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ORIGINAL RESEARCH

Changes in healthcare resource use and costs associated with early versus delayed initiation of atypical antipsychotic adjunctive treatment in major depressive disorder

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ABSTRACT

Aims: The study compared all-cause and major depressive disorder (MDD)-related healthcare resource use (HRU) and costs in patients with MDD treated with atypical antipsychotic (AAP) adjunctive therapy early or later in treatment.

Materials and methods: Adults with MDD and antidepressant treatment (ADT) who newly initiated adjunctive aripiprazole, brexpiprazole, lurasidone, or quetiapine between October 1, 2014 and September 30, 2015 were identified in the IQVIA Real-World Data Adjudicated Claims database; the index date was the date of the first AAP claim. Patients were stratified into three cohorts: AAP initiated in the first year (Y1); in the second year (Y2); and more than 2 years (Y3) of first ADT use. Within each cohort, HRU and costs were compared between the 12 months before and after the index date. Pre–post changes in HRU and costs were then compared between cohorts.

Results: Five hundred and six (36.7%) patients were categorized as Y1; 252 (18.3%) as Y2; and 622 (45.1%) as Y3. AAP use was associated with significantly decreased rates of all-cause and MDD-related hospitalization and emergency department visits, and increased rates of pharmacy fills and physician office visits; and the magnitude of changes was largest in cohort Y1. Cohort Y1 had the largest reductions in mean (±SD) all-cause medical costs per patient (−$10,496 ± $85,022, $p = .015$) compared to Y2 (−$2,474 ± $85,022, $p = .572$) and Y3 (−$472 ± $31,334, $p = .823$), mainly due to the reduction in hospitalization. After adjusting for differences in baseline characteristics, the largest reductions in hospitalization and medical costs were observed in cohort Y1. Similar increases in all-cause pharmacy costs were seen in all cohorts. A similar trend in costs was observed in MDD-related healthcare services.

Limitations and conclusions: AAP treatment was associated with reductions in all-cause and MDD-related medical costs, primarily in decreased hospitalization. The reductions were largest among patients who initiated treatment in the first year.

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Introduction

Major depressive disorder (MDD) is a chronic mental illness characterized by a variety of symptoms including extended depressed mood or loss of interest in daily activities, change in usual mood, and impaired social, occupational, and educational function[1]. MDD affects over 300 million people or 4.4% of the world's population[2]. In the US, MDD affects ~16.1 million adults or 6.7% of the US adult population in a given year[3]. MDD is a leading cause of disability, resulting in almost 400 million disability days per year, and significant increased economic burden[4,5]. In 2010, the incremental economic burden of individuals with MDD was estimated at $210.5 billion, with 45–47% attributable to direct costs, and 48–50% to workplace costs[4].

Antidepressants are the mainstay of treatment for MDD. The American Psychiatric Association recommends the use of antidepressant medication as an initial treatment of choice for patients with all level of MDD severity (mild, moderate, and severe)[6]. Different classes of antidepressants are available, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic or tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. Despite promising results of new-generation antidepressants[7], findings from a large clinical trial, STAR*D, show that only one-third of patients experience remission with initial monotherapy antidepressant treatment[8–10].

Several treatment strategies exist for patients with inadequate response to antidepressant therapy (ADT), including optimizing the current medication dose, switching to a different antidepressant in the same or different pharmacological class, adding an antidepressant of a different class, or adding an augmenting agent such as atypical antipsychotics, lithium, thyroid hormone, or an anticonvulsant[11]. Increasing SNRI or SSRI dose may not improve outcomes for patients with inadequate responses, and may negatively impact tolerability,

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leading to treatment discontinuation[12–14]. Evidence from the STAR*D trial shows that only 25% of patients who did not achieve sufficient response and switched to a different antidepressant achieved remission, defined as returning to baseline level of functioning[8–10]. In a prospective trial of 655 patients with MDD, combination therapy with two antidepressants did not improve remission rates when compared with antidepressant monotherapy, and in some cases increased the risk of adverse events[15]. Of all strategies to augment response with a non-antidepressant drug, use of adjunctive second-generation antipsychotics as a first-line choice for augmentation in patients who failed first-line ADT are supported by the strongest evidence from both prospective and meta-analysis studies[16], which included commonly used AAPs: olanzapine, risperidone, aripiprazole, quetiapine, ziprasidone, lurasidone, and the recently approved drug, brexpiprazole[17–26]. Of all the oral atypical antipsychotics currently available in the US and Canada, only aripiprazole (2007)[27], quetiapine extended-release (XR) (2009)[28], and brexpiprazole (2015)[29] are indicated as adjunctive treatment to antidepressants for major depressive disorder.

Despite the efficacy of oral atypical antipsychotics as adjunctive treatment in major depressive disorder, little is known of the impact of adjunctive AAP use in MDD on healthcare resource use and costs in the real-world practice in the US One population-based study in Taiwan conducted by Lin *et al.*[30] showed a significant reduction in key psychiatric service use, including length of psychiatric hospitalization, number of psychiatric admissions, and emergency room visits, with AAP augmentation in patients with MDD. Another study using a claims database in the US conducted by Hagiwara *et al.*[31] showed that the rates of hospitalization and emergency department (ED) visits, as well as mean MDD-related total healthcare cost, decreased with AAP use. More importantly, the impact of delaying the use of adjunctive AAPs in patients with MDD and inadequate response to ADT is not well studied. Delaying the use of adjunctive AAPs may be associated with more difficult MDD management and other consequences, including increased healthcare resource use and costs, in patients whose disease is not well controlled with antidepressant monotherapy. This study aims to investigate the impact of adjunctive use of AAPs on real-world healthcare resource use (HRU) and costs in patients with MDD, and compare the results across patients who waited varying amounts of time to start an AAP treatment to generate findings for hypothesis testing to help inform future research. Four atypical antipsychotics were assessed in this study: aripiprazole, brexpiprazole, quetiapine, and lurasidone. Aripiprazole, brexpiprazole, and quetiapine are indicated for the treatment of MDD. Lurasidone was selected as it was the newest atypical antipsychotic, with strong evidence from a randomized clinical trial supporting use in patients with MDD[17]. We did not include risperidone or olanzapine-fluoxetine combination therapy in the study, as their efficacy in MDD was actively investigated only up until 2009[32]. We did not include other AAPs in the study because of the small number of patients with MDD treated with these agents in our database.

Methods

Database

This retrospective study utilized patient-level data from the IQVIA (formerly QuintilesIMS) Real-World Data Adjudicated Claims database from 1 July 2010 to 30 September 2016. The database is comprised of adjudicated commercial insurance claims for more than 150 million unique enrollees across the US. The database has information on inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, provider details, and payment amounts. The data are representative of the national, commercially insured population in terms of age and gender for individuals aged 65 and under. No Institutional Review Board (IRB) review was required for this study, because the data are de-identified and Health Insurance Portability and Accountability Act (HIPAA) compliant.

Patient selection

This study included adult patients with an MDD diagnosis who were treated with at least one antidepressant and newly-initiated on an AAP adjunctive therapy. Patients 18 years or older were required to have at least one pharmacy claim for aripiprazole, brexpiprazole, lurasidone, or quetiapine between 1 October 2014 and 30 September 2015 (the selection window). The date of the first claim of an adjunct AAP was the index date. The four AAPs included in this study were selected based on FDA-approved indication for MDD and/or strong evidence supporting its efficacy in reducing depressive symptoms[17,26–28]. Patients were required to have continuous medical and pharmacy coverage for at least 36 months immediately before the index date (the pre-index period) and at least 12 months immediately after the index date (the post-index period), and at least 60 days of treatment with any AAP. During the pre-index period, patients who had been newly treated with antidepressant(s) were identified from a pharmacy claim for any ADT, including TCAs, MAOIs, SSRIs, SNRIs, atypical antidepressants, or other antidepressants. The date of the first antidepressant claim, with at least a 6-month period without prior ADT, was considered the ADT start date. Additional inclusion criterion included a diagnosis of MDD with International Classification of Disease, Ninth Revision, Clinical Modifications (ICD-9 CM) codes, including 296.2x, 296.3x, 311.x; ICD-10-CM: F32.0–F32.5, F32.9, F33.x, on a medical claim was required on the index date or during the pre-index period. To confirm the diagnosis of MDD, patients were required to have a second diagnosis of MDD at any time during the entire continuous enrollment period. Because AAP was indicated as an adjunctive treatment to antidepressant therapy, patients were also required to have at least 30 days of pre-index antidepressant medication supply overlapping with the index AAP medication supply. Patients were excluded from the study if they met any of the following criteria: (1) had any pharmacy claim(s) for aripiprazole, brexpiprazole, lurasidone, or quetiapine during the pre-index period; (2) had a diagnosis for bipolar disorder, schizophrenia, or dementia-related

psychosis during the study period; or (3) had any data quality issue(s) such as missing age or gender. A diagram of study design is shown in Figure 1.

Patients meeting the inclusion and criteria were stratified into three cohorts, based on the length of time between the first ADT use and index. The strata included patients who initiated AAP adjunctive therapy in the first year (Y1), in the second year (Y2), and in the third year or later (Y3) following the first ADT use. Patients in cohort Y1 were considered "early" initiators, while those in cohort Y2 and cohort Y3 were considered "delayed" initiators. The cohorts were mutually exclusive.

Study measures

Demographic and clinical characteristics were described separately for each of the three cohorts using data from the pre-index period or at index. They included age, gender, geographic region, payer type, plan type, prescriber specialty for the index AAP treatment, MDD severity as determined by MDD ICD-9/ICD-10 CM diagnosis on medical claims on or closest to index date, Charlson-Quan comorbidity index (CCI)[33], and selected comorbidities. Treatment history was examined during the variable pre-index period from the ADT start date to the index date. Outcomes of interest included time from the first ADT to index AAP use, the number of different antidepressants used during this period of time, and classes of antidepressants used immediately prior to the index AAP therapy.

Annualized all-cause and MDD-related HRU and costs per patient were evaluated separately during the 12 months prior to index and during the 12-month post-index period for each cohort. Costs were reported as medical, pharmacy, and total (medical plus pharmacy) cost categories. Costs reflected negotiated price of services and medications across all health plans contributing to the dataset, and were adjusted to 2016 US dollar using the medical service component of the US Consumer Price Index. Under medical services, HRU and costs were further broken down into hospitalizations, ED visits, and office visits. MDD-related services included medical claims with a diagnosis for MDD in any position. To assess the changes in HRU and the associated costs following AAP initiation, the difference between the pre- and post-index periods was calculated for each study measure.

In addition to HRU and costs, post-index treatment patterns were examined during the 12-months post-index period. Measures of interest included the number of different AAPs and antidepressants used during follow-up, and the persistence of AAP therapy (regardless of which AAP was used). Persistence was calculated as the time in consecutive days from index to discontinuation of the drug. Discontinuation was defined as a gap in AAP medication supply of 14 days or longer. Change in AAP drug strength was not considered as discontinuation. Patients were considered persistent if they did not discontinue the AAP during the 12-month post-index period.

Statistical analysis

Differences in patient baseline characteristics between Y1 and Y2 and Y1 and Y3 were assessed by Chi-square and *t*-tests. Pairwise comparisons of outcome data were made between measures of 12-month pre- and post-index HRU and the associated costs. Among the cohorts, a difference-in-differences analysis was performed to compare the changes in HRU and the associated costs after initiating AAP adjunctive therapy (Y1 vs Y2: $[(Y1_{\text{post-index}} - Y1_{\text{pre-index}}) - (Y2_{\text{post-index}} - Y2_{\text{pre-index}})]$; Y1 vs Y3: $[(Y1_{\text{post-index}} - Y1_{\text{pre-index}}) - (Y3_{\text{post-index}} - Y3_{\text{pre-index}})]$). This design can mitigate bias related to unobserved factors by using each cohort as its own control[34,35]. In the pre–post analysis, paired *t*-test (mean) and non-parametric Wilcoxon signed-rank test (median) were used for continuous variables. Independent *t*-test (mean) and non-parametric Wilcoxon signed-rank test (median) were used for continuous variables for cross-cohort comparisons. Chi-square test was used for categorical variables, and Fisher's exact test was used for categorical variables with small numbers in both analyses. As a sensitivity analysis, a generalized linear model was used in a multivariate

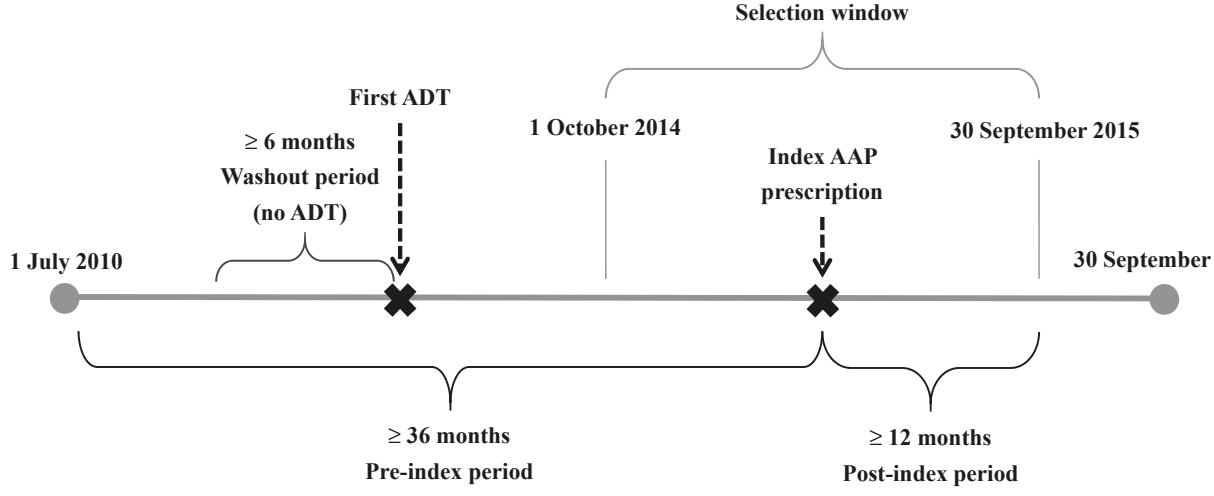

Figure 1. Study design.

regression to evaluate the differences in all-cause and MDD-related hospitalization and medical cost changes (follow-up – baseline) between cohorts. The analysis adjusted for the following covariates: age, gender, geographic region, payer type, plan type, index prescriber specialty, MDD severity, and CCI. A *p*-value of $<.05$ was considered statistically significant for all analyses. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Study cohorts

In total, 216,822 patients who had at least one claim for aripiprazole, brexpiprazole, lurasidone, or quetiapine during the selection window were identified. After applying the selection criteria, a total of 1,380 eligible patients were retained for final analysis (Figure 2). The stratified cohorts included

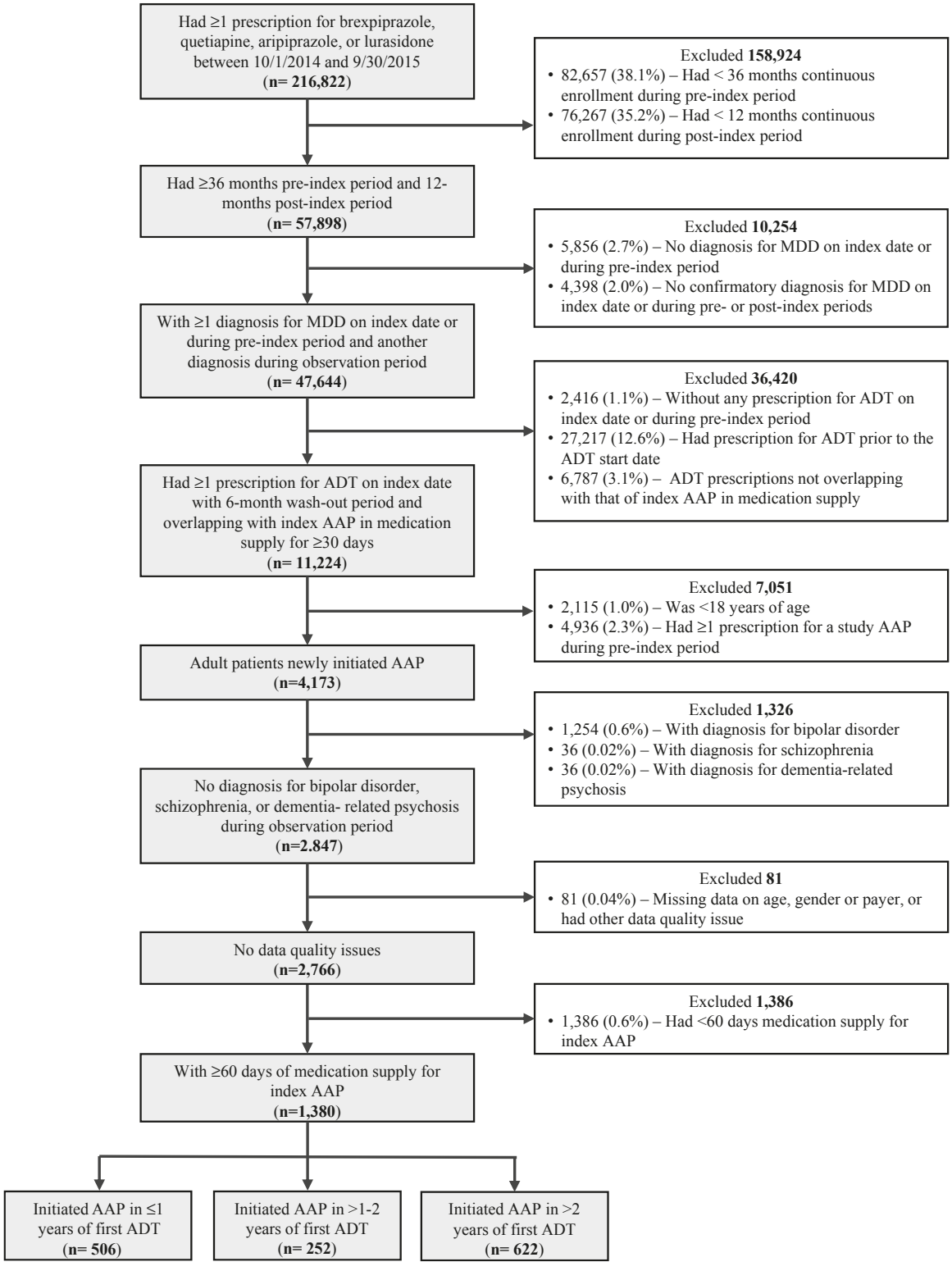

Figure 2. Patient selection.

506, 252, and 622 patients who initiated AAP adjunctive therapy in the first year (Y1), second year (Y2), and third year and beyond (Y3) after their first ADT, respectively.

Demographic and clinical characteristics of patients were similar across cohorts (Table 1). The majority of patients were female, had a PPO health plan, and were commercially or self-insured. Index AAP was prescribed by a psychiatrist for over 30% of patients in all cohorts; psychiatrists appeared more likely to start patients with adjunctive AAP therapy early in therapy, as a higher proportion (40.5%) of index therapy prescribed by a psychiatrist was observed for patients in cohort Y1 (compared to 31.8% in cohorts Y2 and Y3). The majority of patients in each cohort had MDD of unspecified degree prior to starting adjunctive AAP therapy (53.4%, 53.2%, and 57.9% for cohorts Y1, Y2, and Y3, respectively), and a larger proportion of patients with severe MDD

Table 1. Patient characteristics.

Baseline characteristics	AAP initiation in ≤1 year of first ADT use (Y1) ($n = 506$)	AAP initiation in >1–2 years of first ADT use (Y2) ($n = 252$)	AAP initiation in >2 years of first ADT use (Y3) ($n = 622$)	p value Y1 vs Y2	p value Y1 vs Y3
Age (years)					
Mean (SD)	39.4 (16.6)	38.2 (15.1)	42.0 (14.2)	.341	.004
Median (Q1, Q3)	39 (22,54)	39 (22,51)	44 (31,53)	.351	.001
Gender, *n* (%)				.131	.001
Female	276 (54.55%)	152 (60.32%)	399 (64.15%)		
Male	230 (45.45%)	100 (39.68%)	223 (35.85%)		
Geographic region, *n* (%)				.007	.385
Northeast	122 (24.11%)	37 (14.68%)	124 (19.94%)		
Midwest	141 (27.87%)	92 (36.51%)	184 (29.58%)		
South	193 (38.14%)	103 (40.87%)	254 (40.84%)		
West	50 (9.88%)	20 (7.94%)	60 (9.65%)		
Payer type, *n* (%)				.076	.041
Commercial	257 (50.79%)	143 (56.75%)	319 (51.29%)		
Self-insured	218 (43.08%)	102 (40.48%)	284 (45.66%)		
Other	31 (6.13%)	7 (2.78%)	19 (3.05%)		
Plan type, *n* (%)				.320	.827
HMO	47 (9.29%)	25 (9.92%)	52 (8.36%)		
PPO	433 (85.57%)	220 (87.30%)	540 (86.82%)		
Other	26 (5.14%)	7 (2.78%)	30 (4.82%)		
Index AAP prescriber specialty, *n* (%)				.011	<.001
Psychiatrist	205 (40.51%)	80 (31.75%)	198 (31.83%)		
Primary care physician	71 (14.03%)	54 (21.43%)	146 (23.47%)		
Other/Unknown	230 (45.45%)	118 (46.83%)	278 (44.69%)		
MDD severity, *n* (%)				.449	.130
Severe	126 (24.90%)	51 (20.24%)	115 (18.49%)		
Moderate	88 (17.39%)	56 (22.22%)	119 (19.13%)		
Mild	11 (2.17%)	6 (2.38%)	16 (2.57%)		
Unspecified	270 (53.36%)	134 (53.17%)	360 (57.88%)		
In remission	11 (2.17%)	5 (1.98%)	12 (1.93%)		
Charlson Comorbidity Index					
Mean (SD)	1.25 (2.01)	1.36 (2.03)	1.50 (2.07)	.487	.044
Median (Q1, Q3)	0 (0, 2)	1 (0, 2)	1 (0, 2)		
Frequency, *n* (%)				.690	.020
0	266 (52.57%)	119 (47.22%)	266 (42.77%)		
1	103 (20.36%)	57 (22.62%)	144 (23.15%)		
2	49 (9.68%)	30 (11.90%)	80 (12.86%)		
3	28 (5.53%)	14 (5.56%)	48 (7.72%)		
4+	60 (11.96%)	32 (12.70%)	84 (13.50%)		
Comorbidities, *n* (%)					
CNS-related					
Anxiety disorder	331 (65.42%)	171 (67.86%)	392 (63.02%)	.503	.405
Epilepsy	17 (3.36%)	9 (3.57%)	19 (3.05%)	.880	.772
Insomnia	113 (22.33%)	45 (17.86%)	123 (19.77%)	.153	.294
Obsessive-compulsive disorder	23 (4.55%)	12 (4.76%)	25 (4.02%)	.894	.663
Parkinson's disease	2 (0.40%)	2 (0.79%)	2 (0.32%)	.604	1.000
Tourette's syndrome	1 (0.20%)	0 (0.00%)	1 (0.16%)	1.000	1.000
Other					
Asthma	41 (8.10%)	37 (14.68%)	51 (8.20%)	.005	.953
Cancer	42 (8.30%)	27 (10.71%)	64 (10.29%)	.276	.255
COPD	19 (3.75%)	11 (4.37%)	33 (5.31%)	.685	.217
Congestive heart failure	13 (2.57%)	8 (3.17%)	16 (2.57%)	.632	.997
Diabetes	47 (9.29%)	22 (8.73%)	70 (11.25%)	.801	.282
Hepatitis	3 (0.59%)	4 (1.59%)	6 (0.96%)	.229	.739
Hyperlipidemia	116 (22.92%)	50 (19.84%)	181 (29.10%)	.334	.019
Hypertension	130 (25.69%)	71 (28.17%)	198 (31.83%)	.466	.024
Liver disease	15 (2.96%)	4 (1.59%)	24 (3.86%)	.253	.414
Peripheral vascular disease	14 (2.77%)	2 (0.79%)	14 (2.25%)	.075	.580
Stroke	25 (4.94%)	15 (5.95%)	38 (6.11%)	.557	.395

Abbreviations. HMO, Health Maintenance Organization; POS, Point-of-Service; PPO, Preferred Provider Organization; CNS, Central Nervous System; COPD, Chronic Obstructive Pulmonary Disease.

was seen in cohort Y1 (24.9%) compared to cohorts Y2 (20.2%) and Y3 (18.5%). Comorbidity burden as measured using CCI scores increased with delayed AAP initiation (mean CCI ranged from 1.25–1.50 in cohorts Y1 and Y3, respectively). The most common comorbidity in all cohorts was anxiety, followed by hypertension, hyperlipidemia, and insomnia.

Treatment history

Consistent with the study design, patients with delayed AAP initiation (in the second year or later after their first ADT use) had a longer period of time between the ADT start date and index, as compared to those who started adjunctive AAP early (Table 2). The mean time (SD) between the first ADT and index date was 3.9 (3.8) months for cohort Y1, 17.5 (3.5) months for cohort Y2, and 38.6 (8.4) months for cohort Y3. Patients with delayed AAP initiation have tried more antidepressants compared to patients with early AAP initiation (mean number of antidepressants ranged from 1.9–3.2 in cohorts Y1 and Y3, respectively). Moreover, a larger proportion of patients with delayed AAP initiation had been treated with different antidepressant classes before adding AAP to their therapy, compared to those with early AAP initiation. The most common antidepressant class used immediately prior to the index AAP was SSRIs, followed by SNRI and atypical antidepressants.

Healthcare resource utilization

Annualized all-cause and MDD-related HRU evaluated during the 12 months prior to and after index are reported in Table 3. Across the cohorts, there was a reduction in the rates of all-cause hospitalizations and ED visits after initiating AAP adjunctive therapy. The mean number of all-cause hospitalizations per patient for cohorts Y1 and Y3 decreased significantly with AAP initiation (p-value $<.05$, Figure 3), while that for cohort Y2 decreased numerically, but did not reach statistical significance (p-value $=.060$). The same trend was observed for the mean number of all-cause ED visits. In contrast, there was a general increase in the mean numbers of all-cause physician office visits and pharmacy fills per patient in the year following AAP initiation (p-value $<.05$ for all cohorts).

Similar patterns were observed for MDD-related HRU. AAP use, regardless of timing of initiation, was associated with decreased mean numbers of MDD-related hospitalizations and ED visits, but associated with an increased mean number of MDD-related physician office visits (all p-values $<.05$). The only exception was the mean number of MDD-related ED visits in cohort Y3, which was similar between the pre- and post-index periods (0.13 for pre-index and 0.10 for post-index; p-value $=.694$).

Although the trend in HRU changes was similar across the cohorts, the magnitude of changes varied by the timing of AAP initiation. Patients in cohort Y1 had a larger reduction in the mean numbers of all-cause and MDD-related hospitalizations per patient as compared to those in cohort Y3, while the decrease in the rates of ED visits, both all-cause and MDD-related, were similar in magnitude across the cohorts. For the mean numbers of pharmacy fills (all-cause only) and physician office visits (both all-cause and MDD-related) per patient, patients in cohort Y1 had a larger increase compared to those in cohorts Y2 or Y3 (all p-values $<.05$).

Healthcare costs

Table 4 shows the annualized all-cause and MDD-related healthcare costs per patient evaluated during the 12 months prior to and after index. Wide variability was observed in each of the cost categories. For total all-cause healthcare cost per patient, the means appeared to be similar before and after initiating AAP; however, median all-cause healthcare cost increased significantly following AAP initiation across the cohorts. The median increase in total all-cause healthcare cost was $2,027 per patient for cohort Y1, $2,084 for cohort Y2, and $3,779 for cohort Y3. Increases in the mean total pharmacy cost per patient were also observed across cohorts (all p-values $<.05$, Figure 4). In contrast, a significant difference in the mean medical costs before and after AAP initiation was observed in cohort Y1 only. In particular,

Table 2. Treatment history.

	AAP initiation in ≤1 year of first ADT use (Y1) ($n = 506$)	AAP initiation in >1–2 years of first ADT use (Y2) ($n = 252$)	AAP initiation in >2 years of first ADT use (Y3) ($n = 622$)
Time (months) from first ADT to index date			
Mean (SD)	3.9 (3.8)	17.5 (3.5)	38.6 (8.4)
Median (Q1, Q3)	2.5 (0.5, 7.0)	17.4 (14.2, 20.5)	38.6 (31.6, 45.3)
Number of different antidepressants used during pre-index period since ADT start date			
Mean (SD)	1.9 (1.1)	2.8 (1.3)	3.2 (1.5)
Median (Q1, Q3)	2 (1, 2)	3 (2, 4)	3 (2, 4)
Classes of antidepressants used immediately prior to index adjunctive AAP, *n* (%)			
Tricyclic/tetracyclic	31 (6.13%)	15 (5.95%)	35 (5.63%)
MAOI	1 (0.20%)	0 (0.00%)	2 (0.32%)
SSRI	304 (60.08%)	145 (57.54%)	315 (50.64%)
SNRI	88 (17.39%)	68 (26.98%)	171 (27.49%)
Atypical antidepressant	124 (24.51%)	53 (21.03%)	179 (28.78%)
Other antidepressant	1 (0.20%)	0 (0.00%)	0 (0.00%)

Abbreviations. MAOI, Monoamine Oxidase Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor.

Table 3. Unadjusted utilization of healthcare resources.

	AAP initiation in ≤1 year of first ADT use (Y1) ($n = 506$)				AAP initiation in >1–2 years of first ADT use (Y2) ($n = 252$)					AAP initiation in >2 years of first ADT use (Y3) ($n = 622$)				
	Pre-index	Post-index	Pre–post difference		Pre-index	Post-index	Pre–post difference		*p*-value vs Y1†	Pre-index	Post-index	Pre–post difference		*p* value vs Y1†
			Post–pre	*p*-value*			Post–pre	*p*-value*				Post–pre	*p* value*	
All-cause														
Hospitalization														
Patients with ≥1 hospitalization, *n* (%)	180 (35.57%)	91 (17.98%)	−89 (−17.59%)	*<.001*	72 (28.57%)	47 (18.65%)	−25 (−9.92%)	*.009*	.171	130 (20.90%)	76 (12.22%)	−54 (−8.68%)	*<.001*	*<.001*
Length of stay per hospitalization (days)														
Mean (SD)	8.3 (8.2)	6.2 (5.0)	−2.1	*.027*	9.4 (18.1)	5.3 (4.1)	−4.2	.126		5.9 (4.6)	5.2 (3.7)	−0.7	.253	
Median (Q1, Q3)	6 (4, 9)	5 (3, 8)		*.012*	5 (3, 8)	4 (3, 6)		*.033*		5 (3, 7)	4 (3, 6)		.265	
Number of hospitalizations per patient														
Mean (SD)	0.61 (1.30)	0.31 (0.89)	−0.30 (1.21)	*<.001*	0.44 (0.86)	0.29 (0.85)	−0.14 (1.05)	.060	.079	0.32 (0.82)	0.21 (0.86)	−0.11 (1.00)	*.018*	*.005*
Median (Q1, Q3)	0 (0, 1)	0 (0, 0)	0 (−1, 0)		0 (0, 1)	0 (0, 0)	0 (0, 0)			0 (0, 0)	0 (0, 0)	0 (0, 0)		
Outpatient services														
ED visits														
Patients with ≥1 ED visit, *n* (%)	233 (46.05%)	153 (30.24%)	−80 (−15.81%)	*<.001*	101 (40.08%)	77 (30.56%)	−24 (−9.52%)	*.025*	.414	225 (36.17%)	184 (29.58%)	−41 (−6.59%)	*.013*	*.007*
Number of ED visits per patient														
Mean (SD)	0.84 (1.24)	0.60 (1.39)	−0.24 (1.58)	*.004*	0.77 (11.36)	0.57 (1.21)	−0.20 (1.65)	.084	.730	0.83 (2.05)	0.63 (1.63)	−0.20 (1.76)	*.060*	.667
Median (Q1, Q3)	0 (0, 1)	0 (0, 1)	0 (−1, 0)		0 (0, 1)	0 (0, 1)	0 (−1, 0)			0 (0, 1)	0 (0,1)	0 (−1, 0)		
Physician office visits														
Patients with ≥1 office visit, *n* (%)	496 (98.02%)	503 (99.41%)	7 (1.38%)	.051	251 (99.60%)	251 (99.60%)	0 (0.00%)		.250	616 (99.04%)	618 (99.36%)	2 (0.32%)	.525	.240
Number of office visits per patient														
Mean (SD)	18.97 (18.26)	27.09 (22.96)	8.12 (21.22)	*<.001*	22.85 (21.80)	24.58 (23.48)	1.73 (21.55)	.391	*<.001*	21.14 (20.13)	23.62 (22.91)	2.49 (20.50)	*.042*	*<.001*
Median (Q1, Q3)	13 (6, 25)	20 (10, 37)	4 (−3, 16)	*<.001*	15 (8, 31)	17 (9, 32)	1 (−7, 9)	.446	*<.001*	15 (7, 28)	17 (9, 30)	2 (−5, 8)	*.008*	*<.001*
Pharmacy fills														
Patients with ≥1 pharmacy fill, *n* (%)	493 (97.43%)	506 (100.00%)	13 (2.57%)	*<.001*	250 (99.21%)	252 (100.00%)	2 (0.79%)	.499	.163	618 (99.36%)	622 (100.00%)	4 (0.64%)	.124	*.008*
Number of pharmacy fills per patient														
Mean (SD)	22.11 (20.98)	45.93 (32.86)	23.82 (29.35)	*<.001*	40.10 (31.02)	50.83 (37.51)	10.73 (25.55)	*<.001*	*<.001*	41.5 (32.59)	53.32 (35.70)	11.48 (22.42)	*<.001*	*<.001*
Median (Q1, Q3)	16 (7, 31)	39 (23, 57)	18 (6, 32)	*<.001*	31 (19, 56)	43 (27, 61)	8 (−2, 21)	*<.001*	*<.001*	33 (19, 54)	44 (28, 68)	10 (0, 21)	*<.001*	*<.001*
MDD-related														
Hospitalization														
Patients with ≥1 hospitalization, *n* (%)	142 (28.06%)	59 (11.66%)	−83 (−16.40%)	*<.001*	53 (21.03%)	34 (13.49%)	−19 (−7.54%)	*.025*	.066	87 (13.99%)	45 (7.23%)	−42 (−6.75%)	*<.001*	*<.001*
Length of stay per hospitalization (days)														
Mean (SD)	6.8 (6.2)	5.3 (3.6)	−1.5	.073	7.5 (7.1)	5.3 (3.6)	−2.2	.101		6.7 (4.4)	5.1 (3.1)	−1.6	*.029*	
Median (Q1, Q3)	6 (3, 8)	5 (2, 7)		.094	6 (3, 8)	4 (3, 7)		.269		5 (4, 8)	4 (3, 7)		*.032*	
Number of hospitalizations per patient														
Mean (SD)	0.4 (0.7)	0.16 (0.52)	−0.21 (0.79)	*<.001*	0.3 (0.6)	0.17 (0.48)	−0.10 (0.71)	*.038*	.061	0.19 (0.57)	0.10 (0.42)	−0.09 (0.66)	*.002*	*.005*
Median (Q1, Q3)	0 (0, 1)	0 (0, 0)	0 (0, 0)		0 (0, 0)	0 (0, 0)	0 (0, 0)			0 (0, 0)	0 (0, 0)	0 (0, 0)		
Outpatient services														
ED visits														
Patients with ≥1 ED visits, *n* (%)	77 (15.22%)	37 (7.31%)	−40 (−7.91%)	*<.001*	37 (14.68%)	21 (8.33%)	−16 (−6.35%)	*.026*	.890	63 (10.13%)	46 (7.40%)	−17 (−2.73%)	.088	*.047*
Number of ED visits per patient														
Mean (SD)	0.2 (0.4)	0.11 (0.51)	−0.07 (0.65)	*.031*	0.2 (0.6)	0.11 (0.39)	−0.11 (0.64)	*.015*	.359	0.13 (0.50)	0.1 (0.65)	−0.01 (0.66)	.694	.184
Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)		0 (0, 0)	0 (0, 0)	0 (0, 0)			0 (0, 0)	0 (0, 0)	0 (0, 0)		
Physician office visits														
Patients with ≥1 office visits, *n* (%)	395 (78.06%)	437 (86.36%)	42 (8.30%)	*<.001*	209 (82.94%)	208 (82.54%)	−1 (−0.40%)	.906	.061	477 (76.69%)	518 (83.28%)	41 (6.59%)	*.004*	.718
Number of office visits per patient														
Mean (SD)	5.6 (9.0)	11.5 (14.8)	5.88 (13.11)	*<.001*	6.5 (8.9)	10.0 (13.8)	3.54 (11.59)	*<.001*	*.016*	6.1 (10.1)	8.5 (13.7)	2.37 (13.72)	*<.001*	*<.001*
Median (Q1, Q3)	3 (1, 6)	6 (2, 14)	3 (−1, 8)	*<.001*	3 (1, 8)	5 (2, 13)	1 (−1, 5)	*.007*	*.001*	2 (1, 7)	4 (1, 10)	1 (−1, 4)	*<.001*	*<.001*

*Paired *t*-test (mean) and non-parametric Wilcoxon signed-rank test (median) were used to compare pre- vs post-index measures. *p*-values <.05 were considered significant and shown in italics.

†Pre–post differences of cohorts Y2 and Y3 cohorts were compared to those of cohort Y1 using paired *t*-test for means, non-parametric Wilcoxon signed-rank test for medians, Chi-square test for categorical variables, or Fisher's exact test for small cell values. *p*-values <.05 were considered significant and are shown in italics.

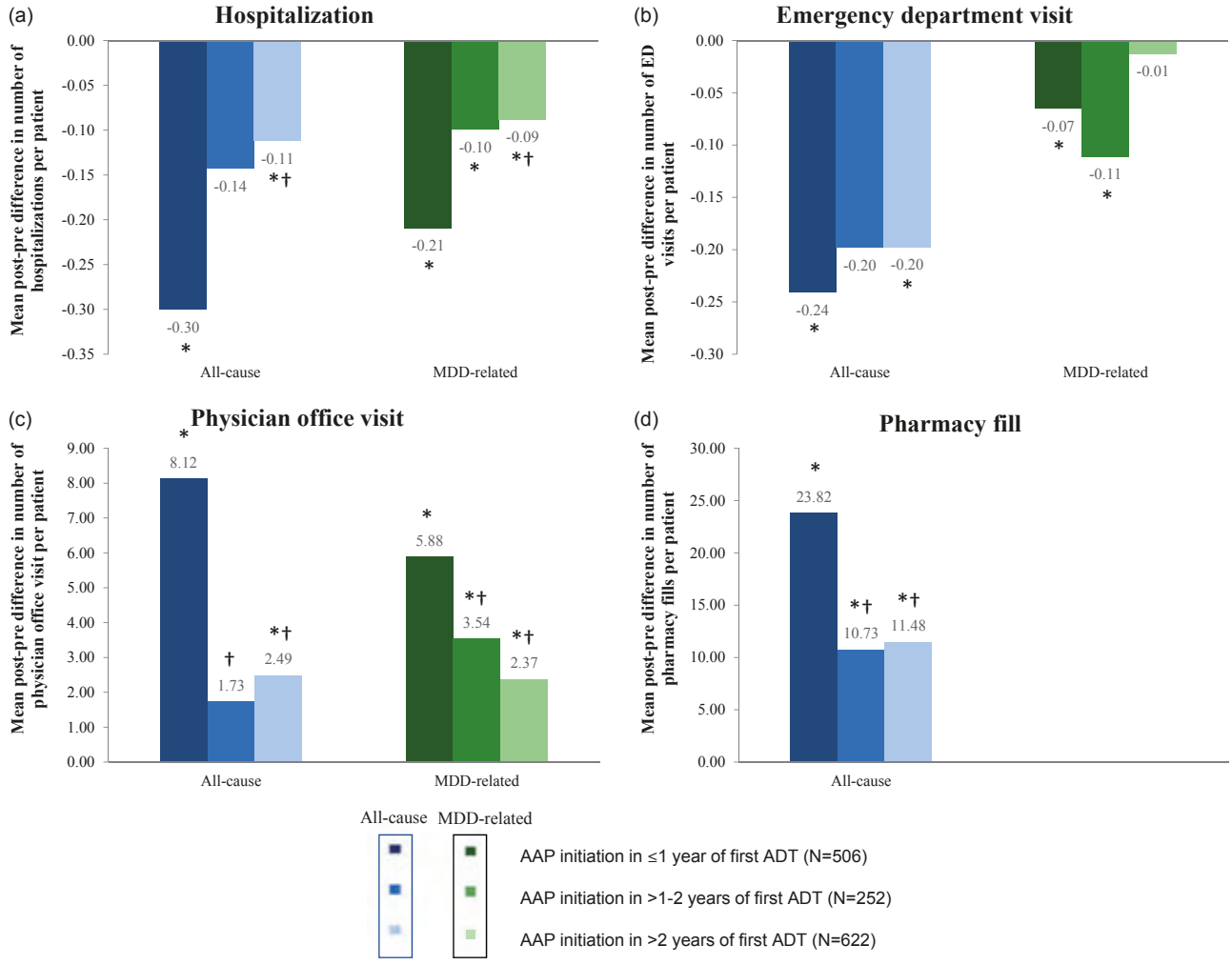

Figure 3. Unadjusted pre–post differences in healthcare resource utilization. *indicates a post–pre difference that was statistically significantly different from zero (*p*-value <.05). †indicates a post–pre difference that was statistically significantly different from that of cohort Y1 (*p*-value <.05).

mean (SD) medical cost and hospitalization cost decreased by $10,496 ($85,022) and $13,945 ($83,731), respectively, for cohort Y1. For outpatient services, the mean (SD) total cost per patient decreased for ED visits (−$322 [$2,188]), but increased for physician office visits ($956 [$3,655]) among patients in cohort Y1.

Unlike total all-cause healthcare costs, there was an overall increase in the total MDD-related healthcare cost per patient in the year following AAP initiation across cohorts (all *p*-values <.05). The mean (SD) increase in total MDD-related healthcare cost per patient was $1,955 ($15,849) for cohort Y1, $3,594 ($14,256) for cohort Y2, and $3,813 ($11,713) for cohort Y3. The cost per patient for MDD-related pharmacy services also increased statistically significantly for all cohorts, whereas that of MDD-related medical services did not change statistically significantly. Similar to the trend in all-cause hospitalization costs, the mean (SD) cost per patient of MDD-related hospitalizations also decreased for cohort Y1 (−$2,320 [$13,726]; *p*-value <.001). The mean cost per patient for physician office visits increased significantly for cohorts Y1 and Y3. The same trend was seen with the mean cost per patient of outpatient services in these two cohorts.

The mean changes in costs in cohort Y2 were similar to those in cohort Y1, but larger than those of cohort Y3. One of the notable exceptions was the mean cost per patient for all-cause hospitalization, for which cohort Y1 had a significantly larger decrease than both cohorts Y2 and Y3 (−$13,945 [$83,731] for Y1 vs −$3,898 [$43,245] for Y2 [*p*-value =.074] and −$870 [$26,634] for Y3 [*p*-value <.001]).

Post-index treatment patterns

AAP and antidepressant treatment patterns were similar across cohorts. On average, patients in all cohorts used 1.1 (0.3) different AAPs during the follow-up, with the index AAP as the only AAP medication in most patients (>90.4%). The mean time of continuous AAP treatment, regardless of which AAP was used, was ~6 months in all cohorts. However, only 1.8%, 2.0%, and 1.6% of patients were considered persistent (i.e. continuous use of AAP during the entire follow-up) among cohorts Y1, Y2, and Y3, respectively. There were, on average, 1.8–1.9 different antidepressants used during the post-index period. Among patients in all cohorts, nearly half

Table 4. Unadjusted costs of healthcare services.

	All-cause					MDD-related				
	Pre-index	Post-index	Pre–post difference		*p*-value vs Y1†	Pre-index	Post-index	Pre–post difference		*p*-value vs Y1†
			Post–pre	*p*-value*				Post–pre	*p*-value*	
AAP initiation in ≤1 year of first ADT use (Y1), n = 506										
Total										
Mean (SD)	$27,518 (89,637)	$21,412 (40,818)	−$6,107	.163		$5,714 (13,590)	$7,669 (11,934)	$1,955 (15,849)	*.015*	
Median (Q1, Q3)	$7,861 ($3,286, $60,674)	$10,361 ($5,872, $20,323)	$2,027 (−$5,281, $8,849)	*<.001*		$1,140 ($304, $5,550	$4,575 ($1,789, $8,865)	$2,052 (−$707, $5,938)	*<.001*	
Pharmacy										
Mean (SD)	$1,855 (10,967)	$6,244 (15,170)	$4,389 (8,140)	*<.001*		$507 (5,249)	$3,707 (7,048)	$3,199 (3,466)	*<.001*	
Median (Q1, Q3)	$452 ($138, $1,307)	$3,787 ($1,387, $6,804)	$2,770 (−$578, $5,605)	*<.001*		$60 ($16, $185)	$2,606 ($448, $5,151)	$2,413 ($314, $4,920)	*<.001*	
Medical										
Mean (SD)	$25,663 (89,013)	$15,168 (37,110)	−$10,496 (85,022)	*.015*		$5,206 (12,635)	$3,962 (9,596)	−$1,244 (15,269)	.078	
Median (Q1, Q3)	$6,503 ($2,461, $18,284)	$5,590 ($2,191, $12,312)	−$458 (−$7,417, $2,900)	*.032*		$775 ($195, $5,358)	$865 ($268, $2,894)	$0 (−$2,095, $940)	.623	
Hospitalization										
Mean (SD)	$17,873 (87,548)	$3,928 (14,405)	−$13,945 (83,731)	*<.001*		$3,844 (12,056)	$1,524 (6,964)	−$2,320 (13,726)	*<.001*	
Median (Q1, Q3)	$0 ($0, $7,083)	$0 ($0, $0)	$0 (−$5,443, $0)			$0 ($0, $2,311)	$0 ($0, $0)	$0 (−$101, $0)		
ED visits										
Mean (SD)	$863 (1,963)	$541 (1,539)	−$322 (2,188)	*.004*		$154 (520)	$90 (472)	−$64 (679)	*.041*	
Median (Q1, Q3)	$0 ($0, $904)	$0 ($0, $375)	$0 (−$561, $0)			$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)		
Physician office visits										
Mean (SD)	$2,424 (3,131)	$3,380 (3,748)	$956 (3,655)	*<.001*		$820 (1,762)	$1,525 (2,523)	$705 (2,477)	*<.001*	
Median (Q1, Q3)	$1,347 ($631, $2,905)	$2,167 ($953, $4,490)	$378 (−$390, $1,645)	*<.001*		$272 ($53, $741)	$570 ($18, $1,668)	$188 (−$81, $919)	*<.001*	
AAP initiation in >1–2 years of first ADT use (Y2), n = 252										
Total										
Mean (SD)	$24,760 (59,341)	$26,380 (51,021)	$1,620 (45,996)	.743	.181	$5,436 (10,940)	$9,030 (13,948)	$3,594 (14,256)	*<.001*	.166
Median (Q1, Q3)	$9,034 ($4,013, $19,784)	$11,212 ($6,226, $22,710)	$2,084 (−$5,090, $8,445)	*.013*	.927	$1,535 ($466, $4,864)	$5,407 ($1,866, $9,734)	$2,272 (−$321, $6,574)	*<.001*	.298
Pharmacy										
Mean (SD)	$4,292 (16,156)	$8,386 (18,013)	$4,094 (9,747)	*.008*	.661	$657 (1,141)	$4,434 (5,004)	$3,778 (4,754)	*<.001*	.057
Median (Q1, Q3)	$1,202 ($349, $3,476)	$4,862 ($2,161, $8,928)	$3,125 ($265, $6,261)	*<.001*	.728	$213 ($107, $586)	$3,391 ($628, $5,989)	$2,667 ($235, $5,243)	*<.001*	.582
Medical										
Mean (SD)	$20,468 (53,985)	$17,994 (43,527)	−$2,474 (45,934)	.572	.162	$4,779 (10,901)	$4,596 (12,341)	−$183 (13,237)	.860	.347
Median (Q1, Q3)	$5,822 ($2,280, $16,331)	$4,544 ($1,950, $13,677)	−$769 (−$6,859, $2,335)	*.090*	.989	$777 ($165, $3,350)	$812 ($210, $2,790)	$0 (−$879, $821)	.950	.620
Hospitalization										
Mean (SD)	$8,927 (40,009)	$5,029 (18,067)	−$3,898 (43,245)	.159	*.074*	$2,996 (9,696)	$2,470 (10,730)	−$526 (12,629)	.564	.082
Median (Q1, Q3)	$0 ($0, $2,804)	$0 ($0, $0)	$0 ($0, $0)			$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)		
ED visits										
Mean (SD)	$641 (1,372)	$539 (1,801)	−$102 (2,086)	.473	.186	$216 (763)	$172 (1,078)	−$44 (1,276)	.598	.777
Median (Q1, Q3)	$0 ($0, $573)	$0 ($0, $330)	$0 (−$363, $0)		.398	$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)		
Physician office visits										
Mean (SD)	$2,831 (3,392)	$3,209 (5,223)	$378 (5,540)	.336	.087	$928 (1,784)	$1,259 (2,035)	$331 (1,993)	.053	*.037*
Median (Q1, Q3)	$1,728 ($858, $3,515)	$1,803 ($880, $3,437)	−$15 (−$879, $756)	.897	*<.001*	$340 ($95, $1,044)	$509 ($139, $1,496)	$47 (−$186, $561)	.036	*.003*
AAP initiation in >2 years of first ADT use (Y3), n = 622										
Total										
Mean (SD)	$17,966 (48,270)	$21,664 (47,142)	$3,698 (31,453)	.172	*.008*	$3,735 (7,442)	$7,549 (9,881)	$3,813 (11,713)	*<.001*	*.024*
Median (Q1, Q3)	$8,319 ($3,314, $17,150)	$12,341 ($7,030, $22,298)	$3,779 (−$1,547, $9,290)	*<.001*	*.003*	$1,284 ($438, $3,452)	$5,288 ($2,532, $9,571)	$3,048 ($466, $6,664)	*<.001*	*.001*
Pharmacy										
Mean (SD)	$3,771 (13,299)	$7,941 (16,643)	$4,170 (6,010)	*<.001*	.605	$745 (1,159)	$4,425 (3,883)	$3,680 (3,716)	*<.001*	*.026*
Median (Q1, Q3)	$1,322 ($438, $3,411)	$5,370 ($2,383, $9,122)	$3,250 ($590, $6,786)	*<.001*	.274	$283 ($101, $847)	$3,616 ($1,067, $6,790)	$2,968 ($460, $5,892)	*<.001*	*.044*
Medical										
Mean (SD)	$14,195 (38,349)	$13,723 (35,897)	−$472 (31,334)	.823	*.007*	$2,990 (7,394)	$3,124 (8,917)	$134 (11,026)	.774	*.079*
Median (Q1, Q3)	$5,348 ($1,863, $13,495)	$5,083 ($2,019, $12,957)	−$32 (−$4,868, $3,909)	.808	*.023*	$425 ($109, $2,102)	$673 ($146, $2,330)	$27 (−$553, $736)	*.041*	*.072*
Hospitalization										
Mean (SD)	$4,805 (20,305)	$3,935 (23,503)	−$870 (26,634)	.485	*.003*	$1,724 (6,559)	$1,237 (6,913)	−$487 (9,207)	.203	*.008*
Median (Q1, Q3)	$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)			$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)		
ED visits										
Mean (SD)	$783 (2,441)	$672 (2,392)	−$112 (2,453)	.415	.133	$98 (463)	$97 (556)	−$1 (651)	.983	.111
Median (Q1, Q3)	$0 ($0, $661)	$0 ($0, $400)	$0 (−$271, $0)		*.022*	$0 ($0, $0)	$0 ($0, $0)	$0 ($0, $0)		
Physician office visits										
Mean (SD)	$3,212 (15,077)	$3,388 (7,849)	$176 (11,063)	.796	.129	$792 (1,622)	$1,233 (3,008)	$440 (3,084)	*.001*	.118
Median (Q1, Q3)	$1,660 ($754, $3,169)	$1,844 ($896, $3,455)	$185 (−$622, $1,115)	*.018*	*.001*	$271 ($40, $750)	$425 ($118, $1,204)	$92 (−$112, $479)	*<.001*	*.007*

*Paired *t*-test (mean) and nonparametric Wilcoxon signed-rank test (median) were used to compare pre- vs post-index measures. *p*-values <.05 were considered significant and are shown in italics.

†Pre–post differences of cohorts Y2 and Y3 were compared to those of cohort Y1 using paired *t*-test for means, non-parametric Wilcoxon signed-rank test for medians, Chi-square test for categorical variables, or Fisher's exact test for small cell values. *p*-values <.05 were considered significant and are shown in italics.

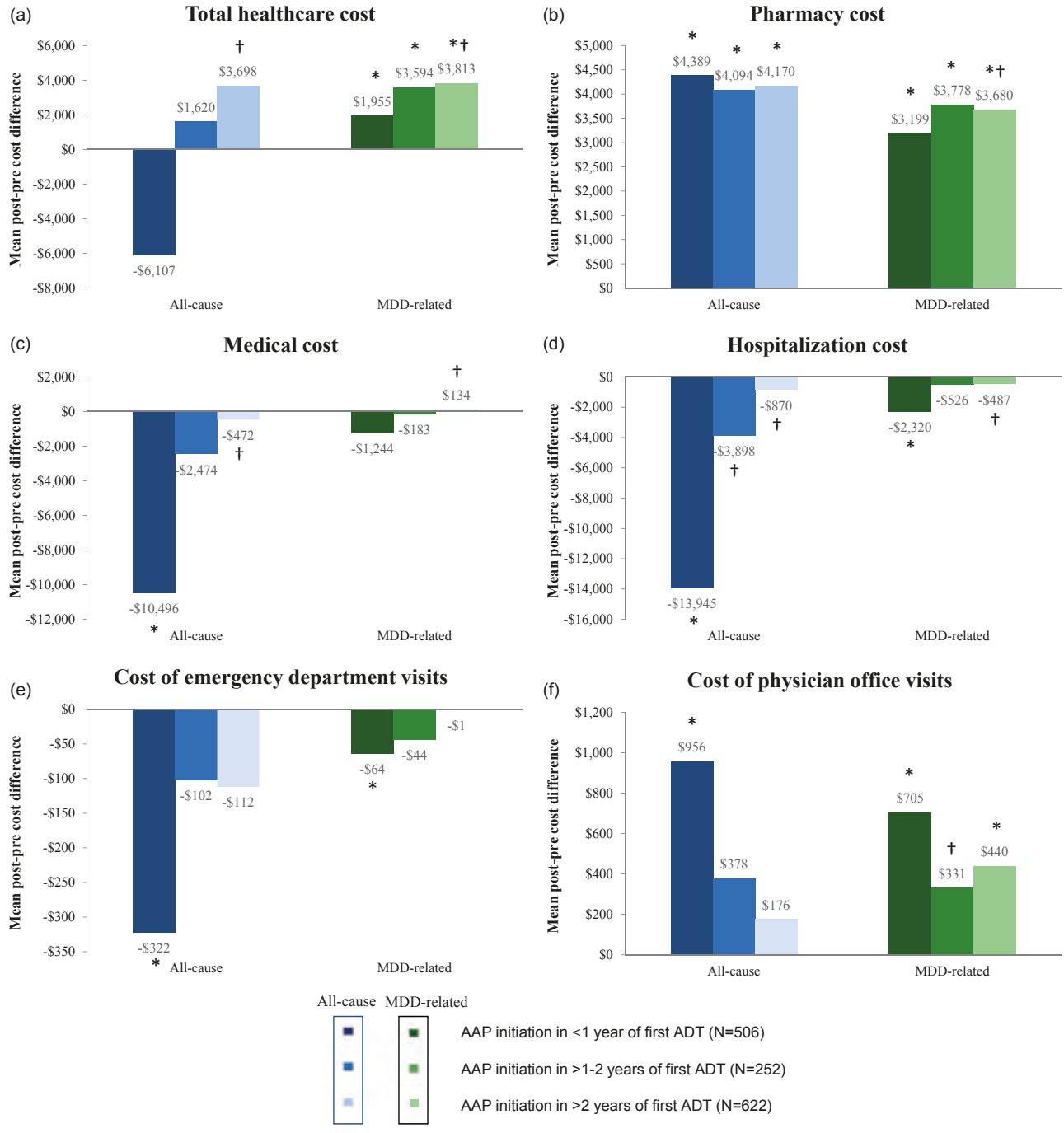

Figure 4. Unadjusted pre–post differences in healthcare costs. *indicates a post–pre difference that was statistically significantly different from zero (p-value <.05). †indicates a post–pre difference that was statistically significantly different from that of cohort Y1 (p-value <.05).

(41.0–48.8%) used only one antidepressant, 30.6–37.8% used two antidepressants, and ~20% used three or more antidepressants during the follow-up.

Adjusted analysis of hospitalization and medical costs

Differences in the reductions of hospitalization and medical cost between patient cohorts were confirmed after controlling for patient baseline characteristics. The estimated difference (follow-up – baseline) between cohorts Y1 and Y2 was −0.16 (95% CI = −0.32–0.01, p = .058) for all-cause hospitalization and −0.10 (95% CI = −0.21–0.01, p = .072) for MDD-related hospitalization. The estimated difference between cohorts Y1 and Y3 was −0.17 (95% CI = −0.30 to −0.05, p = .008) for all-cause hospitalization and −0.10 (95% CI = −0.18 to −0.01, p = .026) for MDD-related hospitalization. Between cohorts Y1 and Y2, the estimated difference in all-cause medical cost was −$9,244 (95% CI = −$18,048 to −$440, p = .040) and −$878 (95% CI = −$2,862–$1,107, p = .386) for MDD-related medical cost. Between cohorts Y1 and Y3, the estimated difference was −$11,255 (95% CI = −$18,123 to −$4,386, p = .001) for all-cause medical cost and −$949 (95% CI = −$2,497–$599, p = .230) for MDD-related medical cost.

Discussion

In this study, we investigated changes in HRU and costs associated with AAP initiation among patients with MDD who waited varying amounts of time to start AAP treatment in the real-world setting using an administrative claims database. We found that AAP use, regardless of timing of initiation, was associated with decreased rates of all-cause and MDD-related hospitalization and ED visits, and increased rates of all-cause and MDD-related physician office visits and pharmacy fills. All-cause medical costs decreased overall with AAP use, primarily driven by the reductions in all-cause hospitalization rates and costs, whereas pharmacy costs increased across cohorts. Changes in total all-cause healthcare costs following AAP adjunctive therapy initiation, however, varied by timing of initiation, with a reduction observed in patients who initiated the therapy in the first year, and increases observed in patients who waited more than 1 year. On the other hand, the total MDD-related healthcare costs increased with AAP use, mainly due to the increases in MDD-related pharmacy costs. When compared across cohorts, patients who initiated AAP treatment in the first year had the highest reduction in rates and costs of all-cause and MDD-related hospitalization, and the largest decrease in all-cause and MDD-related medical costs. Overall, patients in this cohort had the smallest increase in all-cause and MDD-related total healthcare cost. In the adjusted analysis, we found reductions in all-cause and MDD-related hospitalization from the baseline period to be significantly greater in patients who initiated AAP adjunctive therapy within the first year compared to those who waited for more than 2 years. All-cause medical costs reductions were also significantly greater in patients who initiated the therapy in the first year, compared to those who waited more than 1 or 2 years. MDD-related medical reductions were, however, similar across cohorts, regardless of timing of AAP initiation.

The changes in HRU and costs following AAP initiation found in this study are consistent with previous findings. As described in the introduction, Lin *et al*.[30] reported that AAP adjunctive therapy reduced psychiatric service utilization among patients with MDD. In particular, the numbers of psychiatric hospitalizations and emergency room visits decreased by 54.7% and 23.4%, respectively, after AAP augmentation treatment. These data are in line with our finding that AAP initiation was associated with decreased rates of MDD-related hospitalization and ED visits. In addition, Hagiwara *et al*.[31] reported a reduction of 17% in all-cause hospitalization rate, 19.5% in MDD-related hospitalization rate, and 6% in all-cause ED visit rate. These estimates support the decreased rate of 8.68–17.59% for all-cause hospitalization, 6.75–16.40% for MDD-related hospitalization, and 6.59–15.81% for all-cause ED visits observed in our study. Hagiwara *et al*.[31] also found that MDD-related total healthcare costs increased with AAP use, which was similar to the trend observed in this study, particularly among patients in cohort Y1.

The decreased rates of hospitalization and ED visits associated with AAP use are not unexpected, and in particular among patients with MDD, as these events have been shown to be related to suicidal crisis, disease progression, relapse, and functional deterioration[36,37]. Patients with depression have a higher risk of hospital admission for non-psychiatric conditions than others[38]. Depressive symptoms are also associated with higher rates of readmission after medical hospitalization[39]. Clinical trials and meta-analyses have shown that adjunctive AAP treatment for MDD is associated with increased response and remission rates, which suggests better disease management[17–26]. Our data further validates and supports findings from trials and meta-analyses as it provides evidence of improved real-world health outcomes among patients with AAP adjunctive therapy who inadequately responded to ADT.

In addition to the changes in utilization and costs of hospitalization and ED visits, we found that AAP use was in general associated with increases in the rates and costs of all-cause and MDD-related pharmacy fills. Such increases are expected as AAP adjunctive treatment incurs additional prescriptions and costs. In fact, the increases in all-cause pharmacy costs ($4,094–$4,389) was mostly attributed to increased psychotropic medication costs ($3,199–$3,778). Our results also showed an overall increase in utilization of physician office visits with an increasing trend in associated costs among patients with AAP treatment. This is not surprising, since frequent follow-up with physicians is recommended for patients receiving AAP adjunctive therapy to achieve the best therapeutic outcome[40]. Lastly, the duration of AAP treatment observed in our study is worth noting. For each cohort, patients were treated with AAP adjunctive therapy for ~6 months. It is reasonable to assume that some patients achieved sufficient recovery to allow them to reduce their medication burden. However, some patients may have not responded and discontinued the therapy, while others may have simply been non-adherent to AAP adjunctive therapy.

Although reductions in the rates and costs of all-cause and MDD-related hospitalization were observed in all cohorts, the highest and only statistically significant reduction was observed in cohort Y1. In particular, cohort Y1 had significantly greater reductions in the rates and costs of all-cause and MDD-related hospitalization than cohort Y3. Furthermore, cohort Y1 had a reduction in all-cause and the smallest increase in MDD-related total healthcare costs. Our findings from the adjusted analysis are consistent with that observed in the unadjusted analysis, and suggest that improved outcomes among patients in cohort Y1 may be associated with greater benefit with early use of AAP adjunctive therapy for treating MDD. Despite potential benefits of augmenting therapy with an atypical antipsychotic in reducing healthcare resource use and costs demonstrated in our study, the implication of long-term use of atypical antipsychotic medications on the development of metabolic syndrome, such as weight gain, hypertriglyceridemia, hypercholesterolemia, increased glucose level, and diabetes, remains unknown[41,42]. As metabolic syndrome is clearly documented as a risk factor for cardiovascular morbidity and mortality[43], long-term use of AAPs may lead to substantial increases in healthcare resource use and costs that surpass any cost savings observed in our study. Nonetheless, the risk of adverse metabolic conditions in patients treated with atypical antipsychotic medication may be less of a concern due to its shorter use in major depressive disorder (6 months

in our study) relative to schizophrenia. Careful selection of an antipsychotic and proactive monitoring of patients is key in balancing risks and benefits of AAP treatment augmentation in patients with major depressive disorder[42,44].

This study has several important strengths. One major advantage of our study as compared to the studies discussed previously is that it provides a more comprehensive view on the changes in HRU and costs following adjunctive AAP treatment for MDD. In addition, we used a pre–post design to minimize bias arising from patient-level factors which remained consistent during the pre- and post-index periods. The baseline values provide information about what healthcare resource use and costs were leading up to atypical antipsychotic initiation[45]. In addition, the difference-in-differences design was used for comparing across cohorts, which mitigated bias due to unobserved factors[34]. The approach is based on the theory that, if there is no relationship between the timing of atypical antipsychotic initiation and changes in the outcomes, the difference-in-differences estimate between cohorts should be equal to zero. In contrast, if the timing of atypical antipsychotic initiation is associated with changes, after adjusting for differences between cohorts, the outcomes following initiation should improve to a greater or lesser extent[35]. Second, since the average duration of AAP treatment was 6 months, and patients may not respond to the treatment immediately, the 12-month follow-up period allows us to assess the effects of AAP adjunctive therapy in a relatively long-term. Third, the study used data that represent a commercially insured population in the US, which allows the findings to be broadly generalizable in the US. Lastly, the longitudinal records with information on enrollment allow us to evaluate treatment history and patterns, and to obtain a more complete view on utilization and costs of healthcare services.

Study limitations should be considered when interpreting findings. The identification of patients relied on administrative claims that are used for billing purposes, and there is a potential for misclassification or upcoding. Because of limited representation of the elderly, Medicare, and Medicaid beneficiaries in the database, our findings are not generalizable to such populations. Moreover, the duration of ADT and adjunctive AAP treatment were variable during the follow-up, which may bias the study measures. However, bias arising from variability in AAP treatment duration should be minimal, considering that the average duration of AAP treatment was almost the same across all cohorts (6 months). Nonetheless, it is important to note that our 12-month post-index data incorporated HRU and cost during a period where patients were no longer using the AAP treatment. This limited exposure to drug within the study window may, however, increase the variability in our data. Furthermore, changes in prescription drug price during the study period may have impacted overall pharmacy costs. New antidepressants, including vilazodone (2011), levomilnacipran (2013), and vortioxetine (2013), and an atypical antipsychotic indicated for major depressive disorder, brexpiprazole (2015), were available on the market during the study, and may have driven the overall pharmacy cost up. However, prescription drug prices are a function of rebates, volume, formulary tiers, and other factors not available in the database, and we were unable to adjust for changes in prescription drug price.

More importantly, our results show better outcomes with early initiation of AAP treatment compared to late initiation in terms of hospitalization, ED visits, and medical costs. However, differences between cohorts which may have confounded the results should be noted. Our baseline data indicate that patients with early initiation (cohort Y1) may have been in a different stage of depression prior to AAP initiation from those with late initiation (cohorts Y2 and Y3) as they had more all-cause and MDD-related hospitalizations, ED visits, and higher overall costs in the pre-index period compared to those with late initiation. Because patients in cohort Y1 had higher pre-index HRU and costs, their potential for reductions after AAP treatment initiation was greater than those in cohorts Y2 and Y3. We also did not account for any differences in prescriber's clinical motivation for early vs late AAP adjunctive therapy initiation, which may have impacted patient HRU and costs during follow-up. Nonetheless, we attempted to control for potential confounding factors associated with patient baseline characteristics in the sensitivity analysis, and were able to show greater differences in all-cause and MDD-related hospitalization, and all-cause medical cost reductions among patients who initiated AAP treatment early relative to those who waited more than 1 or 2 years. Lastly, we did not stratify by AAP drug type within each cohort, and insights cannot be drawn for individual AAP medications; however, future research can be conducted to measure treatment effects at the drug level to help expand our understanding of early treatment. In addition to reporting average costs over a 1-year period, future research can be conducted to assess differences in per-month cost prior to and after AAP initiation to help understand patient disease severity and associated healthcare resource use and costs during the period leading up to and immediately after treatment initiation.

Conclusions

Our results show that AAP adjunctive treatment is associated with reductions in all-cause and MDD-related medical costs, primarily due to decreases in hospitalization. Further, early initiation of AAP adjunctive treatment is associated with larger reductions in hospitalization and medical costs. The study suggests positive effects of AAP adjunctive therapy on the overall health outcome of patients with MDD, and that early initiation of AAP treatment may provide better outcomes than late initiation.

Transparency

Declaration of funding

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Declaration of financial/other interests

AS and CB were contracted by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, USA to conduct this study. MG is an employee of Otsuka Pharmaceutical Development & Commercialization, Inc.; AH is an employee of Lundbeck, USA. Peer reviewers on this manuscript have received an honorarium from JME for their review work. One reviewer discloses that they served on an advisory board for Otsuka in 2017, but the remaining reviewers have no other relevant financial relationships to disclose.

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Previous presentations

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