Rates and Determinants of Use of Pharmacotherapy and Psychotherapy by Patients With Major Depressive Disorder

Fraser W. Gaspar, Ph.D., M.P.H, Catherine S. Zaidel, M.E.M., Carolyn S. Dewa, Ph.D., M.P.H.

Objective: Rates and determinants of pharmacological and psychotherapy use were assessed after a major depressive disorder diagnosis.

Methods: In a retrospective claims study that included 2007–2016 records from the IBM MarketScan research databases, use of pharmacotherapy and psychotherapy was tracked in a population of 24,579 patients with a diagnosis of major depressive disorder. Univariate and multiple variable analyses were used to identify determinants of antidepressant adherence (proportion of days covered ≥.8) and intensive psychotherapy at the beginning of treatment (at least four psychotherapy visits in the first 4 weeks after initiating psychotherapy).

Results: In the 12 months following a diagnosis of major depressive disorder, most individuals received pharmacotherapy or psychotherapy (94.7%), and unimodal therapy was more common (58.5%) than bimodal therapy (36.2%). When antidepressants were initiated (N=13,524), 41.7% and 32.0% of patients were adherent in the acute and continuation phases, respectively. Initial antidepressant dosages were outside guideline recommendations for 34.5% of patients prescribed these medications. When psychotherapy was initiated, the median number of visits in the year after a patient's diagnosis was seven. Most patients (54.7%) did not continue to receive either antidepressant or psychotherapy treatment after month 5 following their diagnosis. A shorter time from diagnosis to treatment and a lower percentage of treatment costs paid by the patient were associated with increased antidepressant adherence and intensive psychotherapy use.

Conclusions: Findings indicate that treatment guideline recommendations are not followed for a large proportion of patients with major depressive disorder and that improvement is needed in multiple areas to enhance effective treatment.

Psychiatric Services in Advance (doi: 10.1176/appi.ps.201800275)

Over 300 million people worldwide, or 4.4% of the world's population, have depressive disorders (1). As the leading cause of disability worldwide, depression results in substantial impairment and reduced quality of life (2, 3). In the United States, the economic burden of major depressive disorder has been estimated to exceed $210 billion per year (4). The two major treatment modalities for the disorder are pharmacotherapy and psychotherapy, and both treatments have been proven efficacious (5, 6).

Unfortunately, there is a need for improvement in both use of and adherence to treatment among patients with depression (7–10). For example, Soria-Saucedo et al. (10) observed that less than 20% of individuals with a diagnosis of depression received either pharmacotherapy or psychotherapy. Furthermore, when treatment is initiated, not only are patients frequently nonadherent, antidepressant adherence also decreases over time (7, 9). Keyloun et al. (7) observed that first-line antidepressant therapy adherence rates decreased from 41% at three months to only 26% at 12 months. However, the practice guidelines of the American Psychiatric Association (APA) recommend treatment through the continuation phase (4–9 months) to decrease the risk of relapse (11). Treatment guidelines recommend bimodal therapy for patients with more severe depression (11, 12), yet information on how bimodal treatment use changes over time is limited.

HIGHLIGHTS

- Less than half of patients with depression were adherent to antidepressant treatment in the acute and continuation phases.
- Most patients with depression discontinued all treatment after 5 months.
- Decreasing the time from depression diagnosis to treatment may improve adherence to antidepressant treatment and psychotherapy.

Previous research that primarily investigated antidepressant adherence has shown that demographic factors and treatment modality affect mental health treatment use by patients with depression (7, 9, 13–15). In a recent study of antidepressant adherence, Keyloun et al. (7) found greater adherence with increased age, female sex, dysthymia diagnosis, health plan, and the number of comorbidities. Although the literature shows disparate findings on adherence by antidepressant class (9, 13, 15), Keyloun et al. (7) found that patients prescribed selective serotonin reuptake inhibitors (SSRIs) had higher odds of adherence, compared with individuals prescribed tricyclic antidepressants (TCAs), and lower odds of adherence, compared with individuals prescribed serotonin-norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs). Less is known about the determinants of psychotherapy use. Soria-Saucedo et al. (10) reported higher odds of bimodal therapy, compared with unimodal antidepressant therapy, if the patient was covered by a capitated health plan, was 45 to 64 years old, and had a diagnosis of dysthymia. However, the authors did not assess whether bimodal therapy was associated with the overall use of mental health services.

In this retrospective study of claims data, pharmacological and psychotherapeutic treatment utilization over time and determinants of treatment utilization were assessed. Large-scale medical claims databases to assess health care utilization are an important resource, and their use is supported by the 21st Century Cures Act (16). This analysis focused on both unimodal and bimodal treatment use. Although bimodal treatment is a guideline-recommended approach, few studies have examined the factors associated with it. Thus this study contributes to the understanding of factors that increase treatment use and adherence to guideline-recommended treatment. This knowledge may help clinicians identify and mitigate risks to recovery.

METHODS

Data

This retrospective study of claims data used the IBM MarketScan Commercial Claims and Encounters database from 2007 to 2016. Over 260 employers and 40 health plans, representing 350 unique carriers, contribute data to the IBM MarketScan research databases (17). The Commercial Claims and Encounters database is a convenience sample of employees with employer-sponsored health insurance, and the data come mostly from large employers (18). Data were obtained through a data use license agreement. This database is designed to meet the criteria for a limited-use data set under HIPAA, meaning that it does not contain any data elements prohibited by HIPAA for fully deidentified data sets (18). As with multiple other studies that have used the IBM MarketScan research databases, this study was not evaluated by an institutional review board because it did not meet the definition of human subjects research (19).

To generate our study population, we first identified all individuals with a depressive disorder diagnosis noted in their medical claim between 2008 and 2015. [A flow diagram of steps for generating the study population is available in an online supplement to this article.] Depressive disorders were established by using the Healthcare Cost and Utilization Project's Clinical Classification Software (CCS) "depressive disorder" category (20). [A list of the associated medical codes (*ICD-9-CM* or *ICD-10*-CM codes) within the CCS depressive disorder category is included in the online supplement.] We focused on patients with a major depressive disorder diagnosis by including only those whose first diagnosis was specified as a "single-episode, major depressive disorder" and categorized as in remission, mild, moderate, or severe depression [see table in online supplement]. The remission group included patients diagnosed as having full (N=185) and partial remission (N=272). The severe group included those diagnosed as having depression with psychotic features (N=398) and without psychotic features (N=6,609).

Patients were excluded if they did not have health care coverage in the year before and the year after their first reported diagnosis of major depressive disorder. To ensure correct identification of a patient's first diagnosis of major depressive disorder, only those with at least 1-year lead-in time, when the patient did not have any depressive disorder diagnosis, were included. The 1-year follow-up time after the first diagnosis was included to track the patient's health care use over time. Patients were included if their first diagnosis of major depressive disorder was an "unspecified" single-episode diagnosis as long as the most frequent diagnosis of major depressive disorder in the year after the first diagnosis was in the allowed diagnosis groupings [see table in online supplement]. Women for whom childbirth was noted in a medical claim within 1 year of their first diagnosis of major depressive disorder were excluded because the treatment recommendations for the disorder differ during the prenatal and breastfeeding periods (11, 12). To investigate the first-line treatment of major depressive disorder, patients who filled an antidepressant prescription during the 180 days before their first diagnosis of the disorder were excluded (7). Finally, to protect against undocumented depressive disorder diagnoses in our study population, individuals were excluded if their first-line antidepressant was a refill.

Pharmacological and Psychotherapeutic Treatments

By using the National Drug Code attached to each pharmaceutical claim, IBM's Red Book was used to abstract antidepressant strength and class. The following antidepressant classes were analyzed: MAOIs, norepinephrine-dopamine reuptake inhibitors (NDRIs), SSRIs, SNRIs, serotonin antagonist and reuptake inhibitors, serotonin modulators (SMs), TCAs, and tetracyclics. Psychiatric visits were those encoded as a psychiatric visit in the database and included psychotherapy (individual, family,

or group), psychiatric advice, and therapeutic psychiatric services.

Antidepressant Treatment Metrics

Starting dosages of the first filled antidepressant were compared with those recommended by the APA's practice guidelines (11). Patients were excluded from this analysis if they initiated with two medications, defined as receiving prescriptions for more than one antidepressant type during the 14 days after the first prescription, because it might be reasonable for dosages to differ when medications are combined. The National Committee for Quality Assurance's (NCQA's) Healthcare Effectiveness Data and Information Set (HEDIS) acute and continuation treatment measures for antidepressant adherence were used. For these measures, the acute and continuation phases are defined by the NCQA as the first 114 and 231 days, respectively, after filling the first antidepressant. Adherence in the acute or continuation phase is defined as 84 of 114 days or 180 of 231 days, respectively, of continuous antidepressant treatment following the first prescription date (21). The proportion of days covered (PDC) was chosen to calculate the HEDIS adherence metrics, because it is the method for assessing medication adherence preferred by multiple organizations, including the Pharmacy Quality Alliance and the Centers for Disease Control and Prevention (22, 23). In addition to the HEDIS measures, PDC was calculated for the 12 months following the first diagnosis of major depressive disorder. In addition, acute- and continuation-phase adherence was evaluated by whether the patient had a prescription for one or more antidepressant classes during the time frame of interest.

Data Analysis

Chi-square p values from log-rank tests were used to assess statistical significance between groups in univariate analyses. Multiple variable regression methods were used to assess determinants of following recommended antidepressant and psychotherapy treatment. The categorical dependent variables were the HEDIS antidepressant adherence metric in the continuation phase, defined as ≥0.8 PDC in the 231 days after the first antidepressant was filled; and attending at least four psychotherapy visits in the first 4 weeks of psychotherapy treatment. Although the APA and Canadian Network for Mood and Anxiety Treatments guidelines do not specify an exact number or frequency of psychotherapy visits, both recommend more intensive psychotherapy at the beginning of therapy (11, 12). Therefore, this research was aimed at identifying the factors associated with a patient's receipt of at least four psychotherapy visits in the first 4 weeks of psychotherapy treatment.

The following variables were considered potential determinants in the multiple variable regression analyses: age, sex, rural home location, employee's job industry, whether an employee was salaried, whether an employee was a union employee, insurance plan type, time to starting treatment from initial diagnosis of major depressive disorder, severity of the disorder, year of treatment, cost sharing, and coexisting or comorbid conditions occurring in the year prior to first treatment. Individuals with capitated (<.2% of the total population) and noncapitated point-of-service health plans were combined because of the infrequency of these plan types. Comorbid conditions included mental health condition CCS categories (20) and comorbidity groupings from Quan et al. (24), excluding alcohol and drug use disorders, depression, and psychotic disorders, because those conditions are covered in the mental health condition CCS categories. Cost sharing was calculated as the percentage of total payments that were paid by the patient in the form of deductibles, copayments, and coinsurance. Patients located in a metropolitan statistical area were considered urban, and all other patients were considered rural.

In addition to the variables listed above, potential variables for the antidepressant adherence analysis included whether a single antidepressant class was filled, whether any antidepressant dosage matched APA's recommended starting dosage, the antidepressant class of the first filled prescription, the number of psychotherapy visits, the number of depression diagnoses noted in outpatient and inpatient visits, and the number of depression diagnoses noted as the primary reason for the outpatient and inpatient visits in the continuation phase. For the psychotherapy frequency analysis, antidepressant use was categorized as follows: no fills, whether an antidepressant was prescribed before the first psychotherapy, <0.8 PDC during the continuation phase, and ≥0.8 PDC during the continuation phase. [Tables presenting all potential variables for the multiple variable regression analyses are included in the online supplement.]

Missing demographic variables (maximum missing= 29% for the salaried variable) were imputed by randomly assigning a value for the variable by using the observed distribution of values in the data. For the multiple variable models, the least absolute shrinkage and selection operator (LASSO) method with a logistic kernel was used to select the final predictors (25). With 10-fold cross-validation, predictors were chosen by using the largest value of lambda where the error (deviance) was within 1 standard error of the minimum, a common statistical heuristic (26). This procedure was implemented by using the cv.glmnet function from the glmnet package (27). To provide the associated p values and confidence intervals, all predictors selected by the LASSO procedure were fit to the full data in a logistic regression model. All statistical analyses were performed in R, version 3.3.1 (28).

RESULTS

A total of 24,579 individuals were included in the analysis (Table 1). Most of the study population's health insurance was through either a preferred provider organization (56.7%) or a health maintenance organization (15.0%). The mean±SD age at first diagnosis was 41±10 years. The mean number of years enrolled in one's health plan before and

TABLE 1. Characteristics of patients with major depressive disorder (N=24,579)

Characteristic	N	%
Initial depression diagnosis		
Remission	457	1.9
Mild	5,337	21.7
Moderate	11,778	47.9
Severe	7,007	28.5
Sex		
Female	12,975	52.8
Male	11,604	47.2
Industry		
Construction	10	<.1
Finance, insurance, real estate	5,500	22.4
Manufacturing, durable goods	5,074	20.6
Manufacturing, nondurable goods	2,123	8.6
Oil and gas extraction, mining	226	.9
Retail trade	1,021	4.2
Services	3,975	16.2
Transportation, communications, utilities	5,888	24
Wholesale	102	.4
Missing	660	2.7
Salaried		
No	9,875	40.2
Yes	9,349	38
Missing	5,355	21.8
Union		
No	16,803	68.4
Yes	6,258	25.5
Missing	1,518	6.2
Health plan type		
Consumer-driven health plan	1,996	8.1
Comprehensive	613	2.5
Exclusive provider organization	299	1.2
High-deductible health plan	894	3.6
Health maintenance organization	3,692	15
Point-of-service plan	3,000	12.2
Preferred provider organization	13,946	56.7
Missing	139	.6

after the date of the first diagnosis of major depressive disorder was 3.3±1.9 and 3.7±2.1, respectively. Moderate depression (47.9%) was the most common diagnosis of major depressive disorder, which was consistent across provider types. Initial diagnoses of major depressive disorder were typically noted by support therapists (N=7,610, 31.0%), psychologists (N=4,531, 18.4%), psychiatrists (N=4,450, 18.1%), or family physicians (N=2,853, 11.6%) [see table in online supplement].

In the 12 months following the first diagnosis of major depressive disorder, most individuals received pharmacotherapy or psychotherapy (94.7%) (Table 2). Unimodal therapy was utilized by 58.5% of the population, and the percentage receiving bimodal therapy generally increased by depression severity. Mental health treatment use in the year that followed initial diagnosis of major depressive disorder varied by type of health insurance plan [see table in online supplement]. Patients in a point-of-service health plan had the highest utilization rate of treatment (95.4% of the population), whereas patients in a high-deductible health plan (HDHP) had the lowest percentage (90.8%). However, individuals enrolled in HDHPs had the highest percentage of patients receiving unimodal pharmacotherapy (16.6%) and the highest median PDC (0.45). Across all health plans, the median frequency of psychotherapy visits in the 12 months after the first psychotherapy visit ranged from six to eight visits.

In terms of initial antidepressant dosages, 34.5% of individuals prescribed antidepressants had starting dosages outside the APA guideline–recommended dosage, with more dosages below the recommendation (23.1%) than above (11.4%). When grouped by antidepressant type, starting dosages prescribed outside the recommendation were not equally distributed [see table in online supplement]. For example, initial dosages of trazodone (an SM) and duloxetine HCl (an SNRI) were below the APA recommendations in 96.8% and 53.5% of the cases, respectively, and the dosages were above the recommendation in .3% and 0% of the cases, respectively. When the analysis examined initial dosages by depression severity (mild, moderate, or severe), the trends observed were consistent across the three categories [see table in online supplement].

Among the 13,524 individuals who were treated with an antidepressant and had sufficient follow-up time after the antidepressant was prescribed, only 41.7% and 32.0% were adherent in the acute and continuation phases, respectively [see table in online supplement]. Patients with greater depression severity had significantly lower adherence rates in the acute and continuation phases (logistic regression trend analysis, $p<.001$). In both the acute and the continuation phases, except for individuals with depression in remission, those who filled prescriptions for more than one antidepressant class were more likely than those who filled prescriptions for a single class to be adherent ($p<0.001$, chi-squared goodness-of-fit test).

After the initial diagnosis of major depressive disorder, both antidepressant and psychotherapy utilization decreased over time (Figures 1 and 2). For patients initiating antidepressant treatment in the year after the diagnosis, the median PDC in the first month following the diagnosis was 0.80 but decreased to .17 by month 6. By month 8, the median PDC was zero, and only 34% of patients had a PDC ≥0.8. For individuals initiating psychotherapy within a year after receipt of diagnosis, the median number of visits in the follow-up year was seven [see table in online supplement]. As with antidepressant use, psychotherapy visit frequency decreased from a median of two visits per month in the first month following the diagnosis of major depressive disorder to zero by month 3. However, the cessation of psychotherapy in this time frame may have been warranted if the course of therapy was completed, and appropriate clinical management would be monitoring for early signs or symptoms of a relapse and providing booster sessions or other interventions if warranted. When

TABLE 2. Utilization of antidepressants and psychotherapy at 12 months among 24,579 patients with major depressive disorder, by severity of the initial diagnosis

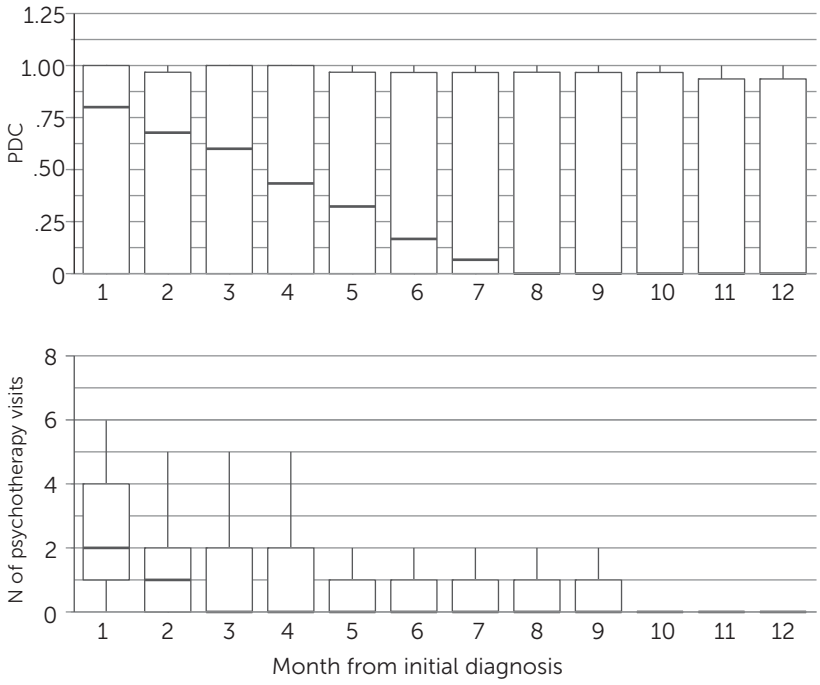
	All		No treatment		Antidepressant only		Psychotherapy only		Antidepressant and psychotherapy	
Initial diagnosis	N	%	N	%	N	%	N	%	N	%
Remission	457	1.9	109	23.9	99	21.7	163	35.7	86	18.8
Mild	5,337	21.7	435	8.2	834	15.6	2,885	54.1	1,183	22.2
Moderate	11,778	47.9	511	4.3	1,405	11.9	5,518	46.9	4,344	36.9
Severe	7,007	28.5	253	3.6	406	5.8	3,072	43.8	3,276	46.8
All	24,579	100	1,308	5.3	2,744	11.2	11,638	47.3	8,889	36.2

individuals who did not receive any treatment during the first year were included in the analysis (N=24,579), most patients were not receiving any treatment 5 months after the initial diagnosis of major depressive disorder (N=13,448, 54.7%). By severity of major depressive disorder, the percentage of patients not receiving any treatment ranged from 6.1% to 33.7% in month 1 to 64.3% to 69.4% in month 12 (Figure 2).

In the multiple variable regression analyses, a number of demographic, treatment, and medical history variables were associated with antidepressant adherence (N=13,524), with adherence defined as having a PDC of ≥0.8 in the first 231 days following a diagnosis of major depressive disorder (Table 3). Patients with an initial diagnosis of mild or moderate depression did not differ significantly in the likelihood of adherence, whereas those in remission or with severe depression had significantly higher and lower odds of adherence, respectively, compared with those with moderate depression. Initiating antidepressant treatment within 30 days of the first diagnosis of major depressive disorder was associated with increased odds of adherence. Furthermore, the number of psychotherapy visits and office visits for which a depression diagnosis was the primary reason for the visit were both associated with increased odds of adherence. Compared with individuals whose initial prescriptions were for other antidepressant classes, those whose initial prescription was for SM or TCA antidepressants were less likely to be adherent and those whose initial prescription was for NDRI or SSRI antidepressants were more likely to be adherent. As the percentage of antidepressant treatment costs paid by the patient increased, adherence decreased. Individuals switching or adding an antidepressant class had higher odds of adherence. Filling at least one prescription with a dosage matching APA's starting recommendation was associated with higher odds of adherence. Because the year of treatment was positively associated with the odds of adherence, there was evidence that adherence rates increased over time. Individuals receiving mail-order antidepressants were also more likely to be adherent in the continuation phase.

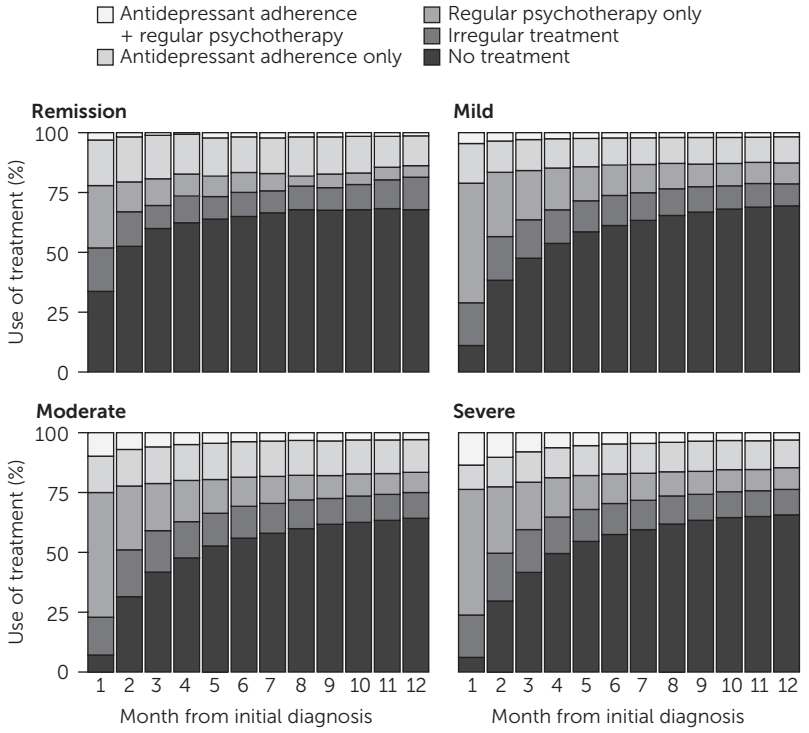
As with antidepressant adherence, initiating psychotherapy treatment within 30 days of the first diagnosis of major depressive disorder and a decreasing share of costs paid by the patient were both associated with higher odds of psychotherapy adherence, which was defined as attending at least four visits in the first 4 weeks of psychotherapy treatment (N=21,035) [see table in online supplement]. In contrast to the results for antidepressant adherence, depression severity was associated with greater odds of intensive psychotherapy utilization. Patients with psychiatric comorbidities, including adjustment and anxiety disorders, had higher odds of intensive psychotherapy utilization, compared with those with general medical comorbidities (for example, obesity and arrhythmia).

FIGURE 1. Distribution of proportion of days covered (PDC) by antidepressants (N=11,640) and number of psychotherapy visits (N=20,527) among patients with a diagnosis of major depressive disorder in the year after initial diagnosis[a]



[a] Values greater than 1.5 times the interquartile range were removed in the bottom panel to aid clarity. Individuals not receiving treatment were excluded from both analyses.

FIGURE 2. Antidepressant and psychotherapy treatment use by patients in the year after initial diagnosis of a major depressive disorder (N=24,579), by depression severity[a]



[a] Antidepressant adherence, proportion of days covered (PDC) ≥0.8 during the month; regular psychotherapy, at least two visits per month; irregular treatment, patient received either an antidepressant at PDC <0.8 or psychotherapy at less than two visits per month.

DISCUSSION

Our research found that most patients were not receiving antidepressants or psychotherapy after the first 5 months following their initial diagnosis of major depressive disorder. Furthermore, when treatment was utilized, antidepressant and psychotherapy adherence was low, and the starting antidepressant dosages were often outside guideline recommendations.

The percentage of patients with depression who received treatment in this study is higher than reported in previous studies (10, 29). For example, Soria-Saucedo et al. (10) observed that fewer than 20% of patients received either pharmacotherapy or psychotherapy. It is unclear why such a discrepancy exists given that Soria-Saucedo and colleagues also used the IBM MarketScan database, but those authors studied a more diverse group of patients with depressive disorders, including patients with recurrent depression and dysthymia. In our study, 43.8% of patients with severe major depressive disorder used psychotherapy alone as their initial treatment, although the APA recommends antidepressants as an integral part of treatment for that cohort (11). Furthermore, the more recent guideline from the Canadian Network for Mood and Anxiety Treatments recommends that patients with moderate and severe major depressive disorder use bimodal therapy (12).

A large portion of our population initiated antidepressants outside the APA's recommended starting dosage; however, some of these findings may represent off-label use. For example, trazodone is used in lower dosages as a sedative-hypnotic rather than an antidepressant in contemporary practice, explaining why the initial dosages were typically lower than APA's guideline recommendations (11). Because we did not know the condition that each prescription was intended to treat, there was a potential for overestimating the use of antidepressants for depression treatment in this study. Our analysis did not take into account additional factors that may have influenced the starting dosage, including body weight and age (11, 30). Our antidepressant adherence rates are in line with recent studies that used claims data (7, 8).

Modifiable characteristics, such as starting treatment immediately after diagnosis of major depressive disorder and lowering out-of-pocket expenses, were associated with antidepressant adherence and intensive psychotherapy utilization. Furthermore, patients who used mail-order prescriptions for antidepressants had higher odds of adherence, although the higher odds might be attributable to the use of prescription fills as the metric for adherence in this study. Our finding that depression severity was negatively associated with antidepressant adherence but positively associated with psychotherapy use is an example of how treatment utilization research can provide insight into subgroups of patients for which a particular treatment may be more effective than another. An encouraging finding is that antidepressant adherence increased in the most recent years. Several predictors of adherence were not studied, including attributes of the patient-provider relationship, adverse effects of medication, patient comprehension of illness, ability to pay for medications, and other barriers to care (31).

Adherence to mental health treatment was unfortunately low in our population of patients with major depressive disorder, and many studies have shown poor medication adherence among patients with other chronic conditions (32–34). Briesacher et al. (32) compared adherence rates among patients with seven medical conditions and found that patients with hypertension had the highest adherence rate (medication possession ratio ≥.8) at 72.3%, whereas patients with gout had the lowest adherence at 36.8%. Comorbid depression has been found to be associated with decreased adherence to treatments for other chronic conditions (35) and is an important factor to address.

Previous research suggests that effective depression treatment may increase health care costs (9, 36–38) but that

TABLE 3. Determinants of antidepressant adherence in the continuation phase among patients with major depressive disorder (N=13,524)[a]

Variable	OR	95% CI	p
Time to antidepressant fill from initial diagnosis of major depressive disorder (reference: ≤30 days)			
31 to ≤365 days	.84	.76–.93	.001
>365 days	.93	.81–1.05	.231
Did not switch or change antidepressant classes (0=no; 1=yes)[b]	.78	.70–.88	<.001
Initial depression severity (reference: moderate)			
Remission	1.35	1.00–1.82	.051
Severe	.73	.67–.80	<.001
Starting antidepressant class (0=no fills; 1=at least one fill)			
Norepinephrine dopamine reuptake inhibitor	1.23	1.06–1.42	.007
Selective serotonin reuptake inhibitor	1.26	1.13–1.41	<.001
Serotonin modulator	.65	.51–.83	.001
Tricyclic or tetracyclic	.49	.35–.69	<.001
Switched antidepressant class (0=no; 1=yes)[b]	1.22	1.10–1.34	<.001
Percentage of antidepressant costs paid by patient[b]	.73	.65–.82	<.001
Any antidepressant fill through mail order (0=no; 1=yes)[b]	5.06	4.49–5.70	<.001
Any antidepressant dosage matching American Psychiatric Association's recommended starting dosage (0=no; 1=yes)[b]	1.65	1.48–1.84	<.001
Initial diagnosis in an inpatient setting (0=no; 1=yes)	1.25	1.09–1.45	.002
N of psychotherapy visits[b]	1.01	1.00–1.01	<.001
N of medical visits with a depression diagnosis noted[b]	1.00	.99–1.02	.638
N of medical visits for which a depression diagnosis was the primary reason[b]	1.02	1.00–1.04	.023
Comorbid or coexisting condition (0=not present; 1=present)[c]			
Hypertension	.82	.74–.92	<.001
Other neurological disorder	1.44	1.04–1.99	.028
Diabetes mellitus	.86	.74–1.01	.07
Substance use disorder	.54	.35–.84	.006
Age[d]	1.02	1.01–1.02	<.001
Male (reference: female)	1.37	1.27–1.49	<.001
Salaried employee (0=no; 1=yes)[d]	1.33	1.22–1.45	<.001
Union member (0=no; 1=yes)[d]	.79	.71–.87	<.001
Lives in a rural location (0=no; 1=yes)[d]	1.22	1.06–1.41	.005
Year starting treatment (2008 to 2015)	1.07	1.05–1.09	<.001
Works in industry (0=not in industry; 1=in industry)[d]			
Retail and trade	1.74	1.46–2.08	<.001
Services	1.56	1.40–1.74	<.001
Transportation, communications, and utilities	.88	.79–.97	.011
In a comprehensive health plan (0=no; 1=yes)[d]	.80	.61–1.05	.104
Setting of initial depression diagnosis (0=not at setting; 1=at setting)			
Multispecialty physician group	1.34	1.02–1.76	.037
Supportive therapist	.89	.81–.99	.033
Other facility not elsewhere classified	.62	.41–.92	.017

[a] From a logistic regression model, with variables selected by using least absolute shrinkage and selection operator procedure. Continuation phase, 0–231 days after the first antidepressant was filled
[b] In the continuation phase.
[c] Noted in medical claim records in the year before the first depression diagnosis.
[d] At the first depression diagnosis.

it results in overall savings attributable to improved health outcomes (38–41). In a global return-on-investment analysis, Chisholm et al. (40) estimated that scaling up the effective treatment of depression and anxiety disorders by $147 billion between 2016 and 2030 would return $310 billion from that investment. Collaborative care—or a multidisciplinary approach that includes primary care physicians, specialists, nurses, and administrators—has been found to improve the quality of care and adherence among patients with depression (41). In addition, given that this study and others have found that increased cost sharing decreases pharmaceutical adherence (42), health policy makers should consider expanding mental health benefits to improve overall savings.

Limitations of this study included the use of retrospective medical claims data; the study was not prospective. The limitations of retrospective claims analyses related to understanding pharmacotherapy utilization include misclassification of diagnoses, limited clinical information, and limited information on outcomes related to effectiveness (43). The MarketScan population is drawn from a convenience sample of employees with employer-provided health insurance and comes mostly from large employers, which

may not generalize to the general population (17). Our analysis included all individuals with at least one major depressive disorder diagnosis, although there are various methods to identify patients with major depressive disorder in administrative data that influence the specificity and sensitivity of constructing the study population (44). The type of psychotherapy was unknown in this study, and guidelines report varying efficacy by type (12, 45). Our analysis did not capture how many patients were prescribed antidepressants but failed to pick up their prescriptions. Previous research has found that approximately 20% to 30% of all prescriptions are never filled at a pharmacy (46, 47).

Our data set allowed us to identify first depression diagnosis only for patients during the period of employment at the companies within the MarketScan database. It is unclear whether this was the patient's first onset of depression. Previous research has found that the median age of depression onset is 32 years (48), whereas the median age of our study population was 41 years. Therefore, some individuals may have had depression diagnoses prior to those tracked in this study. Our data had limited information on insurance type and coverage of mental health services, including whether the employee had access to an employee assistance program that provides telemedicine psychotherapy visits. We used indirect methods of assessing adherence, whereas direct methods, including direct observations or antidepressant biomonitoring, would more accurately determine adherence (31). We could not assess the causal effect of psychotherapy visits on antidepressant adherence, because the time frame of psychotherapy visits overlapped with the antidepressant use time frame.

CONCLUSIONS

Many studies have shown that mental health treatment improves health outcomes and decreases societal costs. Our study identified multiple areas of health care use that may be addressed to facilitate treatment adherence and improve outcomes among patients with major depressive disorder.

AUTHOR AND ARTICLE INFORMATION

MDGuidelines at ReedGroup, Ltd., Westminster, Colorado (Gaspar, Zaidel); Department of Psychiatry and Behavioral Sciences, University of California, Davis (Dewa). Send correspondence to Dr. Gaspar (fraser.gaspar@gmail.com).

Dr. Gaspar and Ms. Zaidel were supported to conduct this research by MDGuidelines at ReedGroup, a company that derives no profit from the results of this study.

The authors report no financial relationships with commercial interests.

Received June 8, 2018; revision received September 12, 2018; accepted November 8, 2018; published online January 11, 2019.

REFERENCES

1. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva, World Health Organization, 2017
2. Kessler RC, Berglund P, Demler O, et al: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289:3095–3105
3. Henderson M, Hotopf M: Work and common psychiatric disorders. J R Soc Med 2011; 198–207
4. Greenberg PE, Fournier A-A, Sisitsky T, et al: The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 2015; 76:155–162
5. Cipriani A, Furukawa TA, Salanti G, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357–1366
6. Kamenov K, Twomey C, Cabello M, et al: The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol Med 2017; 47:414–425
7. Keyloun KR, Hansen RN, Hepp Z, et al: Adherence and persistence across antidepressant therapeutic classes: a retrospective claims analysis among insured us patients with major depressive disorder (MDD). CNS Drugs 2017; 31:421–432
8. Gauthier G, Guérin A, Zhdanava M, et al: Treatment patterns, healthcare resource utilization, and costs following first-line antidepressant treatment in major depressive disorder: a retrospective US claims database analysis. BMC Psychiatry 2017; 17:222
9. Robinson RL, Long SR, Chang S, et al: Higher costs and therapeutic factors associated with adherence to NCQA HEDIS antidepressant medication management measures: analysis of administrative claims. J Manag Care Pharm 2006; 12:43–54
10. Soria-Saucedo R, Eisen SV, Cabral HJ, et al: Receipt of pharmacotherapy and psychotherapy among a nationally representative US sample of privately insured adults with depression: associations with insurance plan arrangements and provider specialty. J Pharm Health Serv Res 2016; 7:53–62
11. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, 3rd ed. Arlington, VA, American Psychiatric Association, 2010
12. Parikh SV, Quilty LC, Ravitz P, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016: clinical guidelines for the management of adults with major depressive disorder: section 2. psychological treatments. Can J Psychiatry 2016; 61:524–539
13. Soria-Saucedo R, Walter HJ, Cabral H, et al: Receipt of evidence-based pharmacotherapy and psychotherapy among children and adolescents with new diagnoses of depression. Psychiatr Serv 2016; 67:316–323
14. Martin Vazquez DMJ: Adherence to antidepressants: a review of the literature. Neuropsychiatry 2016; 6:236–241
15. Sheehan DV, Keene MS, Eaddy M, et al: Differences in medication adherence and healthcare resource utilization patterns: older versus newer antidepressant agents in patients with depression and/or anxiety disorders. CNS Drugs 2008; 22:963–973
16. 21st Century Cures Act. Section 4005. Public Law No 114-255, 2016
17. IBM MarketScan Research Databases for Health Services Researchers. Armonk, NY, IBM Watson Health, 2018. Accessed Aug 31, 2018. https://public.dhe.ibm.com/common/ssi/ecm/hp/en/hpw03041usen/watson-health-healthcare-providers-hp-white-paper-external-hpw03041usen-20180330.pdf
18. Hansen L: The Truven Health MarketScan Databases for Life Sciences Researchers. Armonk, NY, IBM Watson Health, 2017. http://content.truvenhealth.com/rs/699-YLV-293/images/2017 MarketScan Databases for Life Sciences Researchers WP.pdf?aliId=2548593
19. Protection of Human Subjects. Title 45 Code of Federal Regulations Part 46. Revised January 15, 2009. Washington, DC, US Department of Health and Human Services, Office for Human Research Protections, 2009. https://www.hhs.gov/ohrp/sites/default/files/ohrp/humansubjects/regbook2013.pdf.pdf
20. Clinical Classifications Software for ICD-9-CM. Rockville, MD, Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project, 2016. https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp

21. HEDIS 2015: Healthcare Effectiveness Data and Information Set. Washington, DC, National Committee for Quality Assurance, 2014
22. Calculating Proportion of Days Covered (PDC) for Antihypertensive and Antidiabetic Medications: An Evaluation Guide for Grantees. Atlanta, National Center for Chronic Disease Prevention and Health Promotion, 2015
23. PQA Measure Overview. Alexandria, VA, Pharmacy Quality Alliance. https://www.pqaalliance.org/assets/Measures/PQA%20Measure%20Overview%20082018.pdf
24. Quan H, Sundararajan V, Halfon P, et al: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–1139
25. Tibshirani R: The lasso method for variable selection in the Cox model. Stat Med 16:385–395, 1997
26. Hastie T, Tibshirani R, Jerome F: The Elements of Statistical Learning. New York, Springer, 2009
27. Friedman J, Hastie T, Tibshirani R: Regularization paths for generalized linear models via coordinate descent. J Stat Softw 2010; 33:1–22
28. The R Project for Statistical Computing. Vienna, R Foundation, 2016. https://www.r-project.org/
29. Kessler RC, Merikangas KR, Wang PS: The prevalence and correlates of workplace depression in the National Comorbidity Survey Replication. J Occup Environ Med 2008; 50:381–390,
30. Miller M, Swanson SA, Azrael D, et al: Antidepressant dose, age, and the risk of deliberate self-harm. JAMA Intern Med 2014; 174: 899–909
31. Osterberg L, Blaschke T: Adherence to medication. N Engl J Med 2005; 353:487–497
32. Briesacher BA, Andrade SE, Fouayzi H, et al: Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008; 28:437–443
33. Oung AB, Kosirog E, Chavez B, et al: Evaluation of medication adherence in chronic disease at a federally qualified health center. Ther Adv Chronic Dis 2017; 8:113–120
34. Iglay K, Cartier SE, Rosen VM, et al: Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. Curr Med Res Opin 2015; 31:1283–1296
35. Grenard JL, Munjas BA, Adams JL, et al: Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med 2011; 26: 1175–1182
36. Simon GE, Manning WG, Katzelnick DJ, et al: Cost-effectiveness of systematic depression treatment for high utilizers of general medical care. Arch Gen Psychiatry 2001; 58:181–187
37. Melek S, Halford M, Perlman D: Depression Treatment: The Impact of Treatment Persistence on Total Healthcare Costs. Seattle, Milliman, 2012
38. Birnbaum HG, Ben-Hamadi R, Kelley D, et al: Assessing the relationship between compliance with antidepressant therapy and employer costs among employees in the United States. J Occupational Environ Med 2010; 52:115–124
39. Burton WN, Chen CY, Conti DJ, et al: The association of antidepressant medication adherence with employee disability absences. Am J Manag Care 2007; 13:105–112
40. Chisholm D, Sweeny K, Sheehan P, et al: Scaling-up treatment of depression and anxiety: a global return on investment analysis. Lancet Psychiatry 2016; 3:415–424
41. Katon WJ, Seelig M: Population-based care of depression: team care approaches to improving outcomes. J Occup Environ Med 2008; 50:459–467
42. Goldman DP, Joyce GF, Zheng Y: Prescription drug cost sharing: associations with medication and medical utilization and spending and health. JAMA 2007; 298:61–69
43. Rudorfer MV: Psychopharmacology in the age of "big data": the promises and limitations of electronic prescription records. CNS Drugs 2017; 31:417–419
44. Townsend L, Walkup JT, Crystal S, et al: A systematic review of validated methods for identifying depression using administrative data. Pharmacoepidemiol Drug Saf 2012; 21(suppl 1):163–173
45. Kennedy SH, Lam RW, McIntyre RS, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. Can J Psychiatry 2016; 61: 540–560
46. Fischer MA, Stedman MR, Lii J, et al: Primary medication nonadherence: analysis of 195,930 electronic prescriptions. J Gen Intern Med 2010; 25:284–290
47. Tamblyn R, Eguale T, Huang A, et al: The incidence and determinants of primary nonadherence with prescribed medication in primary care: a cohort study. Ann Intern Med 2014; 160:441–450
48. Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593–602