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MEASURING AND PREDICTING THE FACTORS ASSOCIATED WITH PERSISTENCE TO ANTIDEPRESSANT THERAPY IN PATIENTS WITH DIABETES

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MEASURING AND PREDICTING THE FACTORS ASSOCIATED WITH PERSISTENCE TO ANTIDEPRESSANT THERAPY IN PATIENTS WITH DIABETES

BY

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ABSTRACT

Objective: The objective of this study was to measure the rate of persistence to antidepressants and to identify the factors influencing persistence to these medications in patients with diabetes.

Methods: We conducted a retrospective study among patients with diabetes enrolled in a commercial health plan between 2009 – 2012. The study population includes patients who were at least 18 years of age and diagnosed with major depression during this period. The patients were eligible for acute phase treatment and continuation phase treatment if they were enrolled at least 90 days and 180 days after the Index antidepressant Prescription Start Date (IPSD) respectively. The patients were eligible for the study if (1) there was no history of diagnosis of major depression for at least 120 days prior to the first episode of major depression (Index Episode Start Date-IESD) and (2) there was no history of an antidepressant dispensing for at least 90 days prior to the IPSD.

Results: The mean age of the patients in both the phases was approximately 60 years. A majority were prescribed SSRI (Selective Serotonin Reuptake Inhibitors) antidepressants in acute (71.5%) and continuation (74.9%) treatment phases , 81.8% of the patients in acute phase and 72.8% in continuation phase had monotherapy, 210 patients in acute phase and 112 patients in continuation phase had no follow up visits. Only 60.1 % and 43.5% of patients were found to be persistent to acute and continuation treatment phases respectively.

Acute Phase Treatment: The odds of non-persistence were higher for patients in age group 18-40 compared to patients aged 40 above (OR 0.46 P=0.0036). Across the

class of antidepressants patients utilizing trazadone or mirtazapine (OR=2.35 P=0.02) were more likely to non-persist. Patients who had 1 to 3 (OR=0.19 P<0.0001) or more than 3 (OR= 0.63 P<0.0001)follow up visits were found to have lower odds for non persistence compared to patients with no follow up visits during the treatment. Patients who had a combination treatment with either buproprion or tricyclic antidepressants (TCA) were found to be more likely to non-persist (OR 2.85 P=0.003).

Continuation Phase Treatment: The odds of non-persistence were higher for patients in age group 18-40 compared to patients aged 40 above (OR 0.52 P=0.03). Patients who had 1 to 3 (OR 0.1 P<0.0001) or more than 3 (OR 0.13 P<0.0001)follow up visits were found to have lower odds for non-persistence compared to patients with no follow up visits during the treatment period

Conclusion: In this population of commercially-insured patients having diabetes, acute phase persistence with antidepressant therapy was found to be associated with age, antidepressant class, type of therapy and intensity of follow up visits where as continuation treatment persistence was associated with age and intensity of follow up visits.

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CHAPTER 1

INTRODUCTION

In the United States the prevalence of diabetes is increasing with approximately 8% of the population or 26 million people diagnosed with this disease.[1] It is very crucial for patients with diabetes to adhere to their medication to have glycemic control [2]and also to decrease hospitalizations and health care costs.[3]

Approximately 15 million adults in the United States are affected by major depression which is highly recurrent.[4,5] It is estimated that 9.5% of the adult population suffer from depressive illness every year.[6] People with depression have negative effects such as suicidal behavior, higher health care utilization and costs, lower quality of life and reduction in employment productivity.[7-9] To achieve previous levels of functioning and to prevent reoccurrence of depression, adherence to antidepressant medication is critical.[10-12]

The increased prevalence of depressive symptoms and major depressive disorder in patients with diabetes has been documented by many studies.[13] The prevalence of depression in diabetic population is approximately double the prevalence of depression in the general population.[14] Symptoms of depression are present in approximately 30% of people with diabetes [15]and approximately 10% of people with diabetes have major depression.[16] Li et al found that 45% of patients with diabetes have undiagnosed depression which suggests even higher rates of prevalence of both these conditions together.[17] Comorbid depression in diabetes patients is severe and

persistent.[18] Lustman et al found that in patients with comorbid major depression and diabetes the rates of relapse of depression were as high as 79% over 5 year period with a mean of 4 or more episodes during that period.[19,20]

Patients with comorbid diabetes and depression are more likely to be non-adherent to the medication regimen[21] and also show poor diabetes management compared to patients without depression.[22] Depression is associated with higher hemoglobin A1c (HbA1c) levels,[23] poor adherence to diet, exercise and medication regimen in patients with diabetes.[24-27] It is also associated with greater symptom burden,[28] functional impairment,[25,26] micro and macro vascular complications,[29] higher health care costs[26] and mortality.[29] For example a study conducted by Ciechanowski et al on patients enrolled in a health maintenance organization having diabetes with higher severity of depression symptoms, subjects had worse physical and mental functioning, higher non-adherence to oral hypoglycemic regimens (15% vs. 7%) 51% higher primary , 75% higher ambulatory and 86% higher total health care costs compared to patients with low severe symptoms of depression.[26] These facts suggest the importance of effective treatment of depression in patients with diabetes to improve the health outcomes.

When compared to non-depressed patients, depressed patients are three times more likely to be non-adherent to treatment recommendations. [30]In one study conducted amongst primary care patients about one-third discontinued their antidepressant therapy within one month of the initiation of the treatment and about half discontinued within three months.[31] Lowest rates of adherence were found in patients with diabetes (67.5%) compared to patients with other chronic conditions (pulmonary-68.8% and

cardiovascular diseases-76.6%) in a study conducted by DaMatteo et al.[32] These facts together suggest even lower adherence rates in patients with comorbid depression and diabetes. A major barrier to improving care in people with comorbid depression and diabetes is their poor adherence to the treatment.[30]

The objective of this study was to measure the rate of persistence to antidepressants and to identify the factors influencing persistence to these medications in patients with diabetes.

We hypothesized that one of the covariates among the patient demographic (age, gender, health plan) or clinical factors (Comorbidity score, insulin utilization, hospitalization, psychotherapy, type of antidepressant, class of antidepressant, type of therapy) or physician factors (follow up visits) better predicts the persistence to antidepressant therapy.

CHAPTER 2

METHODOLOGY

Study Design: We conducted a retrospective cohort study using a sample of commercially insured patients. The data set consisted of health care claims occurring from 2009 through 2012. All the members of this dataset have at least one International Classification of Disease-9 (ICD-9) code for diabetes during this period. The enrollment file has demographic information describing age, gender, health plan, enrolment start date and end date. The prescription file contains information describing National Drug Codes (NDC), drug names, dates of prescription dispensing , days of supply of the medication provided, national provider ID, copayment and prescription cost. The professional file includes information describing medical service use including diagnosis and procedure codes and payment amounts. The facility file has information describing ICD codes, Current Procedural Terminology (CPT) codes, revenue codes, copayment, cost paid to the facility, admit dates and discharge dates.

Study population: The study population includes patients enrolled in the commercial plan who were at least 18 years of age and diagnosed with major depression during 2009-2012 (International Classification of Diseases codes 296.20-296.25, 296.30-296.35, 298.0, 311). The patients were eligible for acute phase treatment and continuation phase treatment if they were enrolled at least 90 days and 180 days after the Index antidepressant Prescription Start Date (IPSD) respectively.

The patients were eligible for the study if (1) there was no history of diagnosis of major depression for at least 120 days prior to the first episode of major depression (Index Episode Start Date-IESD) and (2) there was no history of an antidepressant dispensing for at least 90 days prior to the IPSD. Since persistence with particular drug therapy was a variable of our interest, we excluded the patients who switched the drug therapy during the treatment period.

Figure 1. Time frame for the enrollment of subjects in the study

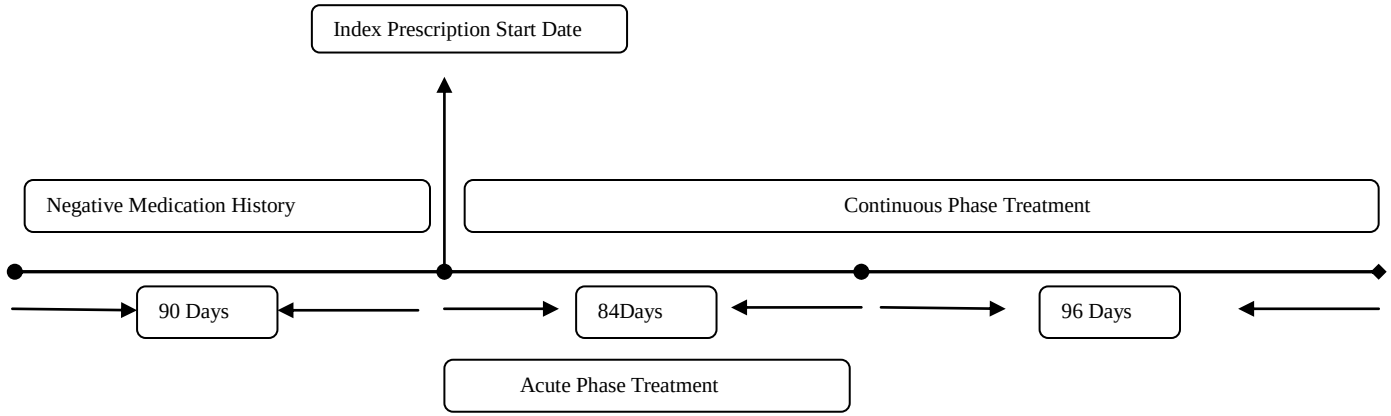


Figure 2. Eligible population for acute phase treatment persistence measurement

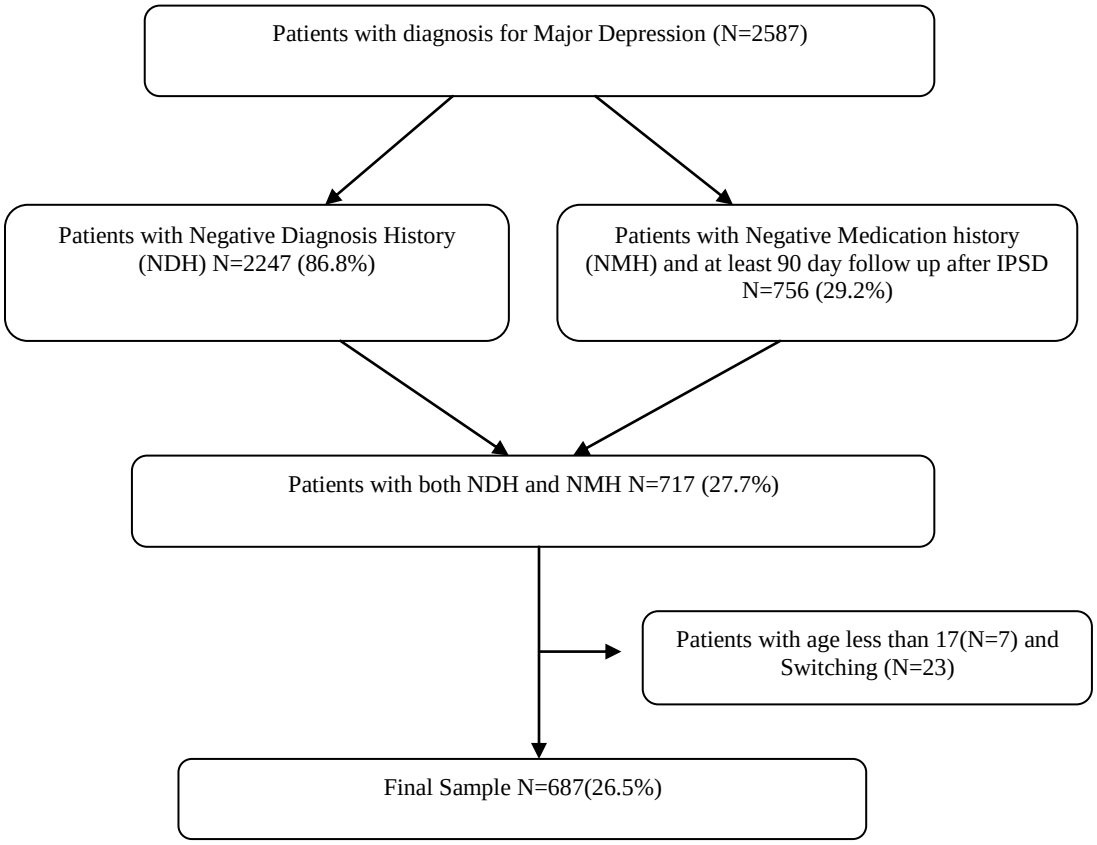
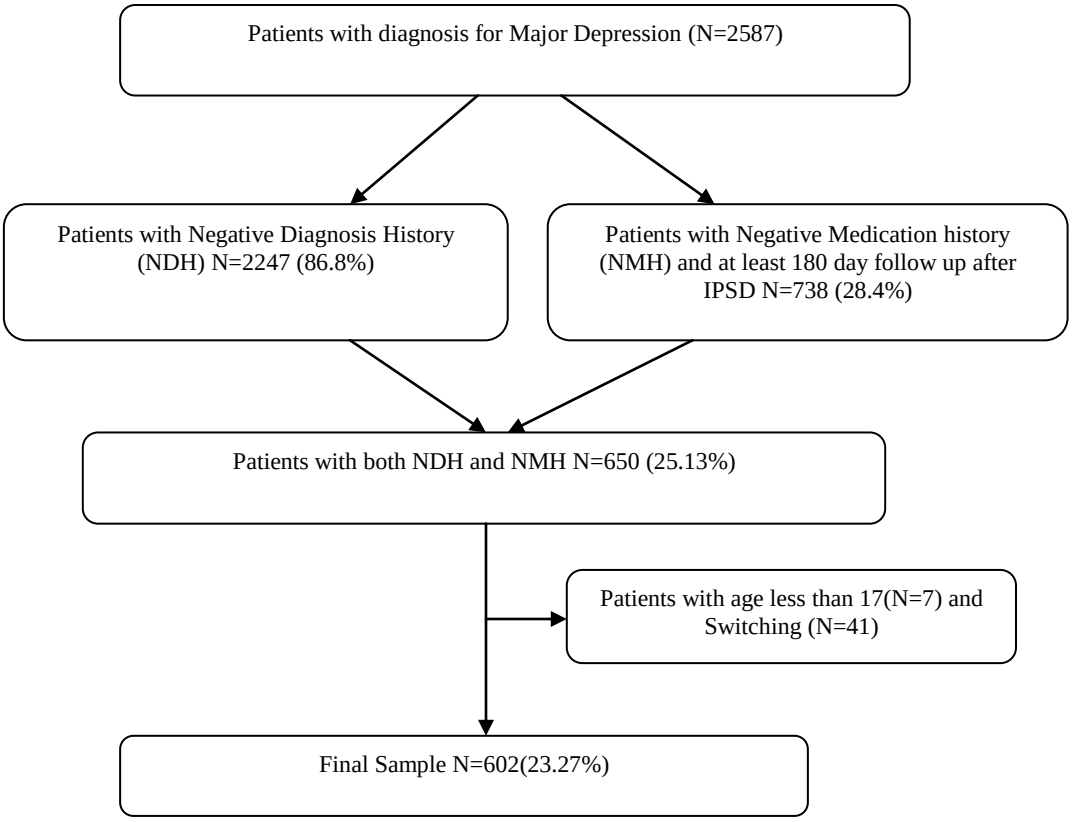


Figure. 3 Eligible population for continuation treatment phase persistence measurement



Dependent Variable: The dependent variable for the study was persistence to the antidepressant therapy. Effective acute phase treatment was defined as at least 84 days of continuous treatment with antidepressants within 114 days after the IPSD. Effective continuous phase treatment was defined as at least 180 days of continuous treatment with antidepressants within 231 days after the IPSD. The patients who meet these criteria were identified as persistent to therapy and who do not meet were identified as non-persistent to the therapy. The persistence to therapy during acute phase and continuous phase were evaluated in different models.

Independent variables: Age, gender, Charlson comorbidity index, insulin utilization, hospitalization, psychotherapy, class and type of the antidepressant, type of antidepressant therapy, health plan and intensity of follow- up care were the independent variables examined in this study. Age was coded in categories with age group 18-40 and above 41. The classes of antidepressants considered were tricyclic antidepressants (TCA), SSRI's (Selective Serotonin Reuptake Inhibitors), SSNRI's (Selective Serotonin Norepinephrine Reuptake Inhibitors), phenyl piperazines, tetracyclic antidepressants and bupropion. The Charlson comorbidity index provides the overall measure of disease burden and predicts the mortality by weighing different comorbid conditions of the patient; this score was calculated for each patient for all the disease conditions in the time frame studied and was used for assessing the comorbidity of the patients in this study. The score was coded in categories with scores of 1 to 3 and more than 3. Follow up visits for any purpose during the treatment phase were counted for both the phases. The visits were coded as 0, 1-3 visits and more than 3 visits.

Statistical Analysis: Descriptive statistics for each variable were used to summarize the study population. Bivariate analyses were conducted to assess the association between the dependent variable and each independent variable. Univariate logistic regression was performed to select the variables with significant P-Values (0.2) for final model (Table 7 and Table 8 in Appendix). Interactions and colinearity were assessed between the independent variables. Multivariate logistic regression was performed to examine the multivariate associations of the independent variables with the dependent variable (persistence to antidepressant therapy during acute phase treatment and continuous phase treatment) and odds ratios were used to measure the association. Separate analyses were performed for the acute and continuous phases. The significance level was set at 0.05 and 95% Confidence Intervals were examined. All the statistical analyses were performed using SAS statistical software version 9.3.

CHAPTER 3

FINDINGS

Acute Phase Treatment Persistence

Table 1 provides the base line demographic and clinical characteristics of the study population. The mean age of this population was 60.5 years and a majority of the patients were females (56.8%).The mean comorbid score in this study population was 3.4. Additionally 44.69% of the patients received psychotherapy during the acute phase treatment. Insulin utilization was observed in 31% of these patients. Forty- four (6.4%) patients were hospitalized. A majority (65.2%) of them were enrolled in non-HMO (Health Maintenance Organization) plans. Most of these patients (81.8%) had antidepressant monotherapy. No follow up visits were in 30.6% of patients during the treatment period. Generic antidepressant drugs were prescribed to 84.6% of the patients. A majority of the population (71.5%) were prescribed SSRI's followed by SSNRI's (8.7%).

In the bivariate analysis (Table 2) age, antidepressant class, type of therapy and follow up visits were found to have a significant association with persistence to antidepressant medication during the acute phase treatment. Patients adherent during the acute phase were aged 41 or above (61.8%) vs. 18-40 years (47.5%), prescribed an SSRI antidepressant (61.7%) or SSNRI (63.3%) or bupropion (64.1%) and were on

monotherapy (62.6%). Higher rates of persistence were found in patients having 1-3 (79.4%) or more than 3 follow up visits (53.9%).

In the multivariate analysis (Table 3) age, class of antidepressant, type of therapy and follow up visits were found to be significantly associated with persistence to acute phase treatment after adjusting for other variables. The odds of non-persistence were higher for patients in age group 18-40 compared to patients aged 40 above (OR 0.46 P=0.0036). Across the class of antidepressants patients utilizing other (trazadone and mirtazapine) antidepressants (OR=2.35 P=0.02) were more likely to not persist compared to patients utilizing SSRI's, whereas no difference was observed in the rates of persistence in patients utilizing SSNRI's, TCA, bupropion and SSRI's. Patients who had 1 to 3 (OR=0.19 P<0.0001) or more than 3 (OR= 0.63 P<0.0001)follow up visits were found to have lower odds for non-persistence compared to patients with no follow up visits during the treatment. Patients who had a combination treatment with either buproprion or TCA were found to be more likely to non-persist (OR 2.85 P=0.003) where as there was no difference in rates of persistence in patients who had a combination treatment either with trazadone or mirtazapine.

Continuation Phase Treatment Persistence

Table 4 shows the baseline demographic and clinical characteristics of the population in the continuous phase. The mean age of the study population during this treatment was 60.4. The proportion of females was higher (56.8%) than males. The mean comorbid score for this population was 3.4. Approximately 43% of patients received psychotherapy during this period. Insulin utilization was observed in 30.7% of the patients. Fourty patients (6.6%) were hospitalized during this period. Similar to the population in acute phase treatment a majority of the patients (65.8%) in this treatment phase were also enrolled in a non-HMO health plan. A higher percentage of people had monotherapy (72.8%). No follow up visits were observed in 18.6% of patients during the treatment period. Most of the patients were prescribed (83.6%) generic antidepressants similar to the patients in acute phase treatment. A majority of them were prescribed SSRI's (74.9%) followed by SSNRI's (9.0%).

In the bivariate analysis (Table 5) age and follow up visits were found to have a significant association with persistence to antidepressant medication during the continuous phase treatment. Patients adherent during the continuous phase were aged 41 or above (45.1%) vs. 18-40 years (30.3%). Higher rates of persistence were found in patients having 1-3 (56.2%) or more than 3 (48.9%) follow up visits compared to patients with no follow up visits (11.6%).

In the multivariate analysis (Table 6) age and follow up visits were found to be significantly associated with persistence to continuous phase treatment after adjusting

for other variables. The odds of non-persistence were higher for patients in age group 18-40 compared to patients aged 40 above (OR=0.52 P=0.03). Patients who had 1 to 3 (OR=0.1 P<0.0001) or more than 3 (OR=0.13 P<0.0001)follow up visits were found to have lower odds for non-persistence compared to patients with no follow up visits during the treatment period.

Table 1. Demographic and clinical characteristics of a population of commercially insured patients: Acute phase persistence with antidepressant medications (N=687)

Variable	*N*	*%*
Age(Mean 60.5,SD16.7)		
18-40	80	11.7
41-64	352	51.3
65 and above	255	37.0
Gender		
Male	297	43.2
Female	390	56.8
Comorbidity Score(Mean 3.4,SD 2.7)		
1	214	31.0
2	106	15.5
3 or more	367	53.5
Insulin		
Yes	213	31
No	474	69
Hospitalization		
Yes	44	6.4
No	643	93.6
Psychotherapy		
Yes	307	44.7
No	380	55.3
Type of Antidepressant		
Generic	581	84.6
Brand	81	11.8
Brand and Generic	25	3.6
Antidepressant Class		
SSRI	491	71.5
SSNRI	60	8.7
Tricyclic Antidepressants	39	5.7
Bupropion	39	5.7
Others	58	8.4
Type of therapy		
Monotherapy	562	81.8
Combination with trazadone/mirtazapine	85	12.4
Combination with Others	40	5.8
Health Plan		
HMO	239	34.8
Non-HMO	448	65.2
Follow up Visits		
0	210	30.6
1 to 3	247	35.9
more than 3	230	33.5

Table2. Bivariate Analysis: Factors associated with persistence to acute phase antidepressant treatment in commercially insured patients

Variable	*Persistent*	*Non-Persistent*	*Chi-Sq P-value*
	413(60.1%)	274(39.9%)	
Age			0.014
18-40	38 (47.5%)	42(52.5%)	
41 and above	375(61.8%)	232(38.2%)	
Gender			0.07
Male	190(64%)	107(36%)	
Female	223(57.2%)	167(42.8%)	
Comorbidity Score			0.59
1 to 3	266(60.9%)	171(39.1%)	
4 and above	147(58.8%)	103(41.2%)	
Insulin			0.4
Yes	123(57.7%)	90(42.3%)	
No	290(61.2%)	184(38.8%)	
Hospitalization			0.42
Yes	29(65.9%)	15(34.1%)	
No	384(59.7%)	259(40.3%)	
Psychotherapy			0.14
Yes	194(63.2%)	113(36.8%)	
No	219(57.6%)	161(42.4%)	
Type of Antidepressant			0.91
Generic	351(60.4%)	230(39.6%)	
Brand	47(58%)	34(42%)	
Generic and Brand	15(60%)	10(40%)	
Antidepressant Class			0.03
SSRI	306(61.7%)	185(37.7%)	
SSNRI	38(63.3%)	22(36.7%)	
Tricyclic Antidepressants	17(43.6%)	22(56.4%)	
Bupropion	25(64.1%)	14(35.9%)	
Others	27(46.6%)	31(53.4%)	
Type Of Therapy			0.01
Monotherapy	352(62.6%)	210(37.4%)	
Combination with Trazadone/ Mirtazapine	44(51.8%)	41(48.2%)	
Combination with Others	17(42.5%)	23(57.5%)	
Health Plan			0.55
HMO	140(58.6%)	99(41.4%)	
Non-HMO	273(60.9%)	175(39.1%)	
Follow up Visits			<0.0001
0	93(44.3%)	117(55.7%)	
1 to 3	196(79.4%)	51(20.6%)	
More than 3	124(53.9%)	106(46.1%)	

Table 3. Estimated odds ratios and 95% confidence intervals of antidepressant treatment persistence during acute phase treatment

Variable	*Odds Ratio*	*95% CI*	*P-Value*
Age			0.0036
18-40	1		
41 and above	0.46	0.27-0.78	
Gender			0.069
Male	0.73	0.52-1.03	
Female	1		
Comorbidity Score			0.6
1 to 3	1		
4 and above	1.09	0.76-1.56	
Antidepressant Class			0.02
SSRI	1		
SSNRI	0.94	0.52-1.71	
TCA	1.62	0.78-3.31	
Bupropion	0.83	0.4-1.7	
Others	2.35	1.29-4.29	
Follow up visits			<0.0001
0	1		
1 to 3	0.19	0.12-0.29	
more than 3	0.63	0.42-0.93	
Type of therapy			0.003
Monotherapy	1		
Combination with Trazadone/ Mirtazapine	1.74	1.05-2.88	
Combination with Others	2.85	1.41-5.78	

Table 4. Demographic and clinical characteristics of a population of commercially insured patients: Continuation phase treatment persistence with antidepressant medications

Variable	*N*	*%*
Age(Mean60.4,SD16.2)		
18-40	66	11.0
41-64	319	52.9
65 and above	217	36.1
Gender		
Male	260	43.2
Female	342	56.8
Comorbidity Score(Mean3.4,SD2.6)		
1	186	30.9
2	94	15.6
3 or more	322	53.5
Insulin		
Yes	185	30.7
No	417	69.3
Hospitalization		
Yes	40	6.6
No	562	93.4
Psychotherapy		
Yes	257	42.7
No	345	57.3
Type of Antidepressant		
Generic	503	83.6
Brand	59	9.8
Brand and Generic	40	6.6
Class of Antidepressant		
SSRI	451	74.9
SSNRI	54	9.0
Tricyclic Antidepressants	35	5.8
Bupropion	29	4.8
Others	33	5.5
Type of therapy		
Monotherapy	438	72.8
Combination with Trazadone/Mirtazapine	109	18.1
Combination with other	55	9.1
Health Plan		
HMO	206	34.2
Non-HMO	396	65.8
Follow up Visits		
0	112	18.6
1 to 3	128	21.3
more than 3	362	60.1

Table 5. Bivariate Analysis: Factors associated with persistence to continuation phase antidepressant treatment in commercially insured patients

Variable	*Persistent*	*Non-Persistent*	*Chi-Sq P-value*
	262(43.5%)	340(56.5%)	
Age			0.02
18-40	20(30.3%)	46(69.7%)	
41 and above	242(45.1%)	294(54.9%)	
Gender			0.8
Male	115(44.2%)	145(55.8%)	
Female	147(43%)	195(57%)	
Comorbidity Score			0.6
0 to 3	163(42.7%)	219(57.3%)	
4 and above	99(45%)	121(55%)	
Insulin			0.8
Yes	79(42.7%)	106(57.3%)	
No	183(43.9%)	234(56.1%)	
Hospitalization			0.1
Yes	13(32.5%)	27(67.5%)	
No	249(44.3%)	313(55.7%)	
Psychotherapy			0.3
Yes	118(45.9%)	139(54.1%)	
No	144(41.7%)	201(58.3%)	
Type Of Antidepressant			0.6
Generic	218(43.3%)	285(56.7%)	
Brand	24(40.7%)	35(59.3%)	
Generic and Brand	20(50%)	20(50%)	
Antidepressant Class			0.3
SSRI	199(44.1%)	252(55.9%)	
SSNRI	28(51.9%)	26(48.1%)	
Tricyclic Antidepressants	11(31.4%)	24(68.6%)	
Bupropion	13(44.8%)	16(55.2%)	
Others	11(33.3%)	22(66.7%)	
Type of Therapy			0.1
Monotherapy	201(45.9%)	237(54.1%)	
Combination with Trazadone/Mirtazapine	38(34.7%)	71(65.1%)	
Combination with Other	23(41.8%)	32(58.2%)	
Health Plan			0.7
HMO	92(35.1%)	170(64.9%)	
Non-HMO	114(33.5%)	226(66.5%)	
Follow up visits			<0.0001
0	13(11.6%)	99(88.4%)	
1 to 3	72(56.2%)	56(43.8%)	
More than 3	177(48.9%)	185(51.1%)	

Table 6. Estimated odds ratios and 95% confidence intervals of antidepressant treatment persistence during continuation phase treatment

Variable	*Odds Ratio*	*95% CI*	*P-Value*
Age			0.03
18-40	1		
41 and above	0.52	0.29-0.94	
Gender			0.86
Male	0.99	0.70-1.41	
Female	1		
Comorbidity Score			0.99
0-3	1		
4 and above	0.97	0.67-1.38	
Follow Up Visits			<0.0001
0	1		
1 to 3	0.1	0.05-0.19	
more than 3	0.13	0.07-0.25	

CHAPTER 4

DISCUSSIONS, LIMITATIONS AND CONCLUSION

In this study we assessed the antidepressant treatment persistence rates and the factors associated with persistence to these medications in the acute phase and continuation phase treatment periods. Results of our study indicate that only 60.12 % and 43.52 % of patients were persistent to acute and continuation phase respectively. Persistence was significantly influenced by age, class of antidepressant, type of therapy and intensity of follow up visits during the acute phase treatment where as only age and intensity of follow up visits had an effect on persistence to the therapy during continuation phase.

As expected a majority of the patients were prescribed SSRI's as they are most frequently utilized for depression and the preferable antidepressants for diabetic patients as they might show beneficial effects on glycemic control.[33-35]

Older age was found to be associated with persistence to the antidepressant medication in both acute and continuous phases. This finding was consistent with the previous research[36-38] that older people were more likely to be adherent to the therapy compared to younger people. For example, in a study conducted by Akincigil et al on privately

insured patients, patients who were age 50 or above were found to be 2.48 times more likely to be adherent compared to patients with 18-25 years. This might be due to the possibility that older people are more experienced in managing their medication regimen to various disease conditions which makes it easier for them to manage antidepressant medication as well. Another possible explanation might be they are more worried about mortality compared to younger population.

The class of antidepressant utilized was significantly associated with persistence during the acute phase but had no influence during the continuation phase. This might be due to the side effects or adverse events due to these drugs during the initial treatment. It could be assumed that patients who had no side effects with these drugs in acute phase treatment persisted with their medication in continuation phase and therefore the class of drug had no influence on persistence in this phase .Patients who were prescribed SSRI's were more likely to be persistent to acute phase treatment which was a similar result in previous studies[39]. There was no difference in the rates of persistence to the therapy among SSRI's SSNRI's, TCA and bupropion. Patients receiving other antidepressants (trazadone and mirtazapine) were less likely to persist with effective acute phase treatment. One reason for this might be that these drugs were prescribed for insomnia while the primary treatment was psychotherapy. Another reason might be due to the adverse effects of these drugs such as weight gain, dizziness etc.

It was also found that patients who had a combination therapy with SSRI/SSNRI and bupropion or TCA were less likely to persist. This might be due to the side effects due to the combination of these drugs such as remarkably lower blood pressure with combination of TCA and SSRI.[40] However a meta-analysis by Seetal et al found that combination of SSRI/SSNRI with bupropion was well tolerated.[41] Another reason might be these patients have severe depression resulting in less motivation to take the medicines.

We also found that patients who have either 1 to 3 or more than 3 follow up visits are more likely to be persistent to the therapy compared to patients with no follow up visits. It was found in the previous research that patients with 3 or more follow up visits were more likely to persist.[36,37,42] One reason for this might be that the physician could possibly educate the patient about the importance of taking the medications regularly. Another reason might be these patients are more cautious about their health and therefore have frequent follow up visits with the physician and take their medications regularly.

Our study has several limitations. (1)Reliance on claims data, which might have coding errors due to insufficient information provided by the physician about ICD codes, CPT codes etc. Also the deliberate miscoding of major depression with other diagnosis codes by physicians[43] further increases the chances of coding errors in identifying patients with major depression. (2)If the patient receives prescription or care outside the health plan network or if the patient receives samples by the provider

in the office it will not be shown in the claims data. (3)We assumed that patients who had prescription for the antidepressants as persistent which might not actually reflect the actual utilization of these drugs by the patients.(4) In the HEDIS (Healthcare Effectiveness Data and Information Set) algorithm patients who switched the therapies are also included in the calculation of rates of persistence but in this study since we excluded them so the rates of persistence in this study might be underestimated if the patients who switched their therapy were persistent.(5)The generalization of these results might be limited to commercial health plans and patients with diabetes.

In this population of commercially insured patients having diabetes, acute phase persistence with antidepressant therapy was found to be associated with age, antidepressant class, type of therapy and intensity of follow up visits where as continuation treatment persistence was associated with age and intensity of follow up visits.

APPENDICES

Table 7. Results of univariate logistic regression analysis for acute phase treatment persistence

Variable	*Persistent*	*Non Persistent*	*Odds Ratio*	*95% CI*	*P-Value*
Age					0.015
18-40	38(5.53%)	42(6.11%)	1		
41 and above	375(54.59%)	232(33.77%)	0.56	(0.35-0.89)	
Gender					0.07
Female	223(32.46%)	167(24.31%)	1		
Male	190(27.66%)	107(15.57%)	0.75	0.55-1.03	
Comorbidity Score					0.59
3-Jan	266(38.72%)	171(24.89%)	1		
4 or more	147(21.4%)	103(14.99%)	1.09	(0.8-1.5)	
Insulin					0.39
Yes	123(17.9%)	90(13.1%)	1.15	0.83-1.6	
No	290(42.2%)	184(26.78%)	1		
Hospitalization					0.4
Yes	29(4.22%)	15(2.18%)	0.77	0.4-1.46	
No	384(55.9%)	259(4.22%)	1		
Psychotherapy					0.14
Yes	194(28.24%)	113(16.45%)	0.79	0.58-1.08	
No	219(31.88%)	161(23.44%)	1		
Tpe of Antidepressant					0.9
Generic	351(51.09%)	230(33.48%)	1		
Brand	47(6.84%)	34(4.95%)	1.1	0.69-1.77	
Generic and Brand	15(2.18%)	10(1.46%)	1.02	0.45-2.4	
Antidepressant Class					0.04
SSRI	306(44.54%)	185(26.93%)	1		
SNRI	38(5.53%)	22(3.2%)	0.96	0.55-1.67	
TCA	17(2.47%)	22(3.2%)	2.14	1.1-4.14	
Bupropion	25(3.64%)	14(2.04%)	0.93	0.47-1.83	
Others	27(3.93%)	31(4.51%)	1.9	1.01-3.3	
Type of Therapy					0.012
Monotherapy	352(51.24%)	210(30.57%)	1		
Combination with Trazadone or Mirtazapine	44(6.40%)	41(5.97%)	1.56	0.9-2.5	
Combination with Other	17(2.47%)	23(3.35%)	2.27	1.18-4.34	
Health Plan					
HMO	140(20.38%)	99(14.41%)	1		
Non-HMO	273(39.74%)	175(25.47%)	0.9	0.66-1.25	
Follow up Visits					<0.001
0	93(13.54%)	117(17.03%)	1		
1 to 3	196(28.53%)	51(7.42%)	0.21	0.14-0.31	
more than 3	124(18.05%)	106(15.43%)	0.68	0.47-0.99	

Table 8. Result of univariate logistic regression analysis for continuation phase treatment persistence.

Variable	*Persistent*	*Non-Persistent*	*Odds Ratio*	*95% CI*	*P-Value*
Age					0.02
18-40	20(3.32%)	46(7.64%)	1		
41 and above	242(40.20%)	294(48.84%)	0.53	0.3-0.9	
Gender					0.76
Female	147(24.42%)	195(32.39%)	1		
Male	115(19.10%)	145(24.09%)	0.95	0.69-1.32	
Comorbidity Score					0.58
0-3	163(27.08%)	219(36.38%)	1		
4 or more	99(16.45%)	121(20.10%)	0.91	0.65-1.27	
Insulin					0.78
Yes	79(13.12%)	106(17.61%)	1.05	0.74-1.49	
No	183(30.4%)	234(38.87%)	1		
Hospitalization					0.15
Yes	13(2.16%)	27(4.49%)	1.65	0.84-3.27	
No	249(41.36%)	313(51.99%)	1		
Psychotherapy					0.3
Yes	118(19.6%)	139(23.09%)	0.84	0.6-1.17	
No	144(23.92%)	201(33.39%)	1		
Type of Antidepressant					0.6
Generic	218(36.21%)	285(47.34%)	1		
Brand	24(3.99%)	35(5.81%)	1.12	0.65-1.93	
Generic and Brand	20(3.32%)	20(3.32%)	0.77	0.4-1.46	
Antidepressant Class					0.29
SSRI	199(33.06%)	252(41.86%)	1		
SSNRI	28(4.65%)	26(4.32%)	0.73	0.42-1.29	
TCA	11(1.83%)	24(3.99%)	1.72	0.82-3.6	
Bupropion	13(2.16%)	16(2.66%)	0.97	0.46-2.07	
Others	11(1.83%)	22(3.65%)	1.58	0.75-3.33	
Type of Therapy					0.1
Monotherapy	201(33.39%)	237(39.37%)	1		
Combination with Trazadone/Mirtazapine	38(6.13%)	71(11.79%)	1.59	1.02-2.45	
Combination with other	23(3.82%)	32(5.32%)	1.18	0.67-2.08	
Health Plan					0.68
HMO	92(15.28%)	114(18.94%)	1		
Non-HMO	170(28.24%)	226(37.54%)	1.07	0.76-1.5	
Follow Up Visits					<0.0001
0	13(2.16%)	99(16.45%)	1		
1 to 3	72(11.96%)	56(9.3%)	0.1	0.05-0.2	
more than 3	177(29.40%)	185(30.73%)	0.14	0.07-0.3	

Model Building

Acute Phase Treatment Persistence:

Univariate logistic regression was performed between the dependent variable and each independent variable and interactions were assessed between the significant variables. Age, gender, psychotherapy, antidepressant class, type of therapy and follow up visits were found to be significant at a P-value significance of 0.2 for the acute phase treatment (Table 7).Psychotherapy and gender became non significant in the multivariate analysis. The model with interaction and the model with no interactions were compared to select the final model.

Model 1: No-interaction model

Model 2: Model with interactions

The AIC (Akaike Information Criterion) of model 1 and model 2 were 847.6 and 847.5 respectively. The models were

compared using log likelihood ratio test.

Likelihood Ratio Test.
H0: Model 1

Ha: Model 2

LR Test:

2 Log L model1 – 2 Log L model 2 = 827.5-823.64=3.9

Degrees of Freedom = 12-10=2 P-Value= 0.14

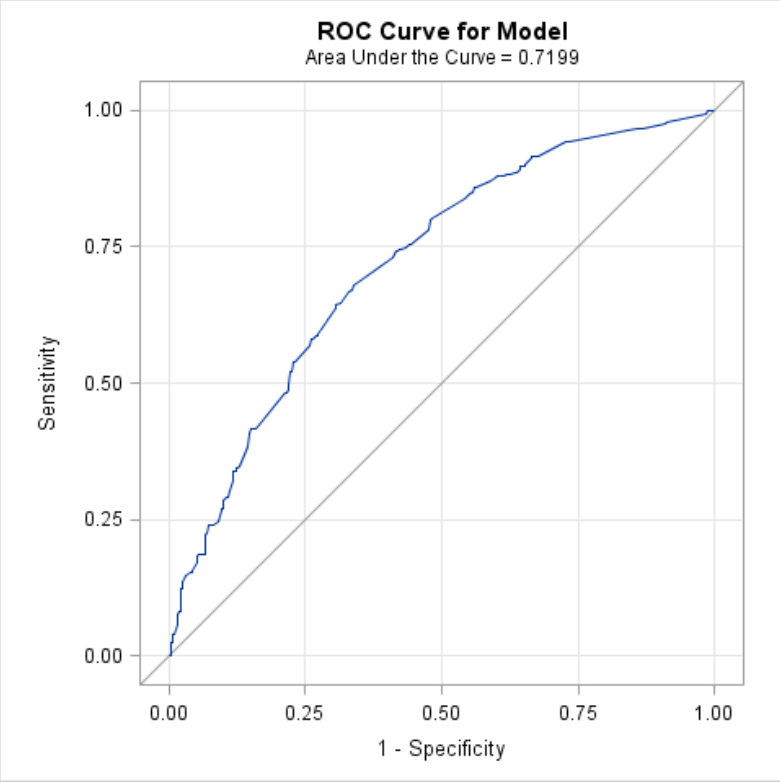
The LR test suggests that the model with no interactions terms included explains better. Also the co linearity diagnostics indicate co linearity in the model with interactions as the variance inflation factors for all the variables (except age) were greater than 6. Thus the model with no interactions was selected as the final model.

The variance inflation factors in the model with no interaction terms were close to 1 and the condition index was less than 30 confirming no colinearity. The model fit was assessed using Hosmer-Lemeshow Goodness of fit (GOF) and ROC curves. The GOF P-value (0.9) was greater than 0.05 and AUC (0.7) was greater than 0.5indicating an adequate model fit

Table 9. Goodness of Fit test for acute phase model

Hosmer- Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	Pr > ChiSq
2.9328	8	0.9385

Figure 4. Receiver Operating Characteristic (ROC) Curve for acute phase model



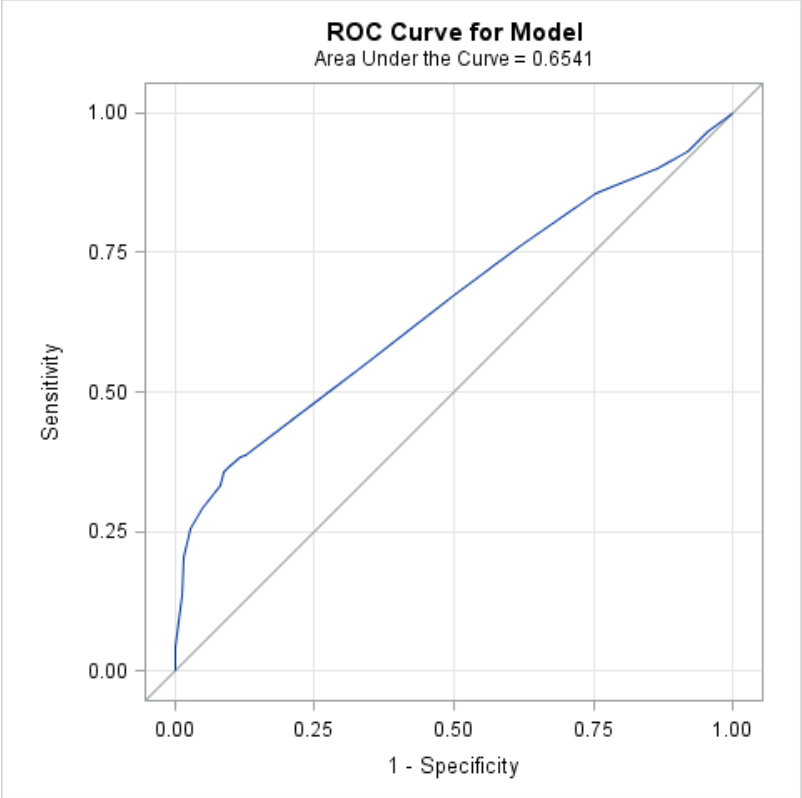
Continuation Treatment Phase Persistence

Age, follow up visits, hospitalization and type of therapy were found to be significant in the univaraite logistic regression for continuation phase treatment. No interactions between these variables were found to be significant. When all variables that were significant in the univariate logistic regression were included in the model hospitalization and type of therapy were non-significant. Therefore, the final model included the clinically important variables such as gender and comorbity score along with significant variables age and follow up visits. This model was then assesses for co linearity. The variance inflation factors were near to 1 and the condition index was less than 30 confirming no co linearity in this model. The model fit was assessed using Hosmer-Lemeshow Goodness of Fit and ROC curves. The GOF P-value (0.6) was greater than 0.05 and AUC (0.65) was greater than 0.5indicating an adequate model fit

Table 10. Goodness of Fit for continuation phase model

Hosmer and Lemeshow Goodness-of-Fit		
Test		
Chi-Square	DF	Pr > ChiSq
4.7911	7	0.6854

Figure 5. ROC Curve for continuation phase model



DV and IV Coding

Dependent Variable

Persistence to antidepressant medication: Yes (1) No (0)

Independent Variables

1. Age : 18-40 (1) 40 Above (2)
2. Gender : Female (1) Male (2)
3. Comorbdity Score

   0-3 (1)

   3 or more (2)
4. Psychotherapy : Yes (1) No (0)

5. Insulin : Yes (1) No (0)
6. Antidepressant Class

   SSRI (1)

   SSNRI (2)

   TCA (3)

   Bupropion (4)

   Trazadone and Mirtazapine (5)
7. Type of Antidepressant

   Generic (1)

   Brand (2)

   Brand and Generic (3)
8. Type of Antidepressant therapy

   Monotherapy (0)

   Combination (1)
9. Hospitalization: Yes (1) No (0)
10. Health Plan: HMO (1) Non-HMO (2)
11. Follow up visits

    0 (1)

    1 to 3 (2)

    More than 3 (3)

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