Lindsey CC, Rasu RS. Adherence to Antihyperlipidemic Medication and Lipid Control in Diabetic Veterans Affairs Patients with Psychotic Disorders. *Psychosomatics*. 2011; 52(4):310–318. <https://doi.org/10.1016/j.psych.2011.03.004>. [PubMed: 21777713]
- Pae CU, Patkar AA. Clinical issues in use of atypical antipsychotics for depressed patients. *CNS Drugs*. 2013; 27(Suppl 1):S39–45. <https://doi.org/10.1007/s40263-012-0032-z>. [PubMed: 23709360]
- Petrak F, Baumeister H, Skinner TC, Brown A, G Holt RI. Depression and diabetes: treatment and health-care delivery. *THE LANCET Diabetes & Endocrinology*. 2015; 3(6):472–485. [https://doi.org/10.1016/S2213-8587\(15\)00045-5](https://doi.org/10.1016/S2213-8587(15)00045-5). [PubMed: 25995125]
- Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *Journal of Affective Disorders*. 2012; 142(Suppl):S8–21. [https://doi.org/10.1016/S0165-0327\(12\)70004-6](https://doi.org/10.1016/S0165-0327(12)70004-6). [PubMed: 23062861]

- Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. Oral antidiabetic medication adherence and glycemic control in managed care. *The American Journal of Managed Care*. 2008; 14(2):71–5. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18269302>. [PubMed: 18269302]
- Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Leucht S. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*. 2010; 123(2): 225–233. <https://doi.org/10.1016/j.schres.2010.07.012>. [PubMed: 20692814]
- Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Medicine*. 2013; 10(3):e1001403. <https://doi.org/10.1371/journal.pmed.1001403>. [PubMed: 23554581]
- Wade RL, Kindermann SL, Hou Q, Thase ME. Comparative Assessment of Adherence Measures and Resource Use in SSRI/SNRI-Treated Patients with Depression Using Second-Generation Antipsychotics or L-Methylfolate as Adjunctive Therapy. *Journal of Managed Care Pharmacy*. 2014; 20(1):76–85. <https://doi.org/10.18553/jmcp.2014.20.1.76>. [PubMed: 24372461]
- Wright BM, Eiland EH, Lorenz R. Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. *Pharmacotherapy*. 2013; 33(3):344–59. <https://doi.org/10.1002/phar.1204>. [PubMed: 23456734]
- Young BA, Lin E, Von Korff M, Simon G, Ciechanowski P, Ludman EJ, Katon WJ. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *The American Journal of Managed Care*. 2008; 14(1):15–23. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3810070&tool=pmcentrez&rendertype=abstract>. [PubMed: 18197741]
- Zhou X, Ravindran AV, Qin B, Del Giovane C, Li Q, Bauer M, Xie P. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: Systematic review and network meta-analysis. *Journal of Clinical Psychiatry*. 2015; 76(4):e487–e498. <https://doi.org/10.4088/JCP.14r09204>. [PubMed: 25919841]
- Zhu VJ, Tu W, Rosenman MB, Overhage JM. A Comparison of Data Driven-based Measures of Adherence to Oral Hypoglycemic Agents in Medicaid Patients. *AMIA Annu Symp Proc*. 2014; 2014:1294–1301. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/25954441>. [PubMed: 25954441]

Figure 1. Non-adherence to oral antidiabetic drug (OAD) therapy comparing second generation antipsychotic (SGA) initiators versus non-SGA initiators in primary and sensitivity analyses

The adjusted odds ratios (OR) and 95% confidence intervals (CI) are graphed for the primary analysis (i.e. 10% decline in adherence to OAD comparing the 180 days post-index versus the 180 days pre-index, where adherence was estimated using the average proportion of days covered (PDC) for patients using multiple diabetes drug classes) and the sensitivity analyses where adherence was measured: 1) over 365 days compared to 180 days in the main analysis; 2) using a 80% PDC cut-off where non-adherence was defined as PDC<0.8 calculated over the 180 and 365 days post-index compared to a 10% decline in the main analysis; 3) using the “Diabetes All Class Rate” instead of the average PDC for patients using multiple diabetes drug classes in the main analysis; 4) measuring a 20% decline over the 180 and 365 days post versus pre-index compared to 10% decline in the main analysis; and 5) excluding patients with any inpatient admission.

Table 1

Baseline Characteristics of SGA and non-SGA Initiators

Baseline Characteristics		Persistence Cohort (N=17,524)		Adherence 180-Day Cohort (N=8,664)	
Baseline Characteristics		SGA Initiator (N=3,734)	Non-SGA Initiator (N=13,790)	SGA Initiator (N=1,865)	Non-SGA Initiator (N=6,799)
Age (years)					
Median (IQR)		54	11	54	11
Age group (n, %)					
18-29		49	1.3%	176	1.3%
30-39		303	8.1%	1113	8.1%
40-49		889	23.8%	3229	23.4%
50-64		2493	66.8%	9272	67.2%
Female (n, %)		2360	63.2%	9075	65.8%
US census region (n, %)					
Northeast		520	13.9%	1961	14.2%
North Central		920	24.6%	3232	23.4%
South		1612	43.2%	5616	40.7%
West		580	15.5%	2613	18.9%
Unknown		102	2.7%	368	2.7%
Health plan (n, %)					
Preferred Provider Organization		2,289	61.3%	8,393	60.9%
Health Maintenance Organization		431	11.5%	1,931	14.0%
Other [‡]		839	22.5%	2,730	19.8%
Missing		175	4.7%	736	5.3%
Index year (n, %)					
2010		784	21.0%	2504	18.2%
2011		763	20.4%	2469	17.9%
2012		656	17.6%	2648	19.2%
2013		542	14.5%	1929	14.0%
2014		521	14.0%	2233	16.2%
2015		468	12.5%	2007	14.6%
Depression severity (n, %)					

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

p-value

Baseline Characteristics		Persistence Cohort (N=17,524)				Adherence 180-Day Cohort (N=8,664)			
Baseline Characteristics		SGA Initiator (N=3,734)		Non-SGA Initiator (N=13,790)		SGA Initiator (N=1,865)		Non-SGA Initiator (N=6,799)	
		p-value		p-value		p-value		p-value	
MGH-AD Score 0-1		547 14.6%		2458 17.8%		203 10.9%		985 14.5%	
MGH-AD Score 1.5-2		2250 60.3%		9002 65.3%		1152 61.8%		4583 67.4%	
MGH-AD Score 2.5-3		434 11.6%		1271 9.2%		228 12.2%		671 9.9%	
MGH-AD Score 3.5		503 13.5%		1059 7.7%		282 15.1%		560 8.2%	
Antidepressant use (n, %)									
SSRI		2577 69.0%		10677 77.4%		1250 67.0%		5228 76.9%	
SNRI		1845 49.4%		4653 33.7%		981 52.6%		2340 34.4%	
Serotonin modulator		710 19.0%		1741 12.6%		353 18.9%		873 12.8%	
Unique number of antidepressants used (n, %)									
1		2187 58.6%		9840 71.4%		1065 57.1%		4806 70.7%	
2		1194 32.0%		3245 23.5%		614 32.9%		1649 24.3%	
3		353 9.5%		705 5.1%		186 10.0%		344 5.1%	
Adherence to SSRI/SNRI[§]									
Median (IQR)		0.91 0.18		0.91 0.18		0.91 0.16		0.91 0.16	
Non-adherent (PDC<0.8)		830 22.2%		2985 21.6%		405 21.7%		1405 20.7%	
Adjunctive vs. monotherapy (n, %)									
Adjunctive [¶]		2986 80.0%		8833 64.1%		1513 81.1%		4462 65.6%	
Monotherapy		748 20.0%		4957 35.9%		352 18.9%		2337 34.4%	
Other psychotropic use (n, %)									
Amphetamines		317 8.5%		771 5.6%		164 8.8%		408 6.0%	
Anticonvulsants		289 7.7%		396 2.9%		155 8.3%		205 3.0%	
Benzodiazepines		2127 57.0%		5662 41.1%		1083 58.1%		2832 41.7%	
Buspirone		241 6.5%		511 3.7%		138 7.4%		265 3.9%	
Diabetes severity (n, %)									
Mild (aDCSI=0)		2082 55.8%		7752 56.2%		1045 56.0%		3887 57.2%	
Moderate (aDCSI=1-3)		1461 39.1%		5388 39.1%		732 39.2%		2640 38.8%	
Severe (aDCSI 4)		191 5.1%		650 4.7%		88 4.7%		272 4.0%	
Diabetes drug use in past year									
OAD only		2628 70.4%		9577 69.4%		1312 70.4%		4763 70.1%	

Baseline Characteristics		Persistence Cohort (N=17,524)				Adherence 180-Day Cohort (N=8,664)			
Baseline Characteristics		SGA Initiator (N=3,734)	Non-SGA Initiator (N=13,790)	p-value		SGA Initiator (N=1,865)	Non-SGA Initiator (N=6,799)	p-value	
OAD + insulin only		721	19.3%	2764	20.0%	357	19.1%	1301	19.1%
OAD + GLP-1/amylin only		244	6.5%	917	6.6%	114	6.1%	469	6.9%
OAD + insulin + GLP-1/amylin		141	3.8%	532	3.9%	82	4.4%	266	3.9%
Unique classes of diabetes drugs used (n, %)									
1		1507	40.4%	5482	39.8%	685	36.7%	2398	35.3%
2		1281	34.3%	4666	33.8%	641	34.4%	2378	35.0%
3		946	25.3%	3642	26.4%	539	28.9%	2023	29.8%
Total OAD fills (median, IQR)		7.0	7.0	7.0	7.0	9.0	8.0	9.0	4.0
Days' supply of last OAD fill (n, %)									
30 days' supply		24	0.6%	102	0.7%	11	0.6%	67	1.0%
31-60 days' supply		2097	56.2%	7590	55.0%	1222	65.5%	4442	65.3%
61-89 days' supply		28	0.7%	107	0.8%	11	0.6%	54	0.8%
90 days' supply		1585	42.4%	5991	43.4%	621	33.3%	2236	32.9%
Time of first OAD fill (n, %)									
90 days of index date		373	10.0%	1329	9.6%	78	4.2%	260	3.8%
91-180 days prior to index date		303	8.1%	929	6.7%	146	7.8%	445	6.6%
181-270 days prior to index date		444	11.9%	1600	11.6%	199	10.7%	648	9.5%
271-365 days prior to index date		2614	70.0%	9932	72.0%	1442	77.4%	5446	80.1%
Psychiatric comorbidities (n, %)									
Anxiety Disorder		1525	40.8%	4375	31.7%	755	40.5%	2095	30.8%
Alcohol abuse/dependence		110	2.9%	326	2.4%	52	2.8%	140	2.1%
Substance abuse/dependence		138	3.7%	373	2.7%	64	3.4%	170	2.5%
Suicide/self-inflicted injury		71	1.9%	104	0.8%	26	1.4%	43	0.6%
Medical comorbidities (n, %)									
Hypertension		2597	69.6%	9682	70.2%	1312	70.3%	4788	70.4%
Coronary atherosclerosis and other heart diseases		428	11.5%	1318	9.6%	212	11.4%	599	8.8%
Hyperlipidemia		2476	66.3%	9518	69.0%	1240	66.5%	4733	69.6%
Obesity diagnosis		846	22.7%	3555	25.8%	385	20.6%	1581	23.3%
Cardiovascular drug use (n, %)									

Baseline Characteristics		Persistence Cohort (N=17,524)				Adherence 180-Day Cohort (N=8,664)					
Baseline Characteristics		SGA Initiator (N=3,734)	Non-SGA Initiator (N=13,790)	p-value	SGA Initiator (N=1,865)	Non-SGA Initiator (N=6,799)	p-value				
	ACE inhibitor/ARB	2364	63.3%	8905	64.6%	1236	66.3%	4523	66.5%	0.839	
	Beta-blockers	263	7.0%	865	6.3%	556	29.8%	1868	27.5%	0.046	
	Calcium channel blockers	1040	27.9%	3708	26.9%	401	21.5%	1307	19.2%	0.029	
	Diuretics	748	20.0%	2610	18.9%	512	27.5%	1757	25.8%	0.161	
	Statins	2345	62.8%	8725	63.3%	1234	66.2%	4451	65.5%	0.573	
Psychiatric hospitalization (n, %)											
0		3609	96.7%	13603	98.6%	1805	96.8%	6724	98.9%	<0.001	
1		112	3.0%	161	1.2%	54	2.9%	65	1.0%		
2		13	0.3%	26	0.2%	6	0.3%	10	0.1%		
Diabetes hospitalization (n, %)											
0		3653	97.8%	13670	99.1%	1858	99.6%	6759	99.4%	0.190	
1		74	2.0%	110	0.8%	5	0.3%	37	0.5%		
2		7	0.2%	10	0.1%	2	0.1%	3	0.0%		
Psychotherapy (n, %)		1671	44.8%	4290	31.1%	837	44.9%	2165	31.8%	<0.001	
Outpatient visits (median, IQR)											
	Depression-related	3	5	2	3	3	<0.001	6	2	3	<0.001
	Diabetes-related	5	5	5	5	5	0.015	5	5	5	0.018
Provider care team [#] (n, %)											
	Primary care only	1605	43.0%	7866	57.0%	793	42.5%	3881	57.1%	<0.001	
	Psychiatry only	95	2.5%	339	2.5%	55	3.0%	150	2.2%		
	Endocrinology only	8	0.2%	33	0.2%	4	0.2%	17	0.3%		
	Primary care + psychiatry only	1316	35.2%	2775	20.1%	661	35.4%	1390	20.4%		
	Primary care + endocrinology only	179	4.8%	1065	7.7%	89	4.8%	484	7.1%		
	Psychiatry + endocrinology only	24	0.6%	47	0.3%	10	0.5%	27	0.4%		
	Primary care + psychiatry + endocrinology	267	7.2%	579	4.2%	137	7.4%	306	4.5%		
	Unspecified/other specialist	240	6.4%	1086	7.9%	116	6.2%	544	8.0%		
Pill burden ^{**} (median, IQR)		7	6	7	6	8	<0.001	5	7	5	<0.001
Polypharmacy ^{††} (median, IQR)		6	5	6	4	7	<0.001	4	6	4	<0.001
Conpayment (\$) (median, IQR)											

Baseline Characteristics		Adherence 180-Day Cohort (N=8,664)			
Baseline Characteristics		Persistence Cohort (N=17,524)		Non-SGA Initiator (N=6,799)	
		SGA Initiator (N=3,734)	Non-SGA Initiator (N=13,790)	SGA Initiator (N=1,865)	p-value
Cohort drug		\$20	\$35	\$6	\$8
		\$58	\$193	\$206	\$2
Diabetes drugs					

^{*} **SGA**: oral formulations of aripiprazole, asenapine, brexpiprazole, iloperidone, olanzapine (including olanzapine/fluoxetine), paliperidone, quetiapine, risperidone, or ziprasidone

[†] **Non-SGA**: bupropion, lithium, mirtazapine, thyroid hormone, or tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)

[‡] **Other health plans** include comprehensive, exclusive provider organization, point-of-service, consumer-driven and high deductible plans

[§] **Mean prescription-based PDC** was used to measure adherence to SSRI/SNRI, where the mean PDC for each medication was calculated for patients using multiple drugs. Analysis restricted to patients who had at least 2 fills of a SSRI/SNRI during the pre-index period.

^{||} **Adjunctive therapy**: concurrent use (minimum 30-day overlap) between cohort drug and SSRI/SNRI. Patients without minimum 30-day overlap were considered monotherapy users.

[#] **Provider care team** (type of providers seen in past year): primary care (primary care, internal medicine, family practice visit), endocrinology (endocrinology/metabolism visit), psychiatry (psychiatrist or psychiatric nurse)

^{***} **Pill burden** was measured for prescriptions where the end date (date of dispense + days' supply) was within 30-days of index drug fill

^{††} **Polypharmacy** was measured by number of medications with 90 day supply and end date within 30-days of index drug fill

ACEI= angiotensin converting enzyme inhibitors; **aDCSI**= adapted Diabetes Complications Severity Index; **ARB**=angiotensin II receptor blockers; **GLP-1**= glucagon-like peptide-1 agonist; **IQR**=interquartile range; **MGH-AD**=Massachusetts General Hospital - Antidepressant; **PDC**=proportion of days' covered; **SD**=standard deviation; **SSRI**=selective serotonin reuptake inhibitor; **SNRI**=selective norepinephrine uptake inhibitor; **TIA**=transient ischemic attack

Adherence to Oral Antidiabetic Drug (OAD) Comparing SGA vs. non-SGA Initiators with Major Depressive Disorder and Pre-Existing Type 2 Diabetes

Table 2

Characteristic	SGA Initiator	Non-SGA Initiator	P-value
Adherence (PDC[*]) to OAD measured over 180-days before and after cohort drug initiation (N=8,664)			
Proportion non-adherent (PDC<0.8) pre-index (n, %)	390 20.9%	1,426 21.0%	0.953
Proportion non-adherent (PDC<0.8) post-index (n, %)	398 21.3%	1,273 18.7%	0.012
Proportion with a 10% decline in PDC (n, %)	310 16.6%	901 13.3%	<0.001
Odds of 10% decline in PDC			
Crude OR (95% CI)	1.31 (1.13-1.50)	Reference	<0.001
Adjusted OR (95% CI) [‡]	1.41 (1.21-1.63)	Reference	<0.001
Adherence (PDC[*]) to OAD measured over 365-days before and after cohort drug initiation (N=8,311)			
Proportion non-adherent (PDC<0.8) pre-index (n, %)	590 32.2%	2,081 32.1%	0.959
Proportion non-adherent (PDC<0.8) post-index (n, %)	612 33.4%	1,985 30.6%	0.025 [‡]
Proportion with a 10% decline in PDC (n, %)	409 22.3%	1,223 18.9%	0.001 [‡]
Odds of 10% decline in PDC			
Crude OR (95% CI)	1.23 (1.09-1.40)	Reference	<0.001
Adjusted OR (95% CI) [‡]	1.34 (1.17-1.53)	Reference	<0.001

* Mean prescription-based PDC was used to measure adherence to OAD, where the PDC for each OAD drug class was averaged for patients using multiple drugs

[‡] Adjusted for age, gender, depression severity (Massachusetts General Hospital - Antidepressant staging score), diabetes severity (adapted Diabetes Complications Severity Index score), polypharmacy, pill burden, last days' supply of OAD filled pre-index, adjunctive versus monotherapy, and adherence to OAD during the pre-index 180 or 365 days period

CI= Confidence interval; IQR=interquartile range; OAD=oral antidiabetic drug; OR= Odds ratio; PDC= proportion of days' covered

Table 3

Non-persistence to Oral Antidiabetic Drug (OAD) Therapy Comparing Second Generation Antipsychotic (SGA) Initiators versus non-SGA Initiators

Permissible Gap	Median (IQR) time to discontinuation (days)		Non-persistence rate (per 100 person-years)		Crude HR (95% CI)	p-value	Adjusted HR (95% CI) *	p-value
	SGA Initiator	Non-SGA Initiator	SGA Initiator	Non-SGA Initiator				
Primary Analysis								
2 times last days' supply	118 (255)	123 (270)	27.2	24.9	1.07 (0.98-1.16)	0.134	1.03 (0.94-1.12)	0.536
Sensitivity Analyses								
45-days	71 (106)	75(137)	49.3	44.5	1.06 (0.98-1.15)	0.165	1.02 (0.94-1.11)	0.599
60-days	90 (155)	90 (155)	40.1	35.4	1.09 (1.00-1.18)	0.041	1.05 (0.97-1.14)	0.232
90-days	106 (156)	120 (190)	28.7	24.8	1.13 (1.03-1.23)	0.010	1.09 (0.99-1.19)	0.069

* Adjusted for age, gender, depression severity (Massachusetts General Hospital - Antidepressant staging score), diabetes severity (adapted Diabetes Complications Severity Index score), use of benzodiazepine therapy in past year, number of unique diabetes drug classes used in past year, and days between first oral antidiabetic drug fill pre-index and index date

CI=confidence interval; HR=hazard ratio; IQR=interquartile range