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**OUTCOMES ASSOCIATED WITH THE UTILIZATION OF ANTIDEPRESSANTS  
AND PSYCHOTHERAPY AMONGST CANCER PATIENTS WITH DEPRESSION**

A thesis submitted in partial fulfillment of the requirements for the degree of Master of  
Science at Virginia Commonwealth University

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## DEDICATION

This research is dedicated to my parents

*'Aai Baba, this would not have been possible without your love and support. I hope to make you proud every single day'*

Also my sisters, Aarya, Kimaya and Shwetha who have been there throughout this entire journey and have stuck with me through thick and thin

## ACKNOWLEDGEMENTS

There are several people that I would like to thank who have made this journey possible and have supported me through out. Firstly, I would like to thank my family and friends who have always encouraged me to learn more and achieve more. Despite of being so far from home, I have never felt too far from my parents, their support has made me what I am today, and their faith in me has made me a better person.

Secondly, I would like to thank my advisor and mentor Dr. Pramit Nadpara. Dr.Nadpara has played a crucial role in shaping my Masters journey. He has been an amazing teacher and has been available to help whenever I had any questions specifically about the study design or specific analysis techniques. His expertise in the field has helped me largely in my thesis and has helped in molding me into a better researcher. I would also like to thank my committee members Dr. Norman Carroll and Dr. D’Arcy Mays. Dr.Carroll’s immense attention to detail has helped me tremendously in improving my research as well as writing skills and has helped in guiding my thoughts. Dr.Mays’ style of teaching made understanding statistics very simple and he has always been available to answer any statistical questions that I had regarding my analyses.

Finally, I would also like to thank my McGuire Room 218 colleagues, who have been my go-to people for any immediate help or questions regarding almost anything and everything. In addition, I would like to thank my roommates and friends here in Richmond who were my family away from home and have helped in maintaining my emotional stability.

I appreciate all the support that all of these people have given me and I would once again like to thank each and every person mentioned above.

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## LIST OF ABBREVIATIONS

US	United States
AHRQ	Agency for Healthcare Research and Quality
QOL	Quality of Life
COPD	Chronic Obstructive Pulmonary Disease
TCA	Tricyclic antidepressants
SSRI	Selective Serotonin Reuptake Inhibitors
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
MAOI	Monoamine oxidase inhibitors
SERT	Presynaptic serotonin transporter
CINAHL	The Cumulative Index to Nursing and Allied Health Literature
FACT-G	Functional Assessment of Cancer Therapy – General
CES-D	Center for Epidemiological Studies-Depression
POMS-DD	Profile of Moods States – Depression
PHQ	Patient Health Questionnaire
EDS	Edinburgh Depression Scale
MEPS	Medical Expenditure Panel Survey
PCS	Physical Component Score
MCS	Mental Component Score
SEER	Surveillance, Epidemiology and End Results

SF	Short Form version
RCT	Randomized Controlled Trial
HrQOL	Health Related Quality of Life
CCS	Clinical Classification Software
ICD	International Classification of Diseases
TC	Therapeutic Class
FPL	Federal Poverty Line
Elem/Mid	Elementary/Middle
OR	Odds Ratio
MA	Miscellaneous Agents
SAQ	Self-Assessment Questionnaire
CI	Confidence Intervals

## ABSTRACT

### OUTCOMES ASSOCIATED WITH THE UTILIZATION OF ANTIDEPRESSANTS AND PSYCHOTHERAPY AMONGST CANCER PATIENTS WITH DEPRESSION

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

Virginia Commonwealth University, 2018

Advisor: Pramit A. Nadpara, Ph.D.

Assistant Professor, Department of Pharmacotherapy & Outcomes Science

**Objective:** To determine patterns of use, prescription medicine costs, office-based visit costs and quality of life (QOL) across classes of antidepressants/psychotherapy in elderly cancer patients. **Methods:** Medical Expenditure Panel Survey data files from 2005-2015 for cancer patients with depression aged 18 years or older were used for the study. Frequencies of patients under specific classes of antidepressants/psychotherapy were identified. Costs and QOL scores were compared using Analysis of Variance (ANOVA). Generalized linear models, linear/multinomial logistic regression were used for analyses adjusted for demographics, overall health status, number and type of comorbidities. **Results:** The study sample consisted of 17,671 cancer patients with depression. 32.08% patients had an antidepressant prescribed whereas 15.30% reported psychotherapy. SSRI (62.44%) was the most frequently prescribed class. The prescription and office-based visits costs were adjusted for demographics, overall health status, number and type of comorbidities. These adjusted prescription costs were the highest for SNRI (Mean = \$112.92), adjusted office-based (psychotherapy) visit costs were the highest for those receiving psychotherapy only without any antidepressant (Mean = \$166.39/visit). QOL scores were higher amongst patients who had combinations of antidepressants prescribed, specifically SSRI with either a TCA or SNRI as compared to those who were prescribed an individual class or those who did not receive any treatment at all. **Conclusion:** Antidepressants were prescribed more often than psychotherapy amongst cancer patients with depression in the United States.

The prescription costs and associated QOL scores were higher amongst those with antidepressants prescribed as compared to those receiving psychotherapy with or without an antidepressant for cancer patients with depression in the United States.

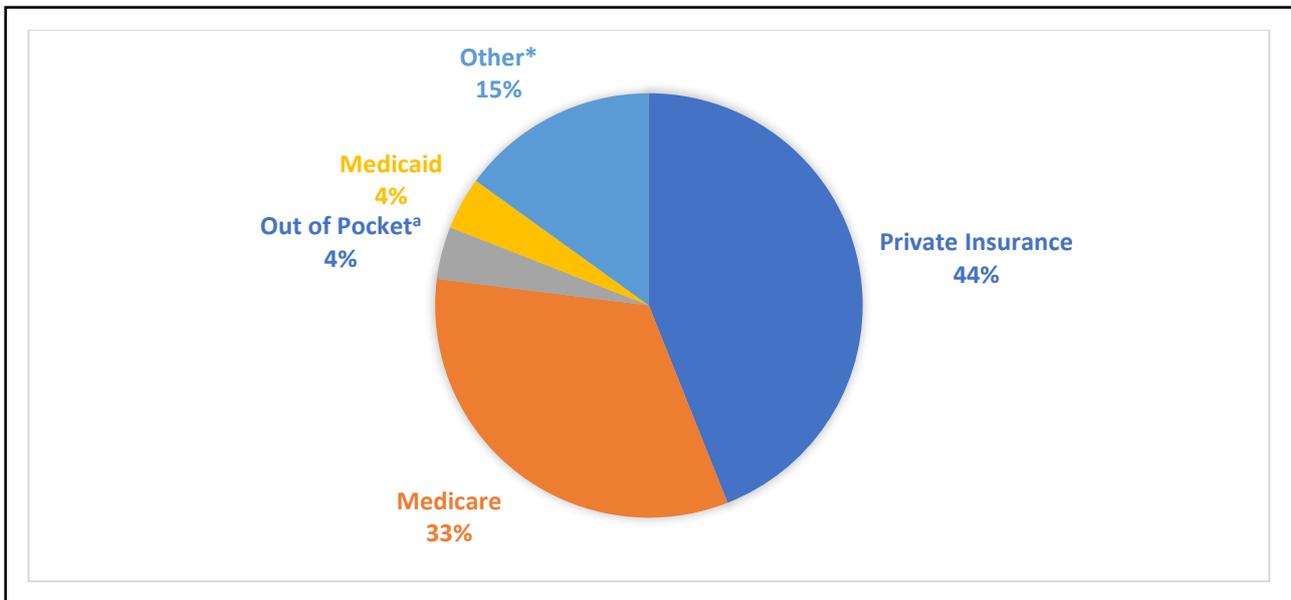
## **CHAPTER I: INTRODUCTION**

### **Section 1.1: Background**

Cancer is one of the most prevalent diseases in the country. In 2014, there were an estimated 14,738,719 people living with cancer of any site in the United States (US) and it was estimated that there would be 1,688,780 new cancer cases in 2017.<sup>1</sup> It has been listed as one of the priority conditions by the Agency for Healthcare Research and Quality (AHRQ).<sup>2</sup> The mean survival rate of cancer patients was around 67% as per 2007-2013 data.<sup>1</sup> Breast cancer is the most common type of cancer with more than 255,000 new cases expected in the United States in 2017. The next most common types of cancers are lung and prostate cancer.<sup>1</sup> Cancer patients have a reduced quality of life (QOL). This could be due to treatment side effects, disability or mental disturbance.<sup>3</sup> There are also certain sociodemographic factors such as gender, marital status, income or job status that affect the mental well-being and thus QOL of cancer patients.<sup>3</sup> Patients who are over 65 years of age have an even more reduced QOL as compared to younger patients.<sup>4</sup>

The AHRQ estimates that the direct medical costs for cancer in the US in 2014 were \$87.7 billion. 58% of this cost was for hospital outpatient or doctor office visits whereas 27% of this cost was for inpatient hospital stays.<sup>5</sup> Thus, it can be seen from these figures that majority of cancer costs are associated with outpatient and physician office visits. Figure 1 below summarizes the major sources of payment for total annual costs of cancer patients for the year 2014. As seen from the figure, the total share of out of pocket costs for all the cancer patients in 2014 was \$3.9 billion.<sup>5</sup> On an average, cancer patients pay around \$2116 to \$8115 out of pocket annually. One in ten patients reported that the costs amounted to at least 63% of their annual income.<sup>5</sup> The financial burden on cancer survivors is thus high.<sup>6</sup> The QOL of cancer patients depends highly on the financial burden, mainly out of pocket costs of cancer patients

along with the cancer treatment provided.<sup>6,7</sup> Cancer survivors with increased financial burden have significantly lower physical and mental component scores and have higher odds of reporting depressed mood.<sup>6</sup> QOL and financial burden of cancer patients are thus correlated and could depend on a lot of factors including the comorbidities involved.<sup>6,8</sup>



a-Total patient out of pocket costs per year = \$3.9 billion

Other\* - Employer’s Insurance, Tricare, Veteran’s Insurance and other state and local government insurance

**Figure 1: Sources of payment for total costs of cancer patients in the US per year 2014**

Cancer and comorbidities:

Past literature suggests that, cancer has common risk factors with various other conditions and hence has several comorbidities associated.<sup>8</sup> Diabetes mellitus, chronic infections, diseases of the immune system and psychosocial disorders are some of the commonly identified comorbidities along with cancer.<sup>8</sup> The impact of such comorbidities tends to be greater for cancers with a better prognosis, since otherwise the patients are more likely to die from their cancer regardless of other comorbidities associated.<sup>9</sup> These comorbidities reduce survival and lower QOL of cancer patients and hence it is necessary to study these and manage such conditions effectively.<sup>9</sup>

### Depression as a comorbidity:

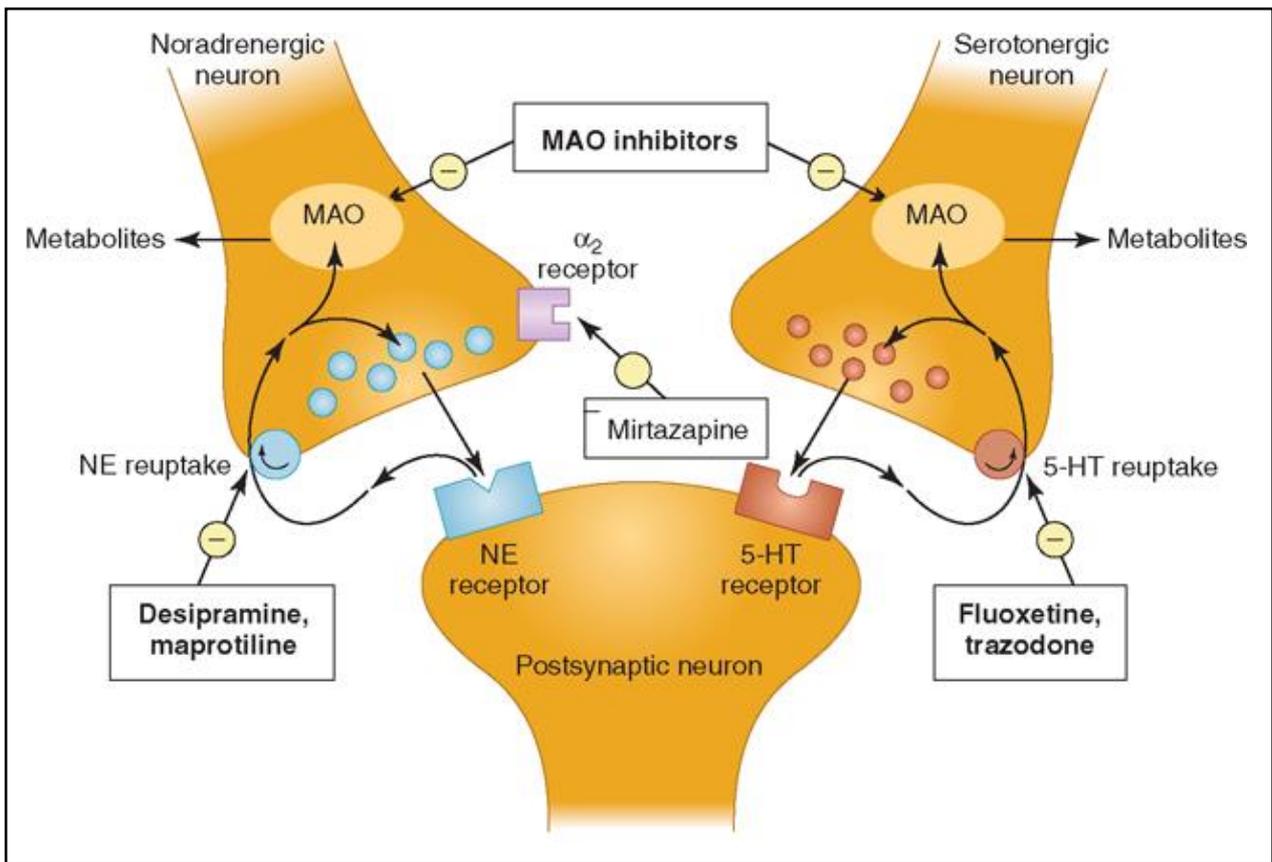
Diabetes, COPD/asthma and psychosocial stress are some of the commonly associated comorbidities with cancer that further lead to a reduced QOL.<sup>8</sup> The prevalence rates of psychosocial stress in cancer patients ranged from around 23% to 53%.<sup>8</sup> Untreated psychiatric comorbidities in patients with cancer have a significant impact on disability, quality of life and they tend to worsen if not treated adequately.<sup>10</sup> Depression is one of the most commonly associated comorbid psychiatric condition with any type of cancer. As compared to anxiety and adjustment disorder, the prevalence of depression is 12% higher amongst cancer patients.<sup>11</sup> In addition, as compared to those without cancer, the prevalence of depression is higher in cancer survivors.<sup>12</sup> Clinicians working in cancer services have recognized that depression is often undiagnosed and untreated and that these shortcomings in care can have substantial effects, not only on patients' quality of life but also on their acceptance of cancer treatments.<sup>13</sup> There is evidence to support that pharmacological treatment mainly tricyclic antidepressants and psychotherapy used to treat depression improve palliative care in cancer patients.<sup>14</sup> There is also evidence to support that the completion rate of cancer treatment is higher when the patient is receiving some treatment for comorbid depression.<sup>15</sup> Managing depression thus along with improving QOL of patients also improves cancer treatment outcomes. Studies have demonstrated that comorbid depression is also associated with an increase in total healthcare expenditure by \$6301 as compared to cancer patients without depression.<sup>16</sup> On comparing expenditures of cancer patients with depression and those without depression, the highest cost difference was found in prescription drugs (\$2,297 higher for those with depression) and other expenses that included office-based and outpatient visits (\$715 higher for those with depression).<sup>16</sup> The overall use of psychotropic drugs in palliative care of cancer has increased from 2002 to 2009.<sup>17</sup> Depression could be treated by either pharmacotherapy using different types of antidepressants or by psychotherapy using methods such as counselling sessions,

certain social media interventions, etc. Studies have suggested that patients report higher interest in counseling as compared to antidepressants however, the prevalence of antidepressants is still higher than support groups or counseling for managing depression.<sup>18,19</sup> Since, the mechanism of action and the side effects of these antidepressant classes differ from each other, it would be hypothesized in our study that they would have varied effect on certain patient outcomes such as quality of life.

### Antidepressants:

There are various classes of antidepressants such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin- norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants (miscellaneous agents). Depression is a result of decreased levels of neurotransmitters like norepinephrine and serotonin in the synapse. All the above-mentioned antidepressants act by increasing the amount of such neurotransmitters. The mechanism of action of all these different classes of antidepressants differ from each other. TCAs, SSRIs and SNRIs are reuptake inhibitors and they block the reuptake of neurotransmitters, which increases their amount in the synapse. TCAs and SNRIs increase serotonin and norepinephrine both whereas SSRIs only increase serotonin. MAOIs act by decreasing the degradation of neurotransmitters in the synapse thus increasing their amount. Monoamine oxidase is the enzyme responsible for breaking down the neurotransmitters, which is blocked by the MAOIs.<sup>20</sup> Miscellaneous agents also act by enhancing the level of dopamine, serotonin or norepinephrine in the synapse. Figure 2 depicts the different mechanism of actions of different classes. SSRIs are usually the most frequently prescribed antidepressants in general population.<sup>21</sup> If the trend is similar in cancer population with depression is still ambiguous. The side effects that are associated with specific classes of antidepressants differ. It has been mentioned in the literature that SSRIs are usually the most tolerable.<sup>22</sup> Table 1 summarizes the side effects and examples of each antidepressant class.

From a financial perspective, MAOIs are the most expensive with around \$50-\$80 out of pocket for 30 tablets followed by SNRIs at \$20 - \$50, TCAs at \$10 - \$15 and the cheapest option is SSRIs at \$6 -\$7 for 30 tablets.<sup>23</sup> Looking at the prices, it is evident that the financial burden arising across these classes would be varied. It is thus necessary to study the patterns of use associated with individual classes of antidepressants and psychotherapy and to assess cost and QOL outcomes associated with the same to manage depression efficiently. It would be hypothesized in our study that the costs of cancer patients would differ significantly based on the antidepressant that they have been prescribed.



Desipramine – TCA, Maprotiline, Trazodone – Miscellaneous Agents, Fluoxetine- SSRI  
**Figure 2: Summary of mechanism of action of all the antidepressant classes<sup>24</sup>**

**Table 1: Side effects along with examples of each class of antidepressant**

<b>Antidepressant</b>	<b>Side effects</b>	<b>Examples</b>
SSRI	Nausea, sleep disturbances, sexual dysfunction, appetite changes, headache, dry mouth, slightly abnormal heart rhythms	Fluoxetine, Paroxetine, Citalopram
SNRI	All of the side effects of SSRIs, hypertension, tachycardia	Duloxetine, Venlafaxine
TCA	Dry mouth, dizziness, blurred vision, constipation, sedation, orthostatic hypotension, tachycardia	Amitriptyline, Imipramine, Desipramine
MAOI*	All of the side effects of TCA, skin reaction, weight gain	Isocarboxazid, Phenelzine, Selegiline
Miscellaneous Agents	Drowsiness, hypercholesterolemia, weight gain	Bupropion, Vilazodone, Trazodone, Maprotiline

\*Monoamine oxidase inhibitors

## **CHAPTER II: LITERATURE REVIEW**

### **Section 2.1: Literature review**

A literature review was conducted in order to assess the effects of antidepressants on improving the quality of life of cancer patients and assessing the healthcare utilization associated with it. The review was conducted using certain specific search terms. Based on the literature and the background knowledge, we hypothesized that the effects of antidepressants on QOL and the healthcare utilization associated with them would differ based on the different classes of antidepressants and the results/findings would then help the patients and providers manage depression more effectively.

### **Section 2.2: Systematic literature review on the effects of antidepressants on improving the QOL of cancer patients and healthcare utilization associated with the same**

A literature review was conducted in March 2017 using PubMed/Medline, CINAHL and Google Scholar. The search term used was a combination of : (((("Antidepressive Agents/economics" [Mesh] OR "Antidepressive Agents/organization and administration" [Mesh] OR "Antidepressive Agents/therapeutic use" [Mesh])) AND ("Depression/drug therapy" [Mesh] OR "Depression/economics" [Mesh] OR "Depression/epidemiology" [Mesh] OR "Depression/prevention and control" [Mesh] OR "Depression/therapy" [Mesh])) AND "Neoplasms" [Major]) AND Humans [Mesh] AND English [lang] AND cancer [sb] AND adult [MeSH]. Titles and abstracts were screened. The following inclusion/exclusion criteria were utilized:

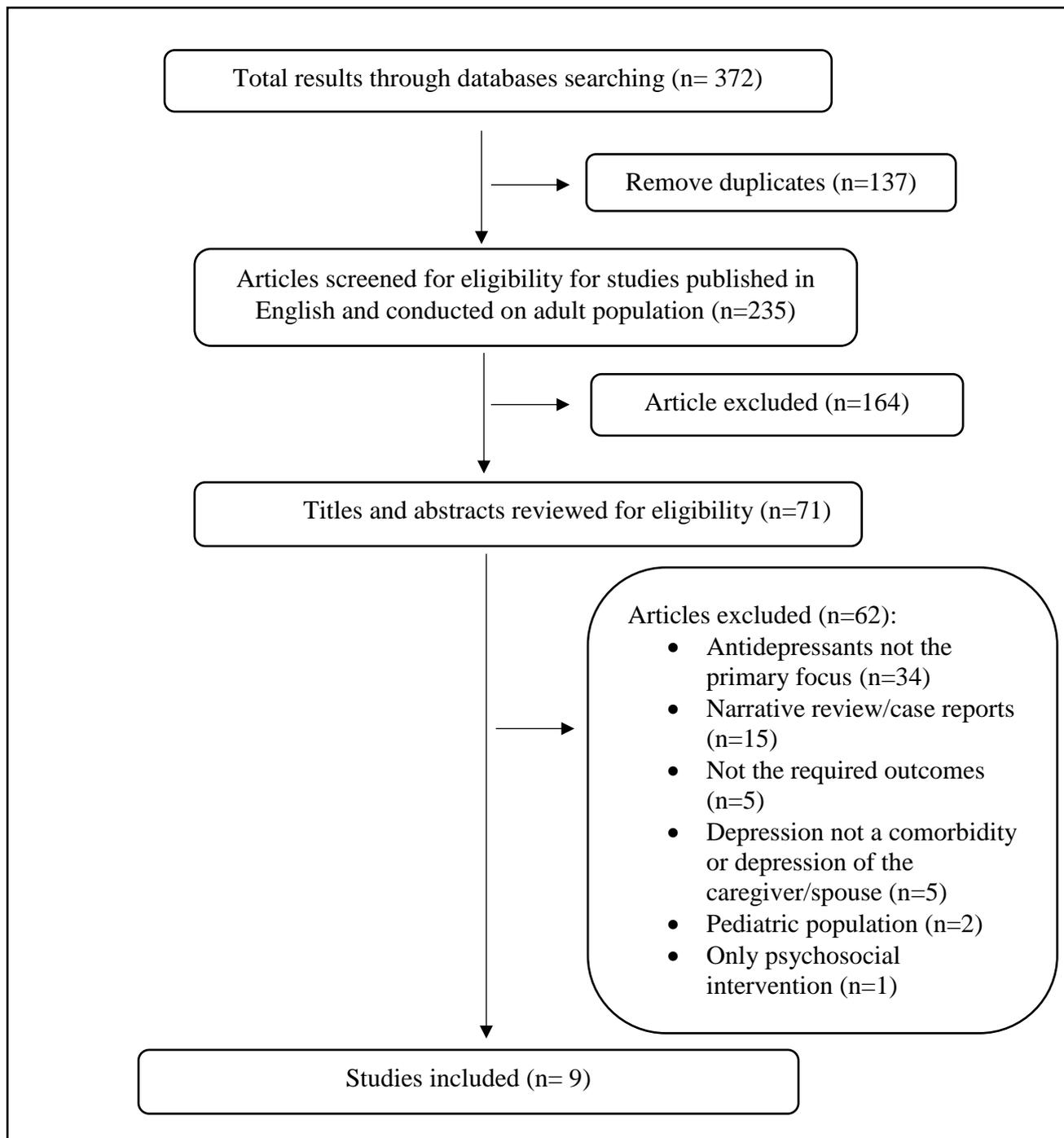
#### **Inclusion Criteria:**

- Studies including outcomes related specifically to antidepressants.
- Studies published in English.
- Studies conducted on adult population over 18 years of age.

**Exclusion Criteria:**

- Not including any health outcomes.
- Not looking at depression as a comorbidity.
- Studies evaluating depression outcomes of the caregiver/spouse.
- Only psychosocial interventions.

The search criteria gave 372 articles. After removing duplicates, there were around 235 articles. Applying the filters as per mentioned in the inclusion/exclusion criteria resulted into 71 articles. These 71 articles were then screened by reading the titles and abstracts, out of which, 9 were included in the final literature review.<sup>15,18,19, 25-30</sup> These were most relevant to the study and focused mainly on patient reported outcomes as opposed to just clinical outcomes. Figure 3 below depicts a flowchart of the article selection process.



**Figure 3: Article Selection Process**

A study was found looking at patterns of use and predictors of antidepressants,<sup>18</sup> another was found looking at the healthcare expenditures<sup>25</sup> whereas all others were looking at QOL.<sup>15,19,26-30</sup> Most of the studies were clinical trials conducted on a small sample size and were restricted to either one type of cancer or just one particular antidepressant intervention. Therefore, our study would help in filling these gaps in the literature by looking at all types of cancers and comparing all the classes of antidepressants in a nationally representative sample thus increasing the generalizability.

### **Section 2.3: Literature summary**

Most of the articles out of the 71, focused mainly on the clinical effects such as level of neurotransmitters in the brain or other pathology resulting from the antidepressants rather than focusing on the patient reported outcomes. In addition, many studies reported only the prescribing trends of antidepressants in the population without cancer or did not focus on QOL or healthcare utilization.

The nine studies that were selected were mainly those that reported QOL of cancer patients or the depression scores for the same.<sup>15,19,26-30</sup> These were mainly clinical trials looking at the effects of one of the antidepressants on depression of cancer patients mainly including specific types of cancers.<sup>15,26-28</sup> Table 2 would summarize the studies finalized for the literature review.

#### **Patterns and predictors of antidepressant use:**

A study conducted by Fisch et al. prospectively looked at patterns of use and predictors of antidepressant use in ambulatory cancer patients with common solid tumors.<sup>18</sup> It was observed that, antidepressants were prescribed in 19% of all patients. The predictors identified with the use of antidepressants were depressive symptoms, family history of depression, concurrent medication use, cancer treatment status and certain other clinical and demographic

variables. However, the authors did not look at classes of antidepressants separately. In addition, the study sample was restricted to ambulatory breast, prostate, colon/rectum or lung cancer patients.

#### Healthcare Expenditures:

A study conducted by Alwhaibi et al. examined the association between depression treatment and healthcare expenditures among elderly with depression and incident cancer using Surveillance, Epidemiology and End Results (SEER) – Medicare.<sup>25</sup> They suggested that, the average 1-year total healthcare expenditures after depression diagnosis were \$38,219 for those not receiving any depression treatment, \$42,090 for those receiving antidepressants, \$46,913 for those who received psychotherapy only and \$51,008 for those receiving both the therapies (antidepressant and psychotherapy). Thus, the costs associated were the highest for those receiving both the therapies followed by psychotherapy only. This study however looked only at elderly population and restricted only to incident breast, colorectal or prostate cancer. In addition, the authors did not look at classes of antidepressants separately.

#### Quality of Life (QOL):

There were studies conducted by Navari et al.,<sup>15</sup> Fisch et al.,<sup>26</sup> Holland et al.,<sup>27</sup> and Roscoe et al.<sup>28</sup> which looked at effects of any one of the antidepressant namely paroxetine, fluoxetine or desipramine on depression amongst cancer patients. The studies mentioned above were prospective clinical trials focusing on one particular antidepressant rather than comparing outcomes across different classes of antidepressants. A study conducted by Navari et al. looked at the effects of fluoxetine on treating depressive symptoms in patients with early stage breast cancer undergoing adjuvant therapy. It was found that 87% of the patients treated with fluoxetine had a significantly higher completion rate of the adjuvant treatment as compared to 50% in the placebo group. The number of patients with a significant improvement in the QOL

was higher in the fluoxetine group as compared to those in the placebo group (79.6% vs 22.2%). The subgroup of patients showing higher levels of depressive symptoms on the two-question screening survey were the most likely to benefit from the treatment.<sup>15</sup> In a study conducted by Fisch et al., the effects of fluoxetine on QOL were studied. It was observed that, patients treated with fluoxetine exhibited a significantly greater improvement in QOL as shown by the Functional Assessment of Cancer Therapy–General (FACT-G) scores (improved by 8.82 points from baseline to the fifth visit), compared with patients given placebo (improved by 5.64 points from baseline to the fifth visit). The level of depressive symptoms expressed was lower in patients treated with fluoxetine.<sup>26</sup> It was observed that, when fluoxetine was compared to desipramine by Holland et al., both were effective in treating depressive symptoms, with fluoxetine being slightly better than desipramine in terms of efficacy and improving QOL (mean change for Short Form Health Survey scores was higher with fluoxetine).<sup>27</sup> Roscoe et al. studied the effects of paroxetine on reducing depression amongst cancer patients. It was found that paroxetine had an effect on decreasing depression, as observed from the reduced CES-D scores (reduced from 14.7 to 8.8 across four cycles) and POMS-DD scores (reduced from 2.9 to 1.2 across four cycles) as compared to placebo group (CES-D scores reduced from 14.7 to only 12.6 and POMS-DD scores reduced from 3.2 to only 2.2 across four cycles). The decrease in depression over time was significant for both the measures namely, CES-D and POMS-DD, which indicate a positive effect of the antidepressant.<sup>28</sup>

A study conducted by Lloyd-Williams et al., looked at the longitudinal effect of antidepressant medication in a cohort of advanced cancer patients. It was a prospective study, where recruited patients were asked to fill baseline and follow-up questionnaires for assessment. The questionnaires used were PHQ 9 (Patient Health Questionnaire) and EDS (Edinburgh depression scale) tools for measuring depression. It was observed that 25% of patients were taking some antidepressant medication at some point during the trial period. 77% patients were

prescribed SSRIs and none were prescribed TCAs. Patients taking some antidepressant reported a significantly lower score on both EDS (3.18 point score reduction) and PHQ 9 (2.71 point score reduction) as compared to those taking none indicating a lesser tendency towards depression and hence a positive effect of the medication.<sup>29</sup> However, in this case, the antidepressants were not compared to psychotherapy.

There was another study conducted by Vyas et al., which was a population-level analysis looking at the impact of depression treatment on health-related QOL among adults with cancer and depression using Medical Expenditure Panel Survey (MEPS). It was observed that, adults who reported psychotherapy with or without any antidepressant had higher Physical Component Score (PCS) indicating a positive effect of the treatment (mean = 40.97), as compared to those without any treatment (mean = 40.72) or with antidepressants only (mean = 39.87), this difference was however not significant. Mental Component Scores (MCS) was the lowest for those receiving psychotherapy with or without any antidepressant (mean = 39.23) as compared to those without any treatment (mean = 43.78) or those with antidepressants only (mean = 44.37), this difference was significant. The study thus, suggested that QOL as measured by PCS was numerically the highest for psychotherapy whereas that measured by MCS was the highest for antidepressants only. However, this study did not look at classes of antidepressants separately.<sup>30</sup>

Based on a study conducted by Wu et al., which was a survey-based prospective study, 51.4% women were extremely interested in individual counseling, 38.1% women were interested in support group whereas antidepressant medications were rated the lowest. Interest for each of the treatments was not related to demographic/disease factors. It was positively related to self-rated health. Women with higher self-rated health reported more interest in counseling than those with lower self-rated health.<sup>19</sup>

**Table 2: Literature Summary**

<b>Study</b>	<b>Objective</b>	<b>Study Design</b>	<b>Sample</b>	<b>Conclusion</b>
<b>Patterns of use/ Predictors</b>				
Fisch et al. <sup>18</sup>	To identify determinants of prescribing antidepressants	Prospective observational study	Ambulatory patients with breast, prostate, colon/rectum or lung cancer	- Antidepressants -19% Individual counseling - 8.6% Support group -8% - <u>Predictors</u> : Depressive symptoms, family history of depression, concurrent medication use, cancer treatment status, poor quality of life and demographic variables
<b>Healthcare expenditures</b>				
Alwhaibi et al. <sup>25</sup>	To examine the association between depression treatment and healthcare expenditures	Retrospective longitudinal study using SEER* dataset	Elderly Medicare beneficiaries with incident breast, colorectal or prostate cancer	- The use of combination of antidepressant and psychotherapy was associated with the highest total expenditures followed by psychotherapy only.
<b>Quality of Life (QOL)</b>				
Navari et al. <sup>15</sup>	Fluoxetine v/s Placebo in breast cancer patients	Randomized prospective trial	Newly diagnosed early stage breast cancer patients	- Higher QOL and completion rate of cancer treatment with the fluoxetine group
Fisch et al. <sup>26</sup>	To determine whether fluoxetine improves overall quality of life (QOL) in advanced cancer patients with symptoms of depression revealed by a simple survey.	Prospective double blinded trial to receive either fluoxetine or placebo for 12 weeks	Advanced cancer patients with an expected survival between 3 and 24 months	- Fluoxetine exhibited a higher significant improvement in QOL as compared to the placebo group and decreased depressive symptoms, as indicated by the FACT-G scores

Holland et al. <sup>27</sup>	Fluoxetine v/s desipramine in depressed women with advanced cancer	Prospective double-blinded trial	Women with advanced cancer	- Both effective, with fluoxetine being slightly better than desipramine in terms of improving efficacy and QOL
Roscoe et al. <sup>28</sup>	Paroxetine v/s Placebo in breast cancer patients	Prospective double-blinded trial	Female breast cancer patients receiving at least four cycles of chemotherapy	- Reduced depression with paroxetine as observed from the CES-D and POMS-DD scores
Lloyd-Williams et al. <sup>29</sup>	To observe the longitudinal effect of antidepressant medications in a cohort of advanced cancer patients	Longitudinal observational prospective study	Patients with advanced cancer	- Patients taking some antidepressant reported a lower EDS and PHQ score compared to those taking none indicating a lesser tendency towards depression
Vyas et al. <sup>30</sup>	To examine the association between depression treatment and HrQOL among US adults with cancer and depression	Retrospective study using Medical Expenditure Panel Survey	Cancer patients above 18 years of age	- PCS was the highest for psychotherapy whereas MCS was the highest for antidepressants
Wu et al. <sup>19</sup>	To investigate treatment preferences for depression	Prospective observational study	Women with breast cancer arriving for a surgical follow-up, chemotherapy or radiation therapy appointment	- 45.2% reported higher levels of interest in counseling compared to antidepressants - Women with higher self-rated health reported more interest in counseling

\* Surveillance, Epidemiology and End Results

## **Section 2.4: Gaps in literature**

It is evident from the existing literature that antidepressants help in improving QOL and outcomes, such as completion rate of the cancer treatment. However, none of the studies have looked and compared all the different classes of antidepressants. Most of the studies have either looked at just one of the antidepressant or just looked at one type of cancer. Moreover, most of the studies conducted have been randomized controlled trials with a small sample size, which limits generalizability of the study. It is thus unclear from the existing literature as to which class of antidepressant would prove to have maximum benefits in improving QOL. In addition, none of the studies have looked at healthcare utilization/ healthcare costs associated with the classes of antidepressants and the sociodemographic factors associated with each. The study conducted by Alwhaibi et al.<sup>25</sup> looked at healthcare utilization associated with antidepressants as a whole and did not look separately at individual classes. In addition, the authors did not look specifically at prescription medicine costs or office-based visit costs, which would be more specific to the depression therapy classes. Our study would thus help in addressing these limitations of the existing literature.

## **Section 2.5: Specific Aims**

**Aim 1: To determine the patterns of use of antidepressants amongst cancer patients in the US with comorbid depression and characterize the utilization of antidepressants based on sociodemographic characteristics**

A: To determine the patterns of use and prescription trends across different classes of antidepressants

B: To characterize the sociodemographic factors associated with the utilization of antidepressants

**Aim 2: To compare costs and healthcare utilization (office-based visits) of cancer patients across different classes of antidepressants in the US**

A: To compare the prescription medicines expenditures, overall costs and out of pocket expenses of cancer patients with comorbid depression across different classes of antidepressants

B: To compare office-based visits along with the expenses related to these across cancer patients with comorbid depression classified based on the class of antidepressants

**Aim 3: To compare quality of life (QOL) of cancer patients in the US with comorbid depression across different classes of antidepressants and psychotherapy**

A: To compare the physical and mental component score (PCS/MCS) across different classes in order to assess quality of life of cancer patients with comorbid depression

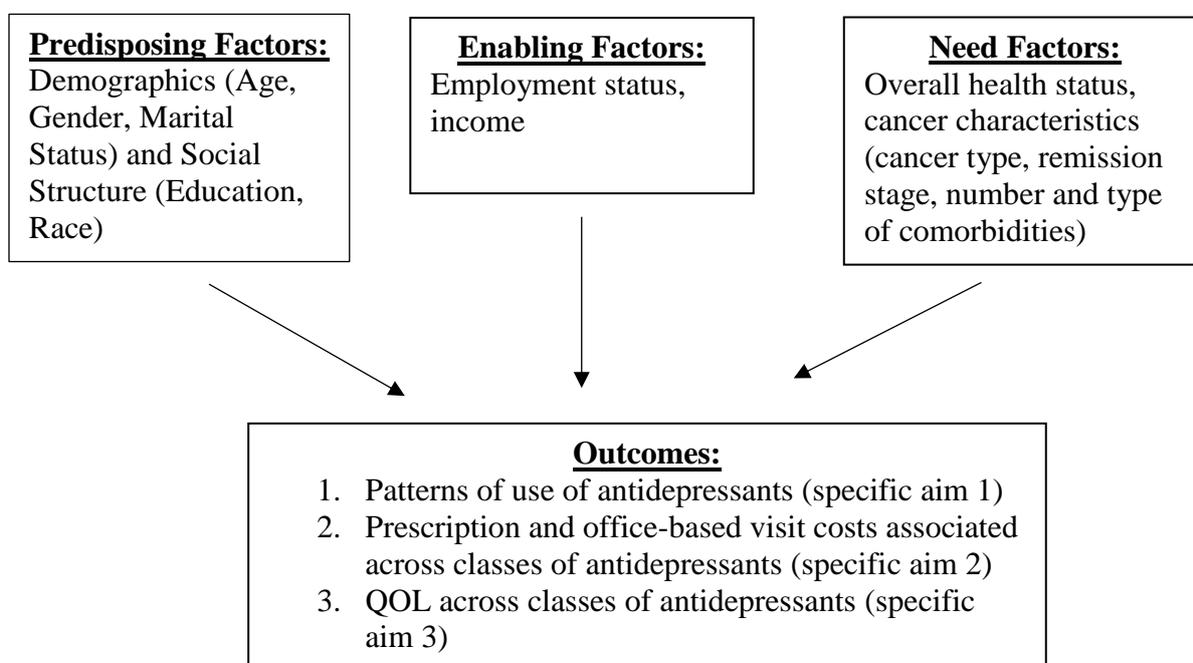
B: To compare Patient Health Questionnaire – 2 (PHQ-2) scores and the frequency of depression obtained from Short Form version 12 (SF-12) to assess quality of life of cancer patients along with comorbid depression

## Section 2.6: Conceptual Framework

Conceptual framework for this research was based on the Andersen Behavioral Model.

The model parameters were guided by existing literature and studies conducted in the same area.

The model was as follows:



Certain predisposing and outcome variables for our study were identified based on studies conducted by Fisch et al. and Wu et al., which looked at patterns of use and predictors for the use of certain drugs.<sup>18,31</sup> Outcome variables for specific aim 2 along with certain enabling and need factors were identified based on past studies looking at the costs associated with a particular class of medication or economic burden studies.<sup>31,32</sup> The outcome variables for specific aim 3 were identified using the past QOL studies that have been summarized.<sup>15,19,26-30</sup> There has also been a study conducted by Üstündağ et al. looking at factors affecting QOL of patients on chemotherapy which also provided the framework for selecting certain predisposing and QOL outcome variables.<sup>3</sup>

## **Section 2.7: Rationale**

As stated above, depression has been proven to worsen the condition of cancer patients and managing the same has shown positive effects not only on the QOL but also on the outcomes associated with cancer treatment.<sup>15,19,26-28</sup> Despite that, there have not been many studies assessing and comparing the effects of different classes of antidepressants on patient outcomes. In addition, many of these studies have restricted to one single type of cancer and none of them have looked at the comparison of healthcare costs or healthcare utilization across classes of antidepressants.<sup>15,19,26,28</sup> There have been cost studies comparing the psychosocial approaches (self-administered psycho-educational intervention, nursing, tele and home care more costly and effective than the usual care with no such intervention) used in treating depression in cancer population; however, those did not take into account the pharmacotherapies available.<sup>33,34</sup> There have been no studies comparing various classes of antidepressants used in the management of depression and comparing these with psychotherapy. Studies have only suggested that the effect on reducing depression is higher when pharmacotherapy is used along with psychosocial interventions and it has been assumed that pharmacotherapy would have greater effect than psychosocial interventions.<sup>35</sup> These have however been narrative reviews and no formal study has been conducted yet comparing classes of antidepressants along with psychotherapy. This study would thus help in providing evidence for the association between antidepressants and QOL along with the costs associated across classes of antidepressants/ psychotherapy.

Furthermore, most of the studies conducted were either meta-analysis/narrative reviews<sup>36,37</sup> or randomized controlled trials (RCTs)<sup>15,26,27,28</sup> which limit generalizability of the study. Hence, there is a need to conduct a population-based study, which would look at effects of different interventions and compare those, and which would help the patients and the healthcare providers manage depression better. This study would thus be a nationally representative population-based study using Medical Expenditure Panel Survey (MEPS)

looking at different classes of antidepressants along with psychotherapy and analyzing which of the intervention is the most effective in improving the quality of life (QOL) and the healthcare utilization/costs associated with each. Sociodemographic characteristics and the general patterns of use of antidepressants would also be studied. Such study is important for understanding the subgroup differences in depression treatment patterns, in order to promote a more effective management of depression amongst cancer patients. In addition, studying costs and quality of life associated with each class of antidepressant would help in understanding the economic burden on cancer patients and the value associated with each. Existing literature suggests that the economic burden on cancer patients other than the costs incurred from the cancer treatment are mainly because of office-based visit costs and prescription medicine costs.<sup>16,32</sup> These costs and QOL outcomes along with patterns of use would be explored in our study across the classes of antidepressants and psychotherapy.

Based on the already existing literature, this would be the first population-based study that would compare the different classes of antidepressants along with just psychotherapy and would also include all types of cancer and not restrict to just one. This study would provide certain guidelines to the provider, encouraging/ discouraging prescription of any particular class of antidepressant or psychotherapy and providing evidence to make certain decisions so as to choose the depression therapy effectively. QOL outcomes would help clinicians in making a better-informed decision regarding prescription of any therapy. In addition, it would also help policy makers in guiding their decision for coverage of any particular antidepressant or encouraging coverage of specific psychotherapies in a specific population.

### **CHAPTER III: SPECIFIC AIM I**

**Aim 1: To determine the patterns of use of antidepressants amongst cancer patients in the US with comorbid depression and characterize the utilization of antidepressants based on sociodemographic characteristics**

A: To determine the patterns of use and prescription trends across different classes of antidepressants

B: To characterize the sociodemographic factors associated with the utilization of antidepressants

#### **Section 3.1: Methods**

##### **Design:**

A cross-sectional, retrospective study design was implemented for all the specific aims

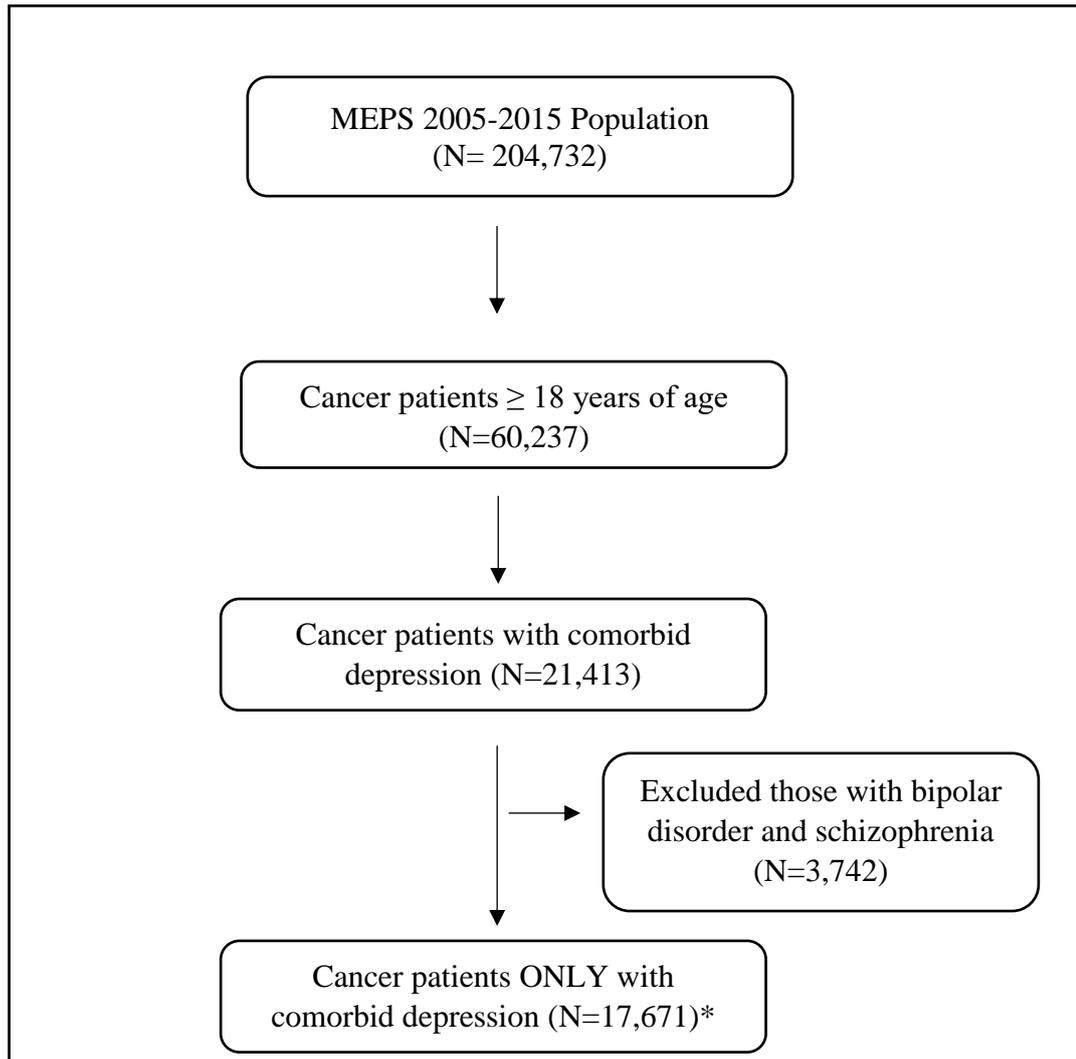
##### **Data:**

A nationally representative publicly available dataset called Medical Expenditure Panel Survey (MEPS) was used for the study. MEPS, which began in 1996, is a set of large-scale surveys of families and individuals, their medical providers (doctors, hospitals, pharmacies, etc.), and employers across the United States conducted by the Agency for Healthcare Research and Quality (AHRQ). The MEPS household component files provide data on demographics of the participants, population characteristics, medical conditions, prescribed medicines, data on inpatient and outpatient/office-based visits and all the expenses made by the patient including out of pocket and any type of insurance coverage offered. The full year consolidated file of the household component also contains information on the quality of life and the physical/mental wellbeing of the patient, which was used for the study. Data from January 2005 to December 2015 data files was used for this study. Full year consolidated files were used to identify patient demographics, medical conditions files were used to identify patients, prescription medicines

files were used to identify the use of antidepressants, and office-based medical provider visits files were used to identify psychotherapy visits for depression.

**Study sample:**

The medical conditions file of the household component provides the International Classification of Diseases (ICD-9) codes for patient diagnoses. These codes were used to identify patients. Clinical Classification Software (CCS) collapses categories based on ICD-9 codes and generate more meaningful codes which can be used to look at broader categories like ‘cancer’ and not a specific type of cancer. Hence, clinical classification codes of 11-44 were used to identify cancer patients.<sup>38</sup> There were around 204,732 people who responded to MEPS from 2005 to 2015. The study sample was then restricted to adult respondents who were diagnosed with or had cancer after the age of 18 years (n = 60,237), as identified by the CCS. Adults who died during the process of reporting were excluded and hence the study sample consisted of cancer survivors. The sample was then restricted to 21,413 patients who also had an ICD code of 296 or 311 or a clinical classification code of 657, indicating depression condition. These 21,413 patients thus had cancer along with depression. Patients who also had an ICD code for bipolar disorder or schizophrenia (n = 3,742) were further excluded, since, in these cases antidepressants are used for non-depression conditions. The final study sample, thus include 17,671 cancer patients along with comorbid depression, diagnosed after the age of 18 years in the US. Figure 4 depicts the final sample size.



\*These were the cases identified in the US with cancer and depression diagnoses and formed the final sample size

**Figure 4: Sample size flow chart for all the study aims**

**Variables:**

**Therapeutic drug class variables:**

Prescription Medicines files from 2005-2015 were used to identify the antidepressants, if any, prescribed to a patient. MEPS classifies drugs based on their therapeutic class under ‘Multum Therapeutic Class’. A specific code is given to one class of drugs under these Multum classes. These codes were used to capture the drug use. Following Table 3 summarizes the codes used.

**Table 3: Codes used to identify antidepressant classes using MEPS Prescription Files**

Multum class	Code	Antidepressant class
TC1S1	208	SSRI
TC1S1	209	TCA
TC1S1	308	SNRI
TC2S1	250	MAOI
TC2S1	76	Miscellaneous*
TC1S1	307, 306	Miscellaneous (including Tetracyclic, Phenyl piperazine)**

\* Separately coded as miscellaneous antidepressant agents by MEPS

\*\* Considered these categories as miscellaneous for this study's purposes

Based on the codes mentioned above, a new categorical variable was created indicating the classes of antidepressants (one specific or in combination) that were prescribed to a patient. This variable also had two more categories. One was for identifying patients who did not have any antidepressant prescribed but had psychotherapy or counseling session in order to manage depression and another identifying those who used antidepressants and psychotherapy both prescribed. Psychotherapy or counseling sessions were identified using office-based medical provider visits files. These files capture psychotherapy by asking questions like: 'Type of Medical person the patient talked to on the visit' (10 = Psychologist) and 'Best category for care the patient received on visit' (4 = Psychotherapy/Mental Health Counseling). In addition, modified CCS code of 657 captured under office-based procedural codes was also used to identify these visits. The final categorical variable for the treatment of depression thus had six categories, namely: SSRI, TCA, SNRI, Miscellaneous (tetracyclic and phenyl piperazine agents,

other unclassified antidepressants), Psychotherapy only and both (Antidepressant and Psychotherapy). MAOIs were removed from the classification since, they were not prescribed anymore for depression amongst cancer patients and the sample size in that particular class was found to be null. The combinations of antidepressants prescribed were identified using the round number and the panel number that the medicine was obtained in, each unique round consisting of approximately 3 months. The patients were considered to be using combinations of antidepressants, if they had the same round number for any two classes of antidepressants. The names of antidepressants under each class included by MEPS are summarized in Appendix Table 1.

#### Prescription drug characteristics and patterns of use variables:

Prescription medicines files were used to obtain drug characteristics. Variables such as the quantity of prescribed medicines and days supplied of prescribed medicine were used as prescription drug characteristics. Antidepressants were considered to be given in combinations if the round number that the patient reported for these was the same. It is possible that within 3 months of a specific round a patient was switched to another class, this would however be captured as a combination in our study. Combinations of antidepressants with psychotherapy were identified too. The trends in the use of different classes of antidepressants from 2005-2015 was identified using the drug codes specific to a particular year, which was obtained from the Panel Round number captured in the full year consolidated files. The patterns of use were further described using sociodemographic variables.

#### Cancer characteristics and comorbidities:

Type of cancer was identified using full year consolidated files. Cervical, breast, colon and lung were the major types of cancer identified and prostate, melanoma, liver, kidney and pancreatic cancer were clubbed under one “other/non-specified” category along with some non-

specified cancers. Arthritis, asthma, diabetes and high blood pressure were identified as major comorbidities associated with cancer patients along with depression based on the past literature.<sup>8,30,39</sup> The number of comorbidities (combinations of those mentioned above) were identified across classes of antidepressants/psychotherapy.

#### Sociodemographic variables:

Full Year Consolidated files were used to obtain sociodemographic characteristics of patients and compare them across different classes of antidepressants. The variables included were sex, race, age, marital status, income, education and employment status. Sex, race and marital status were used directly from MEPS whereas age, income, education and employment status were recoded into meaningful categories. Age was a continuous variable and it was recoded into 3 categories: “18-44 years”, “45-65 years” and “>65 years”. Income was also a continuous variable which was collapsed into 3 categories: “low” (< \$12,060), “middle class” (\$12,060 - \$48,240) and “high” (> \$48,240). These income ranges for these categories were identified based on the federal poverty line (FPL). The FPL for 2018 was \$12,060 annual income which was considered 100%, hence below this limit was identified as low income, between 100-400% (\$12,060 - \$48,240) of FPL was identified as middle class income and over 400% FPL (>\$48,240) was identified as high income. These ranges were identified based on another study looking at drug expenses and the FPL guidelines.<sup>31,40</sup> Education was recoded to 5 categories: “0: No education” (Kindergarten only and no years of schooling), “1: Elementary (Elem)/ Middle (Mid) School” – grades 1-8, “2: High school” (grades 9-12), “3: ≤ 4 years of college” (≤ 4 years of college after the 12<sup>th</sup> grade) and “4: 5+ Years College”. Employment was recoded to form two broader categories, namely: “Employed” and “Unemployed”.

**Statistical Analyses:**

Patterns of use of antidepressants and the combinations used were assessed using number of prescriptions that were obtained from the Prescription Medicines Files using the drug codes. Event-level files were summarized to patient-level files using PROC MEANS and PROC TRANSPOSE procedures in SAS. ANOVA procedure was used to compare means of quantity and days across different classes of antidepressants. Chi square tests were used to compare and assess the significance of sociodemographic characteristics across different classes of antidepressants and based on these results, characteristics were included in a multinomial logistic model predicting the likelihood of receiving any particular class of antidepressant. The preliminary chi square tests (PROC SURVEYFREQ) were significant for all the sociodemographic factors such as sex, age, income, race, marital status, employment status and education, hence, all of these were included in the regression model. Multinomial logistic regression approach (PROC SURVEYLOGISTIC) was then used to calculate odds ratios (OR) and estimate the likelihood of receiving any particular antidepressant and hence define the patterns of use and predictors of receiving the treatment further. The model used for multinomial logistic regression was as follows:

$$\text{Logit}(y=a^*) = \log \left\{ \frac{p(y=a^*)}{1-p(y=a^*)} \right\} = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Gender} + \beta_3 \cdot \text{Race} + \beta_4 \cdot \text{Marital Status} + \beta_5 \cdot \text{Education} + \beta_6 \cdot \text{Employment Status} + \beta_7 \cdot \text{Income} + \epsilon^a$$

\*-Either SSRI, Miscellaneous agents, SNRI, TCA, Psychotherapy (Reference = No antidepressant/psychotherapy), a-Error Term

Trends in the utilization of antidepressants across the study period of 2005 to 2015 were compared by plotting graphs for each class of antidepressant/ psychotherapy. For trends, the percentages, calculated using the following formula, were plotted for each year:

$$\left( \frac{\text{Number of those who were prescribed } x^a \text{ in one particular year}}{\text{Total number of antidepressant/psychotherapy prescription in that particular year}} \right) \times 100$$

a – SSRI/Miscellaneous Agents/SNRI/TCA/Psychotherapy

Trends throughout the study period were compared for each individual class by conducting Cochran-Armitage trend test for categorical data. After running the analyses, the data was summarized using means and frequencies for continuous and categorical variables respectively and OR for logistic regression results. All the analyses was weighted by using pooled weights from all the years. All the analyses were conducted using 0.05 as the significance level. The hypothesis tested in this analysis was that the patterns of use and the trends of antidepressants would differ significantly across the groups. In addition, the sociodemographic characteristics would also differ and would be significantly associated with the likelihood of receiving any specific class of antidepressant/ psychotherapy. SAS v9.4 and MS Excel 2016 were used for the analyses and for plotting graphs.

## Section 3.2: Results

### Aim 1A: To determine the patterns of use and prescription trends across different classes of antidepressants

Total sample size for the study consisted of 17,671 (weighted frequency = 16,478,908) cancer patients with depression. Out of this, 32.08% (n = 5,669) had some antidepressant prescribed to them either in combination or of one particular class. 15.30% (n = 2,705) reported psychotherapy or mental counseling for managing their depression. There were around 7.25% patients (n = 1,282) who reported the use of both that is pharmacotherapy (antidepressant) and psychotherapy both at a time. There were around 53.64% patients (n = 9480) with no treatment for depression and hence were untreated. Hence, patients either had untreated depression or were prescribed an antidepressant, psychotherapy or a combination of both for managing their depression. Amongst those who were prescribed antidepressants, 62.44% patients (n = 3,540) were on SSRI, whereas 20.19% (n = 1145) were on miscellaneous agents that also included 1.09% tetracyclic (n = 62) and 3.2% phenyl piperazine (n = 187) agents in addition to those defined as miscellaneous by MEPS, around 13.31% (n = 755) were on SNRI. 4.03% (n= 229) patients were on TCA. The sample sizes of patients per antidepressant class along with their weighted frequencies are summarized in Table 4.

**Table 4: Sample sizes (unweighted and weighted) per antidepressant class**

<b>Antidepressant</b>	<b>Frequency</b>	<b>Weighted Frequency</b>	<b>Unweighted Percent</b>
SSRI	3,540	3,545,671	62.44
Miscellaneous Agents	1,145	1,182,517	20.19
SNRI	755	803,590	13.31
TCA	229	199,423	4.03
<b>Total</b>	<b>5,669</b>	<b>5,531,052</b>	<b>100</b>

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

Amongst those who were prescribed antidepressants, around 5.6% patients (n=318) reported using combinations of different classes. Out of these 318 patients who were using combination therapy, most of them (56.28%, n = 179) were prescribed a combination of SSRI and one of the miscellaneous agents (usually Bupropion). Some other combinations identified were, SSRI - TCA, SSRI - SNRI and SNRI – miscellaneous agent. There were very few who were prescribed some other combinations such as, TCA with either SNRI or a miscellaneous agent. SSRI and miscellaneous agents were the most frequently prescribed classes individually or in combination. The frequencies of patients receiving a combination therapy are summarized in Table 5 along with their weighted frequencies per combination.

**Table 5: Frequencies for combinations of antidepressants**

<b>Combination of antidepressants</b>	<b>Frequency</b>	<b>Weighted Frequency</b>	<b>Unweighted Percent</b>
SSRI – MA*	179	193,074	56.28
SNRI – MA*	47	53,902	14.77
SSRI – SNRI	42	44,889	13.20
SSRI – TCA	34	27,236	10.69
Other combinations <sup>a</sup>	16	20,432	5.03
<b>Total</b>	<b>318</b>	<b>343,002</b>	<b>100</b>

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\* - Miscellaneous Agents

<sup>a</sup> Other combinations include TCA either with a miscellaneous agent or SNRI

As mentioned above, some antidepressants were also used in combination with psychotherapy (n = 1282). SSRI was the most commonly prescribed class along with psychotherapy (n = 733, 57.17%). TCA (n = 29, 2.26%) was a rarely prescribed class in combination with psychotherapy. These combinations are summarized in Table 6 using weighted and unweighted frequencies.

**Table 6: Frequencies for combinations of antidepressants along with psychotherapy**

<b>Antidepressant with psychotherapy</b>	<b>Frequency</b>	<b>Weighted Frequency</b>	<b>Percent</b>
SSRI	733	802,998	57.17
Miscellaneous agents	338	392,011	26.36
SNRI	182	122,321	14.19
TCA	29	25,242	2.26
<b>Total</b>	<b>1,282</b>	<b>1,282,751</b>	<b>100</b>

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

All the above findings suggest that SSRI and miscellaneous agents were the most frequently prescribed antidepressants to manage depression amongst cancer patients. These were also the classes of antidepressants used most frequently in combination with one another or with psychotherapy.

Cancer characteristics including the type of cancer, the remission state and other comorbidities associated with cancer patients are summarized below in Table 7. Cancer type and remission state had more than 90% missing values and hence were excluded from further analyses, since they did not have any effect on the outcome variables. Number and type of comorbidities had fewer missing values and hence were included in the analyses further.

**Table 7: Cancer Characteristics across classes of antidepressants and psychotherapy**

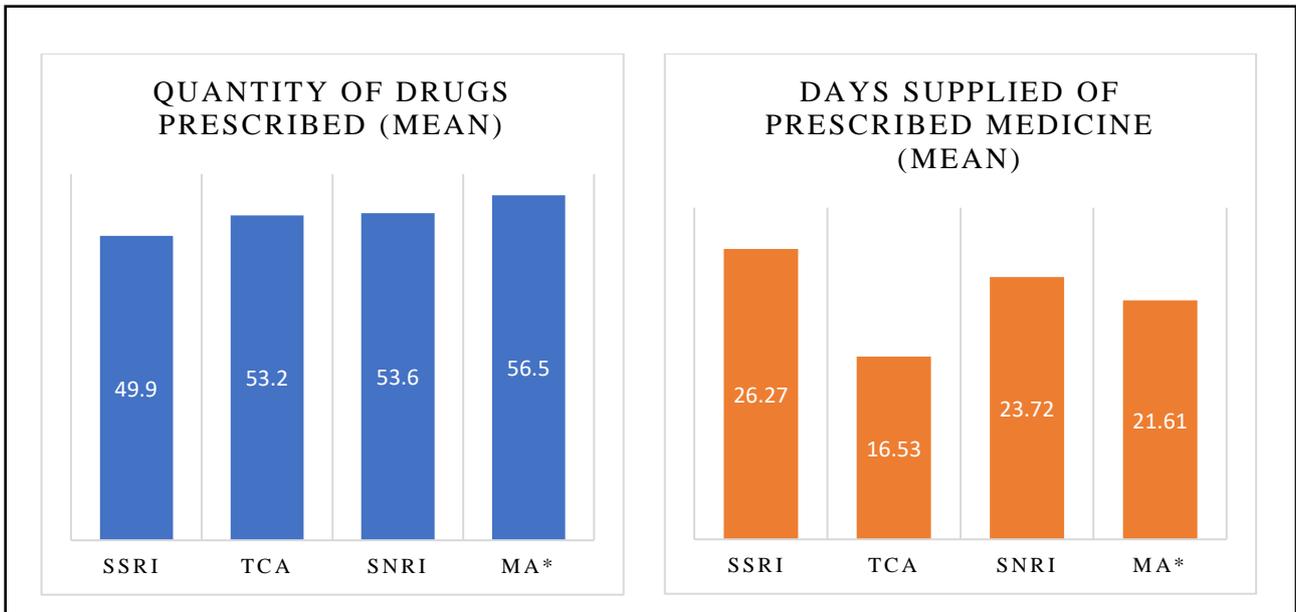
<b>Cancer characteristic</b>	<b>Antidepressants</b>				<b>Psychotherapy (N=2705)</b>
	<b>SSRI (N=3540)</b>	<b>MA* (N=1145)</b>	<b>SNRI (N=755)</b>	<b>TCA (N=229)</b>	
<b>Cancer Type</b>					
Cervical	37 (1.04)	8 (0.69)	9 (1.19)	1 (0.43)	19 (0.70)
Breast	46 (1.29)	17 (1.48)	17 (2.25)	2 (0.87)	31 (1.14)
Colon	11 (0.31)	6 (0.52)	2 (0.26)	2 (0.87)	9 (0.33)
Lung	6 (0.16)	5 (0.43)	3 (0.39)	1 (0.43)	1 (0.03)
Other/Non-specified	64 (1.80)	23 (2.00)	15 (1.98)	3 (1.31)	33 (1.21)
Missing	3,376 (95.36)	1,086 (94.84)	709 (93.90)	220 (96.09)	2,612 (96.56)
<b>Remission State</b>					
Yes	75 (2.11)	25 (2.18)	23 (3.05)	4 (1.75)	30 (1.10)
No	6 (0.16)	1 (0.08)	0 (0.0)	0 (0.0)	1 (0.03)
Missing	3459 (97.71)	1,119 (97.72)	732 (96.95)	225 (98.25)	2674 (98.85)

<b>Comorbidities</b>					
Diabetes	311 (8.78)	112 (9.78)	88 (11.65)	26 (11.35)	351 (12.97)
Arthritis	1,029 (29.06)	393 (34.32)	290 (38.41)	90 (39.30)	659 (24.36)
Asthma	413 (11.66)	158 (13.79)	96 (12.71)	31 (13.53)	513 (18.96)
High blood pressure	1,068 (30.16)	402 (35.10)	272 (36.02)	80 (34.93)	696 (25.73)
Missing	719 (20.31)	80 (6.98)	9 (1.19)	2 (0.87)	486 (17.96)
<b>Number of comorbidities</b>					
2	2,790 (78.81)	1,045 (91.26)	734 (97.22)	219 (95.19)	2,175 (80.41)
≥3	31 (0.87)	20 (1.74)	12 (1.59)	9 (3.94)	44 (1.63)
Missing	719 (20.31)	80 (6.98)	9 (1.19)	2 (0.87)	486 (17.96)

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\* - Miscellaneous Agents

Thus, as seen from the table above, the findings regarding the type of cancer and the remission state across classes of antidepressants/ psychotherapy were inconclusive, since majority of values were missing. With respect to comorbidities, arthritis and high blood pressure were the most commonly associated conditions across all the groups. Almost the entire population had at least 2 of these comorbidities. Some even reported having 3 or all of these conditions.

Quantity of prescribed drugs and days supplied per prescription were then compared across different classes to further explore patterns of use. It was found that the quantity of drugs prescribed were the highest for miscellaneous agents (mean = 56.57), however the differences within classes were not statistically significant (p-value > 0.05 for all comparisons). Days supplied of prescribed medicine were the highest for SSRI (mean = 26.27), these were significantly higher than that for TCA (p-value = 0.0357), however the other differences were not statistically significant (p-value > 0.05). The means for quantity and days supplied of prescribed drug are summarized below in Figure 5.

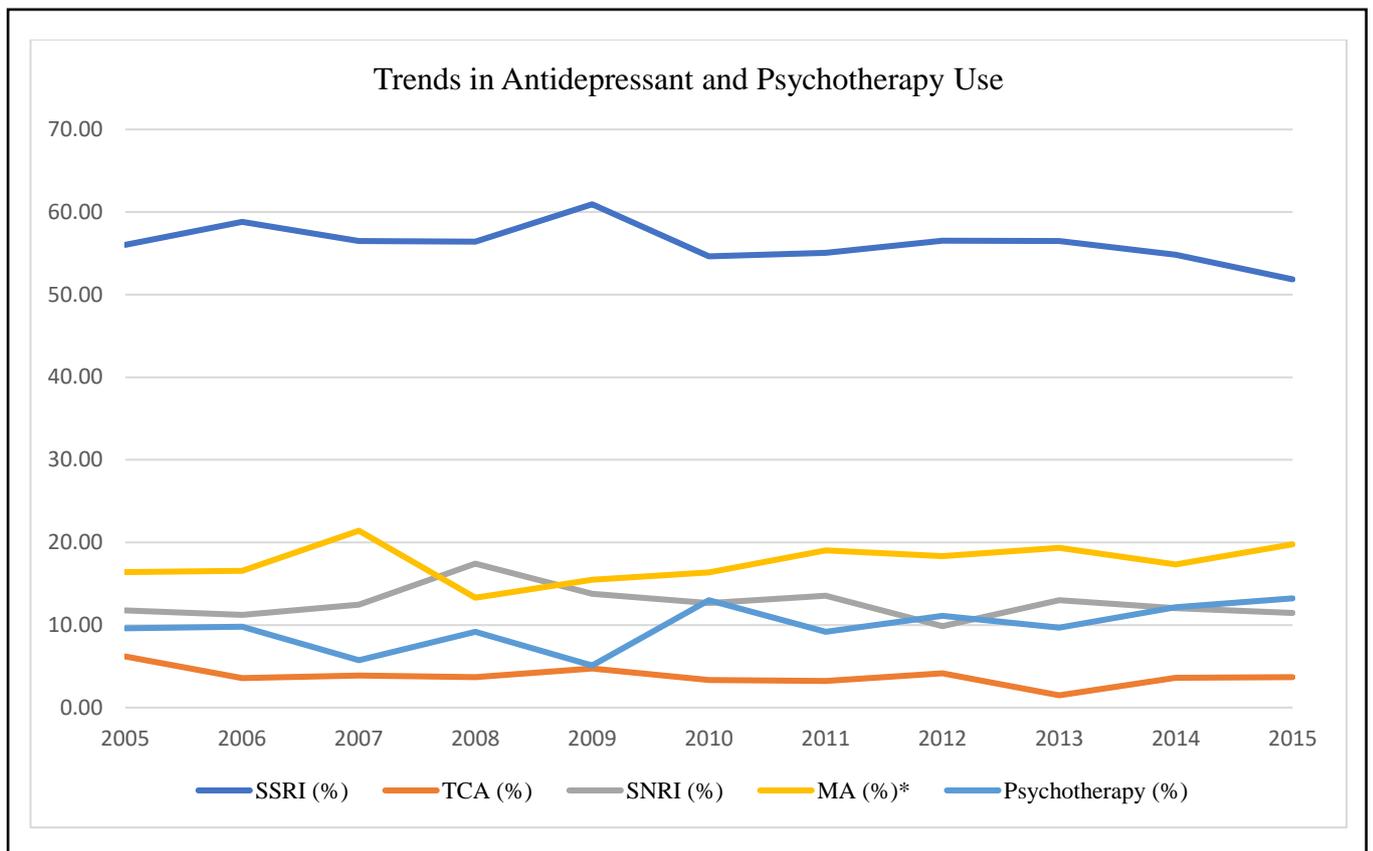


Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* – Miscellaneous Agents

**Figure 5: Mean quantity and days supplied of medicine per fill across antidepressant classes for cancer patients with depression in the US for the years 2005-2015**

Since the differences were not statistically significant, it can be concluded that the patterns of use with respect to the quantity and days supplied are similar across different classes of antidepressants.

In addition, antidepressant and psychotherapy use was tracked across the study period to identify the trends. Figure 6 depicts the trends per class. The observed trends remain consistent with the findings above where SSRI is the most frequently prescribed class of antidepressant followed by miscellaneous agents.



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* – Miscellaneous Agents  
 Trends reported are percentages observed per year out of all the antidepressants/psychotherapy prescribed in that particular year

**Figure 6: Trends in the use of antidepressants and psychotherapy throughout the study period**

As seen from the graph, the use of TCA from 2005-2015 has been minimum and has been steady. The use of psychotherapy has increased until 2010 and has been stable ever since. In the year 2008, there was a spike increase in the use of SNRI, however, the use decreased in 2009 and has again increased slightly in 2013 and remained stable ever since. The use of SSRI has been more than 50% of all the antidepressants throughout the study period. The year 2009 witnessed an increase in the use of SSRI over 60%, however it decreased by 2010 and has been stable ever since. Out of all of these, a significant change in trend (upward or downward) was observed only for SNRI (p-value=0.0385 for a two-sided test), others were all non-significant.

**Aim 1B: To characterize the sociodemographic factors associated with the utilization of antidepressants**

Sociodemographic characteristics included in our study, age, gender, race, marital status, education employment status and income were compared across the classes of antidepressants and psychotherapy. The distribution of people per antidepressant/ psychotherapy class by the sociodemographic factors mentioned above are summarized in Table 8.

**Table 8: Sociodemographic characteristics of patients receiving antidepressant/psychotherapy**

Sociodemographic Factor	Antidepressants				Psychotherapy (N=2705)
	SSRI (N=3540)	MA* (N=1145)	SNRI (N=755)	TCA (N=229)	
<b>Age, years (range)</b> Mean	48.13	47.54	49.03	50.55	43.23
<b>Age groups</b>					
18-44 years	1,381 (39.01)	350 (30.57)	247 (32.72)	57 (24.89)	1,333 (49.29)
45-65 years	1,325 (37.42)	401 (35.02)	333 (44.11)	99 (43.23)	897 (33.16)
>65 years	446 (12.60)	157 (13.71)	78 (10.33)	26 (11.35)	128 (4.73)
Missing	388 (10.96)	237 (20.70)	97 (12.85)	47 (20.52)	346 (12.81)
<b>Gender</b>					
Male	1,063 (30.03)	319 (27.86)	186 (24.64)	55 (24.02)	976 (36.08)
Female	2,341 (66.13)	545 (47.60)	487 (64.50)	134 (58.52)	1,633 (60.36)
Missing	136 (3.84)	281 (24.54)	82 (10.86)	40 (17.47)	96 (3.54)
<b>Race</b>					
Whites	1,943 (54.89)	752 (65.68)	620 (82.12)	85 (37.12)	2,296 (84.87)
Blacks	668 (18.87)	146 (12.75)	39 (5.17)	114 (49.78)	216 (7.98)
Asians	534 (15.08)	34 (2.97)	7 (0.93)	3 (1.31)	37 (0.93)
Multiple Races	300 (8.47)	67 (5.85)	17 (2.25)	3 (1.31)	84 (3.10)
Missing	95 (2.68)	146 (12.75)	72 (9.54)	24 (10.48)	72 (2.66)
<b>Marital Status</b>					
Married	1,478 (41.75)	323 (28.21)	322 (42.65)	79 (34.50)	681 (25.17)
Widowed	254 (7.18)	58 (5.07)	51 (6.75)	20 (8.73)	96 (3.54)
Divorced	552 (15.59)	289 (25.24)	146 (19.34)	34 (14.85)	494 (18.26)
Separated	126 (3.56)	42 (3.67)	24 (3.18)	4 (1.75)	115 (4.25)
Never Married	871 (24.60)	223 (19.48)	127 (16.82)	48 (20.96)	962 (35.56)
Missing	259 (7.32)	210 (18.34)	85 (11.26)	44 (19.21)	355 (13.19)
<b>Education</b>					
No education	10 (0.28)	14 (1.22)	7 (0.93)	0 (0.00)	108 (4.36)
Elem/Mid School	229 (6.47)	156 (13.62)	38 (5.03)	23 (10.04)	477 (17.64)

High School	1,037 (29.29)	347 (30.31)	204 (27.02)	97 (42.36)	937 (34.64)
≤ 4 Years College	872 (24.63)	318 (27.77)	224 (29.67)	42 (18.34)	811 (29.99)
5+ Years College	204 (5.76)	68 (5.94)	155 (20.53)	10 (4.37)	354 (13.09)
Missing	1,188 (33.56)	242 (21.14)	127 (16.82)	57 (24.89)	9 (0.33)
<b>Employment status</b>					
Employed	1,635 (46.19)	385 (33.62)	340 (45.03)	68 (29.69)	1,147 (42.41)
Unemployed	1,534 (43.33)	432 (37.73)	318 (42.12)	112 (48.91)	1,288 (47.61)
Missing	371 (10.48)	328 (28.65)	97 (12.85)	49 (21.40)	270 (9.98)
<b>Income, per year</b>					
Mean (\$)	30,007	31,993	32,513	24,229	24,931
<b>Income groups <sup>a</sup></b>					
Low	610 (17.23)	135 (11.79)	80 (10.60)	24 (10.48)	639 (23.62)
Middle class	2,268 (64.07)	587 (51.27)	468 (61.99)	145 (63.32)	1,654 (61.16)
High	526 (14.86)	142 (12.40)	125 (16.56)	20 (8.73)	316 (11.68)
Missing	136 (3.84)	281 (24.54)	82 (10.86)	40 (17.47)	96 (3.54)

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\* - Miscellaneous Agents

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

As seen from the table above, majority of the people in any antidepressant/pharmacotherapy group were in the 18-44 years or 45-65 years age group and were females. In addition, except TCA (49.78% - Blacks), most of the population in any antidepressant/pharmacotherapy group was White. The marital status and education was varied across the groups. The distribution between the employed and unemployed groups was uniform. Majority of the population belonged to middle class income category across all the groups. In bivariate analyses, all these factors were significantly associated with the class of antidepressant/psychotherapy at the significance level of 0.05.

Multinomial logistic regression approach produced the results as stated in Table 9 using ‘no depression therapy’ as a comparison group for the outcome variable. People who were above 65 years of age were less likely to receive any antidepressant/ psychotherapy and those between 18-44 years were more likely to receive psychotherapy as compared to those between the age group of 45-65 years. It was observed that, males were less likely to receive SNRI as compared

to females. Blacks were less likely to receive SSRI, SNRI or any miscellaneous agent as compared to Whites. Asians were less likely to receive SNRI, whereas those who reported multiple races including Hispanic were more likely to report the use of psychotherapy as compared to Whites. Those who were divorced were more likely to receive any miscellaneous agent or psychotherapy, whereas those who never married were more likely to receive psychotherapy as compared to those who were married. Those who reported no education, elementary/middle school or high school were less likely to receive any treatment for depression as compared to those who attended college for  $\leq 4$  years. Those who attended college for more than 5 years were more likely to receive any miscellaneous agent or psychotherapy as compared to those who attended college for  $\leq 4$  years. People who were employed were more likely to receive SSRI, whereas less likely to receive TCA or psychotherapy as compared to unemployed. Income was not significantly associated with the likelihood of receiving any antidepressant/psychotherapy. These results are summarized using OR in Table 9.

**Table 9: Multinomial regression results for likelihood of receiving any antidepressant/psychotherapy**

Sociodemographic Factor	Antidepressants (OR, Confidence Intervals) <sup>a</sup>				Psychotherapy (OR, Confidence Intervals)
	SSRI	MA*	SNRI	TCA	
<b>Age**</b>					
18-44 years	1.145 (0.966,1.357)	1.127 (0.858,1.480)	1.030 (0.776,1.368)	0.802 (0.420,1.533)	<b>1.951**</b> <b>(1.247,3.052)</b>
>65 years	0.842 (0.661,1.073)	<b>0.410**</b> <b>(0.260,0.646)</b>	<b>0.504**</b> <b>(0.288,0.882)</b>	0.549 (0.272,1.107)	<b>0.154**</b> <b>(0.043,0.556)</b>
45-65 years	Reference	Reference	Reference	Reference	Reference
<b>Gender**</b>					
Males	0.898 (0.777,1.038)	1.175 (0.913,1.513)	<b>0.686**</b> <b>(0.521,0.902)</b>	0.758 (0.425, 1.351)	1.119 (0.753, 1.662)
Females	Reference	Reference	Reference	Reference	Reference
<b>Race**</b>					
Blacks	<b>0.476**</b> <b>(0.377,0.601)</b>	<b>0.415**</b> <b>(0.271,0.636)</b>	<b>0.297**</b> <b>(0.169,0.523)</b>	0.575 (0.316,1.039)	0.573 (0.316,1.039)
Asians	0.859 (0.454,1.626)	0.925 (0.366,2.337)	<b>0.128**</b> <b>(0.017,0.983)</b>	0.983 (0.129,7.481)	2.658 (0.871,8.113)

Multiple Races reported	0.804 (0.521,1.241)	0.977 (0.357,2.673)	0.384 (0.139,1.063)	0.276 (0.038,2.028)	<b>2.725**</b> <b>(1.140,6.511)</b>
Whites	Reference	Reference	Reference	Reference	Reference
<b>Marital Status**</b>					
Widowed	0.891 (0.667,1.192)	1.166 (0.745,1.824)	0.779 (0.454,1.335)	1.070 (0.469,2.439)	1.217 (0.285,5.196)
Divorced	0.817 (0.674,0.991)	<b>1.432**</b> <b>(1.013,2.025)</b>	1.027 (0.725,1.456)	1.043 (0.541,2.013)	<b>2.412**</b> <b>(1.416,4.108)</b>
Separated	0.823 (0.572,1.184)	0.772 (0.346,1.721)	0.561 (0.256,1.229)	0.461 (0.098,2.178)	1.694 (0.443,6.470)
Never Married	0.907 (0.744,1.106)	1.257 (0.911,1.733)	0.854 (0.583,1.252)	1.396 (0.646,3.018)	<b>2.775**</b> <b>(1.646,4.680)</b>
Married	Reference	Reference	Reference	Reference	Reference
<b>Education**</b>					
No education	<b>0.210**</b> <b>(0.060,0.737)</b>	0.750 (0.180,3.127)	<b>0.088**</b> <b>(0.012,0.668)</b>	N/A <sup>b</sup>	<b>0.072**</b> <b>(0.009,0.532)</b>
Elem/ Mid School	<b>0.593**</b> <b>(0.431,0.814)</b>	<b>0.506**</b> <b>(0.300,0.855)</b>	<b>0.492**</b> <b>(0.283,0.858)</b>	1.728 (0.731,4.087)	0.697 (0.259,1.871)
High school	<b>0.838**</b> <b>(0.722,0.974)</b>	<b>0.626**</b> <b>(0.472,0.830)</b>	<b>0.584</b> <b>(0.433,0.788)</b>	0.818 (0.442,1.514)	0.759 (0.480,1.199)
5+ Years College	1.094 (0.833,1.437)	<b>1.835**</b> <b>(1.194,2.821)</b>	0.851 (0.511,1.417)	1.143 (0.374,3.497)	<b>2.183**</b> <b>(1.210,3.936)</b>
≤ 4 Years College	Reference	Reference	Reference	Reference	Reference
<b>Employment status**</b>					
Employed	<b>1.378**</b> <b>(1.149,1.652)</b>	0.960 (0.695,1.327)	0.804 (0.570,1.133)	<b>0.518**</b> <b>(0.284,0.945)</b>	<b>0.520**</b> <b>(0.303,0.892)</b>
Unemployed	Reference	Reference	Reference	Reference	Reference
<b>Income<sup>c</sup></b>					
Low income	1.184 (0.933,1.503)	1.007 (0.676,1.500)	0.833 (0.489,1.416)	0.496 (0.216,1.140)	0.776 (0.428,1.406)
High income	1.042 (0.845,1.285)	0.946 (0.663,1.350)	1.251 (0.875,1.788)	1.099 (0.469,2.573)	1.560 (0.821,2.966)
Middle class income	Reference	Reference	Reference	Reference	Reference

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\* - Miscellaneous Agents

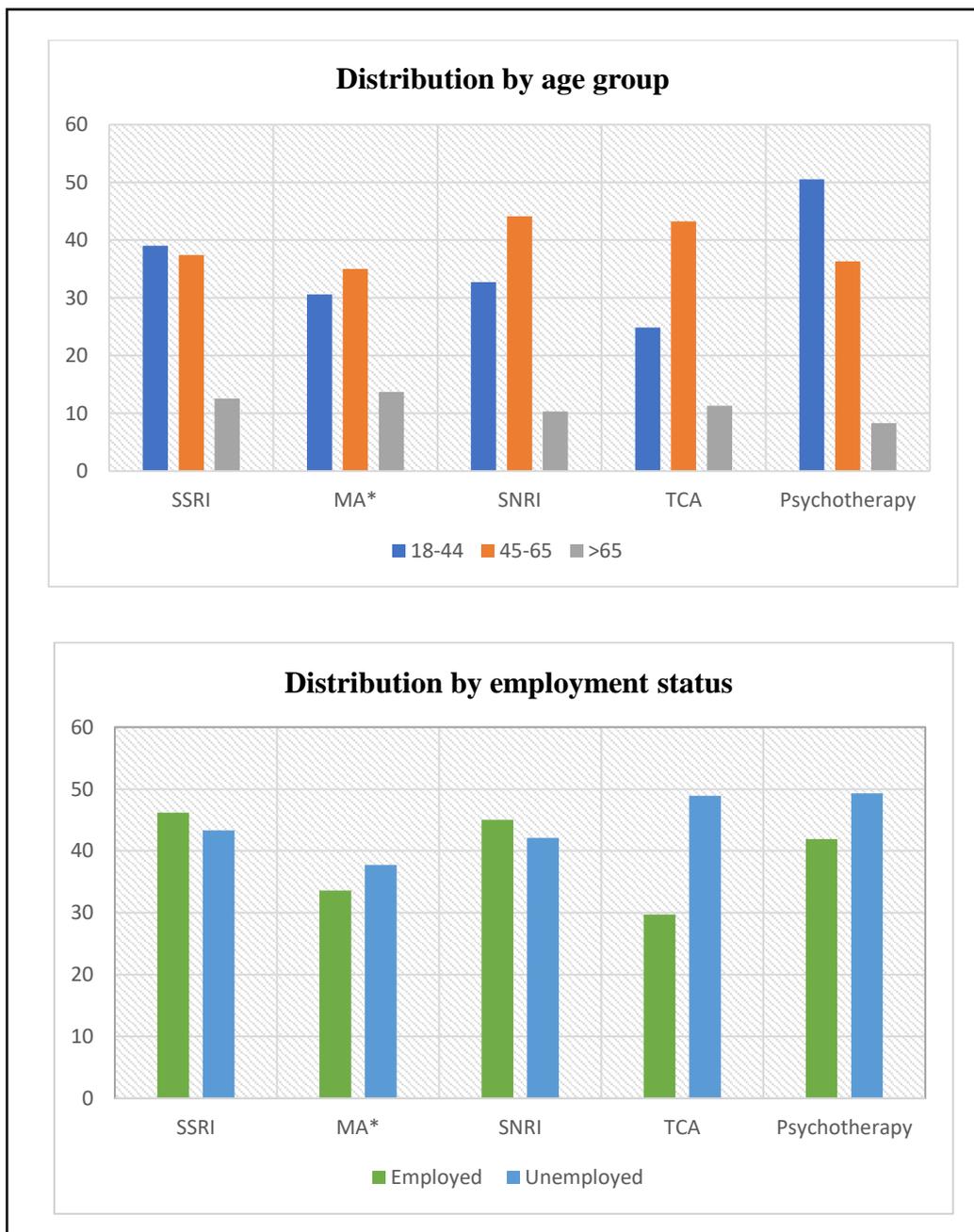
<sup>a</sup>The reference class for therapy was getting no antidepressants/pharmacotherapy at all

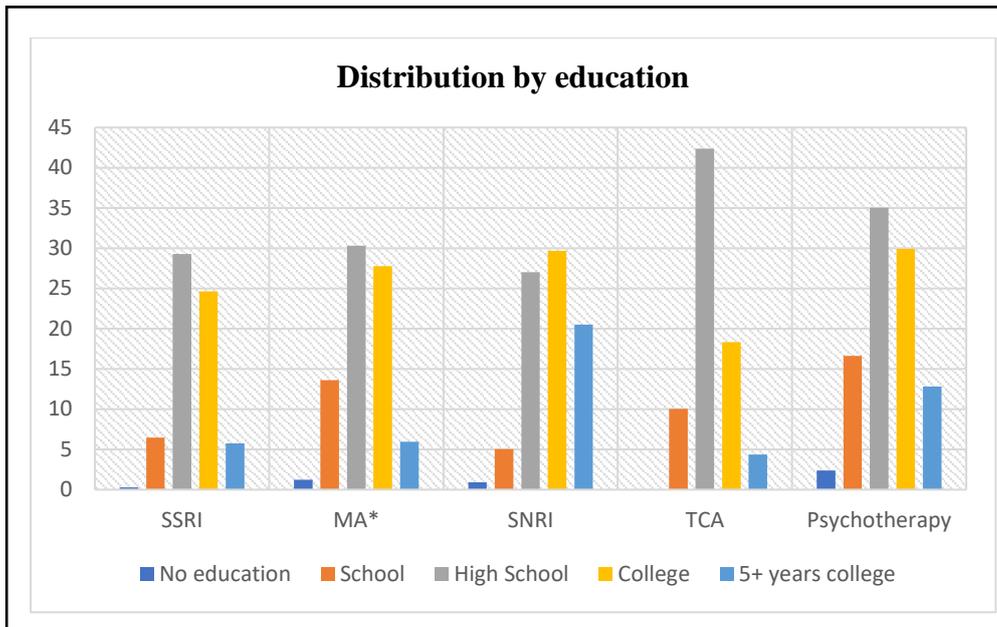
\*\* - Significant results

<sup>b</sup> - N/A – Not applicable, since there were almost no patients in that group and the sample size for that cell was < 5, the OR obtained for that particular group were absurd

<sup>c</sup> - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

Type 3 analysis effects of multinomial logistic regression suggested that all the sociodemographic factors, except income, were significantly associated with the class of antidepressant/psychotherapy. The odds ratios suggested that age, employment and education were the most significantly associated factors. The percentages of those who are in that particular sociodemographic characteristic across the classes of antidepressants/ psychotherapy are represented graphically in Figure 7.





Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* - Miscellaneous agents

**Figure 7: Most significantly associated sociodemographic characteristics**

As seen from the graphs and the findings above, SSRI and psychotherapy have a higher percentage of people in the age group of 18-44 years whereas all the other groups have a higher percentage of people in the age group of 45-65 years. Looking at the employment status, SSRI and SNRI have a higher proportion of employed people whereas other groups have a higher proportion of unemployed people. On comparing the education received in every group, it was observed that SNRI had the highest proportion of people who completed college whereas all others had the highest proportion of people who completed high school.

### **Section 3.3: Discussion**

The study thus suggested that in majority of cancer patients in the US, depression was untreated. Out of those treated, antidepressants were prescribed more frequently (32%) than psychotherapy (15%). SSRI was the most frequently prescribed class of antidepressant with or without psychotherapy followed by miscellaneous agents. Around 7.25% patients were prescribed psychotherapy and an antidepressant both. Some antidepressants were also prescribed in combination with one another. SSRI along with a miscellaneous agent was the most commonly prescribed combination of antidepressants. The finding of SSRI being the most commonly prescribed antidepressant was consistent with the findings found in the previous literature where, prescribing of SSRI occurred in most of the patients, along with SNRI.<sup>18,21</sup> However, one of these studies was conducted only in ambulatory cancer patients<sup>18</sup> and the other one was not in general population.<sup>21</sup> Also, with respect to antidepressants, exposure to SSRI/SNRI was the only outcome considered and comparison to other classes was not considered. In our study, it was also found that out of all the comorbidities included, arthritis and high blood pressure were the most commonly associated along with cancer and depression and most of the people had two comorbidities associated. These were consistent with the findings in the literature, where a majority of patients also reported asthma.<sup>30,39</sup>

The quantity of prescribed drugs and the days supplied per prescription were not found to be significantly different from one another in this study across the classes of antidepressants. However, numerically, the quantity was found to be lowest whereas the days supplied per prescription were found to be the highest for SSRI as compared to other antidepressant classes. Higher quantities of SSRI were reported to be associated with abnormal heart rhythms, which could be the reason for the quantity of SSRI prescribed being lower.<sup>41</sup> In addition, the frequency of dosing was lower (usually once per day as opposed to 2 times in a day) which could be the

reason for days supplied being maximum for SSRI.<sup>41</sup> Hence, the findings were in compliance with the reported dosing requirements for SSRI.

The trends in antidepressant use suggested that throughout the study period SSRI was the most frequently prescribed class. The use of miscellaneous agents and psychotherapy has eventually increased. The spike in the prescription of SNRI in the year 2008 could be because of FDA approval of Desvenlafaxine and some other SNRI with lower side effects.<sup>42</sup> The findings of increase in SSRI use were consistent with the findings of a previous study conducted by Kantor et al.<sup>43</sup> This study however, looked at the trends in overall prescription of SSRI only from 1999 to 2012 in general population.<sup>43</sup> There have been some articles discussing side effects of TCA. These are higher than those associated with other classes, TCAs are also associated with many drug-drug interactions and hence their use has gone down over a period of time and if prescribed, the patients have to be thoroughly monitored.<sup>44-47</sup>

On comparing the sociodemographic factors, it was found that all of them individually were significantly associated with the class of antidepressant/psychotherapy. On conducting for other factors, income was found to be non-significant. Age, employment status and education were found to be the most significant factors. It was suggested that, people who were above 65 years of age were less likely to receive any therapy as compared to those who were below 65 years. This is consistent with the past findings of a study where patients <55 years were more likely to receive any antidepressant. However, as mentioned earlier this study only consisted of ambulatory cancer patients and did not compare various classes of antidepressants/psychotherapy.<sup>18</sup> A study conducted by Waitzfelder et al. has also suggested that patients aged > 60 years had lesser odds of initiating depression treatment. However, this study was in general population, and there has not been any other study looking specifically at cancer patients.<sup>48</sup> Studies have shown that females are more likely to be treated for depression than males, this complies with the regression results of our study.<sup>49</sup> Those who were employed

were more likely to receive SSRI and less likely to receive any other antidepressant/psychotherapy as compared to unemployed.

There are several limitations for this study. Firstly, it was a retrospective cross-sectional study and hence causality could not be assigned. The associations found with the sociodemographic factors could not be proven to be true over a longitudinal duration. In addition, it is possible that some patients were later switched to another class of antidepressant/psychotherapy, different than the one to begin with or the one that was reported in MEPS, these would not be captured in the dataset, since it was not longitudinal. Also, since the date of prescription fill was not captured under MEPS. It is possible that some patients were switched within 3 months (one round) to another class of antidepressant but in our study, they were captured as combinations of antidepressants. Secondly, the prescription of any class of antidepressant or psychotherapy and the demographics associated with each could also depend on the stage of cancer which due to the data source limitation could not be controlled. Thirdly, since the survey was patient-reported there could also be some recall bias involved.

Despite the limitations stated above, this study adds to the past literature by providing certain novel findings. Patterns of use across classes of antidepressants/ psychotherapy or the predictors associated with each class had not been explored amongst cancer patients with depression using a nationally representative sample in the past studies. A study conducted by Fisch et al. identified the predictors of antidepressant use, however, if these persist across all the antidepressant classes and psychotherapy or differ had never been studied.<sup>18</sup> This study states that these predictors differ by classes, which increases the significance of our results. In addition, prescription trends have been identified for antidepressants in general, this study adds more to it by looking at trends per class of antidepressant and also comparing it with psychotherapy.<sup>17</sup> This study also produces a framework for conducting future studies where, significant sociodemographic factors and predictors identified could be studied in depth.

## **CHAPTER IV: SPECIFIC AIM II**

**Aim 2: To compare costs and healthcare utilization (office-based visits) of cancer patients across different classes of antidepressants in the US**

A: To compare the prescription medicines expenditures, overall costs and out of pocket expenses of cancer patients with comorbid depression across different classes of antidepressants

B: To compare office-based visits with the expenses related to these across cancer patients along with comorbid depression classified based on the class of antidepressants

### **Section 4.1: Methods**

#### **Data source and study design:**

As mentioned above, it was a cross-sectional retrospective study conducted using Medical Expenditure Panel Survey. For this specific aim, along with full year consolidated files for demographics and medical condition files for sample selection, prescription medicine files and office-based visits files were mainly used to identify the costs associated with each of the antidepressant class and psychotherapy. The study sample was same as specific aim 1 with 17,671 patients diagnosed with cancer along with a comorbid depression condition.

#### **Variables:**

##### **Demographics and controlling factors:**

Aim 1 identified that almost all the sociodemographic characteristics were associated with the use of antidepressants. Age, gender, race, marital status, education, employment status and income were thus the demographic factors that were obtained from the full year consolidated files, were recoded as mentioned in aim 1, and were controlled for while comparing costs along with the associated comorbidities. The study also controlled for the overall health status of the patients since that could affect the frequency of dosing of antidepressants and some cost and utilization outcomes across all the groups. This variable was obtained from the full

year consolidated files as well. MEPS captures the overall health status of the patients into 5 main categories namely: “excellent”, “very good”, “good”, “fair” and “poor”. It is a variable captured from the short form-12 version 2 (SF-12), self-assessment questionnaire (SAQ).

Prescription medicine costs:

The costs associated with prescription medicines per purchase/fill were captured from the prescription medicines files from January 2005 to December 2015. MEPS reports the total amount per patients and the sources of payment for the same. These costs were associated with each prescription fill per month. For the prescription medicine costs purposes, psychotherapy alone was not considered as a treatment arm, since they did not have any antidepressants prescribed. The costs were thus compared against the 4 major classes of antidepressants and those who were prescribed psychotherapy and antidepressants both. Other than the total costs, the amount paid out of pocket and by private insurance was also compared across these classes, since these two were the major sources of payments identified. New variables were created to indicate the patients who paid out of pocket entirely and for those who paid using out of pocket and private insurance both. Other sources of payment such as Tricare, Veterans Insurance, other state and local government insurance, Medicare and Medicaid were also included to assess the proportion of patients who used these as their sources of payment.

Office-based visits frequency and costs:

Similar to prescription medicines costs, similar variables were obtained from the office-based visits files. As mentioned above, psychotherapy visits were identified by using modified clinical classification codes for office-based visits (657-psychotherapy/mental counseling visits), ‘Type of Medical person the patient talked to on the visit’ (10 = Psychologist) and ‘Best category for care the patient received on visit’ (4 = Psychotherapy/Mental Health Counseling). The frequency/number of visits were identified across the classes of antidepressants. Other categories for office-based visits like general checkup, treatment/diagnosis purposes which were

used the most were also identified across the classes of antidepressants. The costs associated with these visits, mainly psychotherapy, were obtained from the office-based visits files from January 2005 to December 2015. The costs captured by MEPS were the costs per visit. The sources of payment for these visits were also identified. Similar to prescription medicines, out of pocket and private insurance were the two main sources of payment. New variables in this case were created too, indicating those who paid entirely out of pocket and those who paid using private insurance and out of pocket both. Variables for other sources such as Tricare, Veterans insurance, other state and local insurance, Medicare and Medicaid were also used to assess the proportion of patients who used these sources of payments. For aim 2B, the costs and the frequency of psychotherapy visits were compared across 5 main classes: SSRI, miscellaneous agents, SNRI, TCA and psychotherapy only.

### **Statistical Analyses:**

All the analyses for this aim, was conducted on patient-level files created by summarizing the event-level files. The costs were summarized per patient using PROC MEANS. In order to summarize the office-based visit categories per patient, PROC TRANSPOSE was used. Means were used to summarize total prescription costs and total costs per visits across different classes of antidepressants. Frequencies/ proportions were used to calculate the number of psychotherapy visits across classes of antidepressants. While calculating means for out of pocket costs and private insurance, non-positive values were excluded to avoid the skewing of mean. There were no non-positive values for total costs since all the patients had some costs, however there were non-positive zero out of pocket (15% patients) and private insurance (9% patients) prescription costs and non-positive zero out of pocket (7% patients) and private insurance (11% patients) office-based visit costs based on the patient's source of payment. The means were calculated separately for those who paid out of pocket completely and for those who paid using both the sources namely, by private insurance and by out of pocket.

These means were calculated by restricting the analyses to patients who were identified using new variables (indicating if they paid out of pocket entirely or by using both the sources). These means (out of pocket only, out of pocket when accompanied by private insurance and out of pocket and private insurance both) were compared using graphs. While calculating costs for office-based visits, only patients with psychotherapy as an office-based visit were included. Those who had general checkups and treatment as reasons for office-based visits were excluded so the costs obtained could be associated with psychotherapy alone. ANOVA approach was used to conduct unadjusted analyses and to assess if there is a difference in total mean costs across antidepressant classes. All the means calculated were weighted using PROC SURVEYMEANS. In order to conduct adjusted regression analyses, PROC GLM was used. The distribution of total cost was non-normal and it had unbalanced variances, generalized linear model was thus used to conduct the analyses. Adjusted costs were then calculated by exponentiating the parameter estimates obtained from the generalized linear model using the log link function. PROC GLM was also used to conduct regression analyses on costs paid out of pocket and by private insurance. The GLM model used for all the costs was as follows:

$$\hat{Y} = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Gender} + \beta_3 \cdot \text{Race} + \beta_4 \cdot \text{Marital Status} + \beta_5 \cdot \text{Education} + \beta_6 \cdot \text{Employment Status} + \beta_7 \cdot \text{Income} + \beta_8 \cdot \text{Overall Health Status} + \beta_9 \cdot \text{Comorbidities} + \beta_{10} \cdot \text{Number of comorbidities} + \beta_{11} \cdot \text{Antidepressant/Psychotherapy prescribed} + \epsilon^a$$

$\hat{Y}$ - Total prescription/ office-based visits/out of pocket/ private insurance costs

All the analyses were conducted at a significance level of 0.05. The hypothesis tested in this analysis was that the prescription and office-based visit costs would differ significantly across the groups. The analyses were conducted using SAS v9.4 and MS Excel 2016 was used to plot graphs.

## Section 4.2: Results

### Aim 2A: To compare the prescription medicines expenditures, overall costs and out of pocket expenses of cancer patients with comorbid depression across different classes of antidepressants

To assess the economic burden on cancer patients mainly because of depression, prescription and office-based visit costs were compared across different classes of antidepressants and psychotherapy. The results for mean prescription costs are summarized in Table 10.

**Table 10: Per fill total prescription costs across depression therapy classes**

Therapy Class	Sample Size	Mean (\$ per fill/purchase)	Std Error of Mean	95% CL for Mean	
SSRI	3,401	68.34	2.0812	64.23	72.44
MA*	1,098	79.84	5.0571	69.90	89.77
SNRI	730	132.28	6.5123	119.49	145.08
TCA	224	39.96	3.3478	33.39	46.52
Both	1,278	67.15	4.1117	66.94	93.10

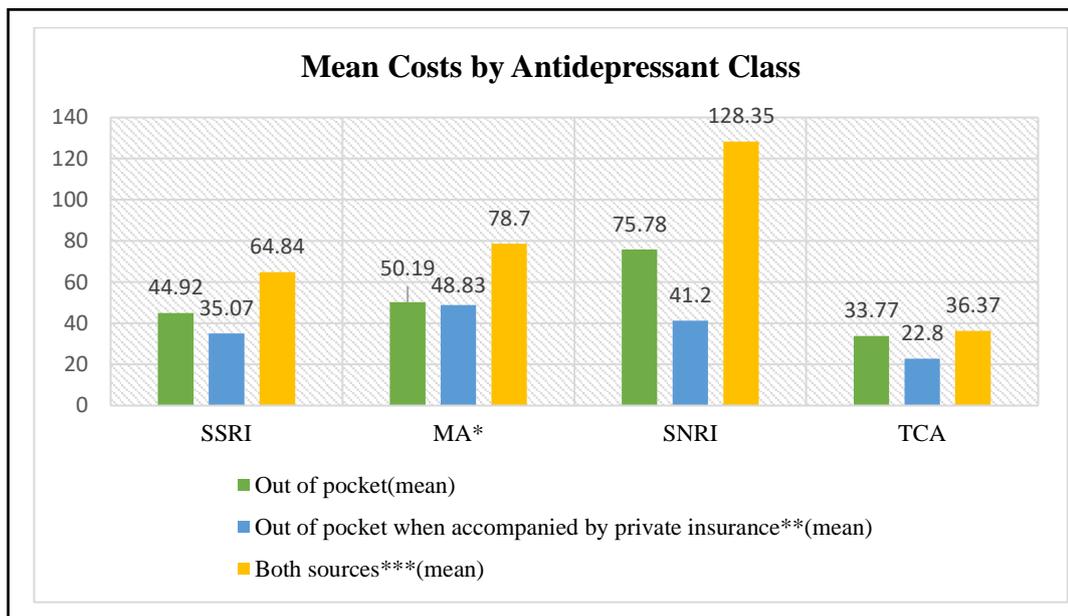
Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*- Miscellaneous Agents

Both – Antidepressant and psychotherapy

The prescription costs per purchase were the highest for SNRI (mean= \$132.28). These findings were consistent with the prices reported earlier where SNRI had the highest prices reported. ANOVA test suggested that the cost for SNRI and TCA differed significantly from each other and from all other classes at a p-value of 0.05. The source of payment for total costs were further studied across 4 major classes of antidepressants. Most of the share of total prescription cost was paid either completely out of pocket or by out of pocket and private insurance both. There were around 48.87%, 43.06%, 49.80%, 34.06% of patients receiving SSRI, miscellaneous agents, SNRI and TCA respectively who reported a combination of both out of pocket and private insurance as sources of patients. Around 19.29%, 13.71%, 13.25%, 17.90% patients receiving SSRI, miscellaneous agents, SNRI and TCA respectively reported

only out of pocket, others reported state and local government insurance, Tricare, Veterans insurance or other combinations. Around 6-6.5% patients in every group also reported using Medicaid as a source of payment, whereas there were very few reporting Medicare. The out of pocket mean values (mean of positive values, excluded the patients who had non-positive costs) for patients who paid entirely out of pocket, the mean share of out of pocket costs when accompanied by private insurance and the total mean costs for patients who paid entirely using out of pocket and private insurance both are summarized in Figure 8.



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\* - Miscellaneous Agents

\*\* The share of out of pocket costs when the source of payment was out of pocket and private insurance both

\*\*\* The total cost paid by private insurance and out of pocket

**Figure 8: Mean costs paid out of pocket and by private insurance across classes of antidepressants**

As seen from the findings above, all costs, except the share of out of pocket when accompanied by private insurance (highest for miscellaneous agents), were the highest for SNRI. The mean costs associated with both sources (out of pocket and private insurance) were similar to the means reported above in Table 10 since that was the source of payment in majority of patients in all the groups. As expected, the out of pocket costs were significantly lower when

a share was also paid by private insurance in the SSRI, SNRI and TCA groups, whereas it was almost the same in the miscellaneous agents group. These costs reported were mean costs without controlling for other factors. An adjusted regression analyses was then conducted using generalized linear models controlling for demographics and the overall health status. Regression results for total costs paid by the patients across classes of antidepressants using generalized linear models are summarized in Table 11.

**Table 11: Regression results for total prescription costs**

<b>Predictors</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>p-value</b>
<b>Intercept*</b>	62.20582066	24.7190825	2.52	0.0119
<b>Age Groups</b>				
18-44 years	-6.92739417	3.6807988	-1.88	0.0599
>65 years	-3.65931933	5.0099021	-0.73	0.4652
45-65 years	-	-	-	-
<b>Gender*</b>				
Males	12.30309422	3.3529060	3.67	0.0002
Females	-	-	-	-
<b>Race</b>				
Blacks	3.71937511	4.5828044	0.81	0.4171
Asians	-11.28274071	13.6726905	-0.83	0.4093
Multiple races	-11.17445652	9.6305885	-1.16	0.2460
Whites	-	-	-	-
<b>Marital Status</b>				
Widowed	0.36601644	5.8745367	0.06	0.9503
Divorced	-9.18654975	4.1045221	-2.24	0.0252
Separated	0.83341885	7.5886217	0.11	0.9126
Never married	5.89124176	4.2672297	1.38	0.1675
Married	-	-	-	-

<b>Education*</b>				
No education	-22.67872928	21.1740225	-1.07	0.2842
Elem/Mid School	-16.34956478	6.0321145	-2.71	0.0067
High school	-3.19607752	3.4618290	-0.92	0.3559
5+ years college	5.30329548	6.2251900	0.85	0.3943
≤4 years college	-	-	-	-
<b>Employment Status</b>				
Employed	-6.29026083	3.8528733	-1.63	0.1026
Unemployed	-	-	-	-
<b>Income<sup>a</sup></b>				
Low	-3.13492511	4.8804709	-0.64	0.0599
High	9.10056345	4.9352345	1.84	0.0652
Middle class	-	-	-	-
<b>Overall Health Status</b>				
Excellent	-1.37070499	8.2432892	-1.62	0.1048
Very good	-10.32440132	6.2116093	-1.66	0.0965
Good	0.42975078	5.6753561	1.49	0.1375
Fair	-7.40559351	5.6348821	-1.31	0.1888
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	2.25400711	5.1539475	0.44	0.6619
Arthritis	-11.31680318	3.9533362	-0.33	0.7391
Diabetes	-8.40233433	8.4895345	-0.99	0.3223
High blood pressure	-9.85627442	5.6943373	-1.73	0.0835
None	-	-	-	-
<b>Number of Comorbidities</b>				
2	15.64873631	13.0680208	0.43	0.6656
≥ 3	-	-	-	-
<b>Antidepressant/Psychotherapy*</b>				
SSRI	27.82665706	19.8866508	1.40	0.1618
MA**	30.76547665	20.6221038	1.49	0.1358
SNRI	63.21644585	20.7578952	3.05	0.0023

TCA	-6.33866732	23.2797759	-0.27	0.7854
Both***	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants MA\*\* - Miscellaneous Agents, Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

Thus, as seen from the regression results, the total mean costs per prescription increases when SSRI, miscellaneous agent or SNRI is prescribed as compared to both (antidepressant and psychotherapy) being prescribed. These findings are consistent with the mean of total prescription costs reported above in table 10 where the means for SSRI, miscellaneous agents and SNRI are higher than the mean when both the therapies are prescribed. The total adjusted mean costs per prescription are summarized in Table 12, and these were the highest for SNRI (\$112.92). On regressing the costs paid out of pocket against the predictors, these increased for SSRI and SNRI whereas decreased for TCA and miscellaneous agents as compared to those who were prescribed both the therapies. On regressing the costs paid by private insurance against the predictors, these increased for all the classes of antidepressants as compared to both the therapies being prescribed. These results are summarized in Appendix Tables 2 and 3.

**Table 12: Adjusted per fill total prescription costs across depression therapy classes**

Therapy Class	Sample Size	Mean (\$ per fill/purchase)	Std Error of Mean	95% CL for Mean	
SSRI	3,397	77.06	0.332020	76.409347	77.714610
MA*	1,072	80.84	0.724687	79.419274	82.268223
SNRI	713	112.92	0.722216	111.502743	114.341979
TCA	217	44.31	1.366258	41.628754	46.999902
Both	1,139	51.35	1.644457	48.122168	54.586994

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants MA\*- Miscellaneous Agents Both – Antidepressant and psychotherapy

**Aim 2B: To compare office-based visits along with the expenses related to these across cancer patients with comorbid depression classified based on the class of antidepressants**

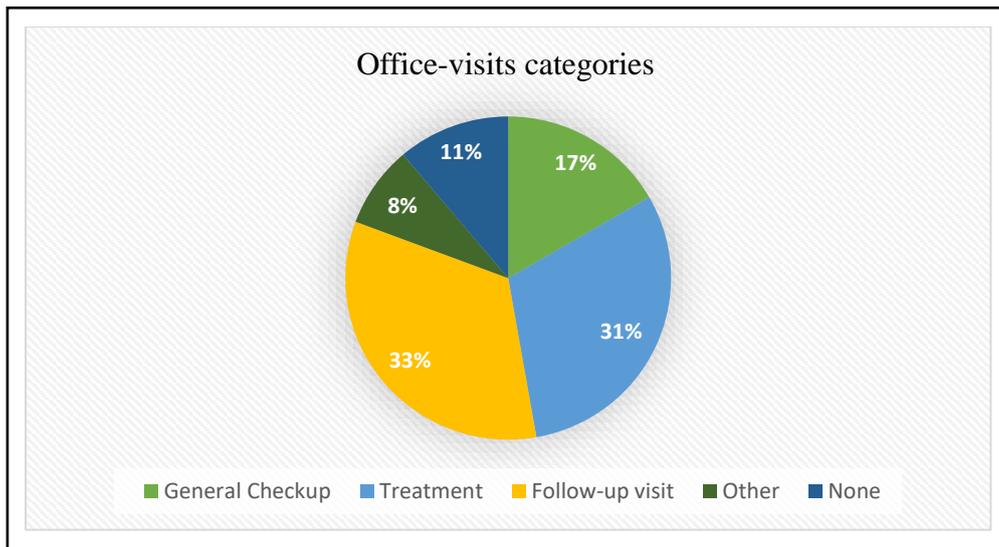
Office-based visits are more common in cancer patients since they have more frequent general checkups and require psychotherapy or mental health counseling more often than those who do not have cancer. In this study, out of all the office-based visits, psychotherapy/ mental counseling and the costs related to these were studied in depth, since these are used frequently to manage depression amongst cancer patients. These costs were studied across different classes of antidepressants and those receiving psychotherapy alone. Table 6 above, summarizes the number of patients using psychotherapy along with antidepressant, which suggests that 47.39% (n=1282) of patients using psychotherapy use it along with an antidepressant whereas 52.60 % (n=1423) use it alone. Table 13 below summarizes the total number of office-based visits across class of antidepressants including psychotherapy the other categories.

**Table 13: Office-based visit category by class of antidepressant**

<b>Visit category</b>	<b>SSRI (n, %)</b>	<b>MA* (n, %)</b>	<b>SNRI (n, %)</b>	<b>TCA (n, %)</b>
General checkup	1,338 (31.97)	399 (27.74)	265 (27.31)	79 (29.15)
Treatment	1,881 (44.95)	621 (43.18)	453 (46.70)	137 (50.55)
Psychotherapy	733 (17.51)	338 (23.50)	182 (18.76)	29 (10.70)
Other	232 (5.54)	80 (5.56)	70 (7.21)	26 (9.5)
<b>Total</b>	<b>4,184 (100%)</b>	<b>1,438 (100%)</b>	<b>970 (100%)</b>	<b>271 (100%)</b>

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\* - Miscellaneous Agents

Miscellaneous agents thus had the highest percentage of patients reporting the use of psychotherapy/counseling in order to manage depression. General checkups, treatment purposes (which could either be receiving any treatment or discussing the options) and psychotherapy were the major reasons for office-based visits amongst cancer patients with depression. The other visit categories for patients receiving psychotherapy alone are reported in Figure 9.



\*Percentages calculated are over n=1423 (sample size for psychotherapy alone)

**Figure 9: Classification of office-based visits for those receiving psychotherapy alone**

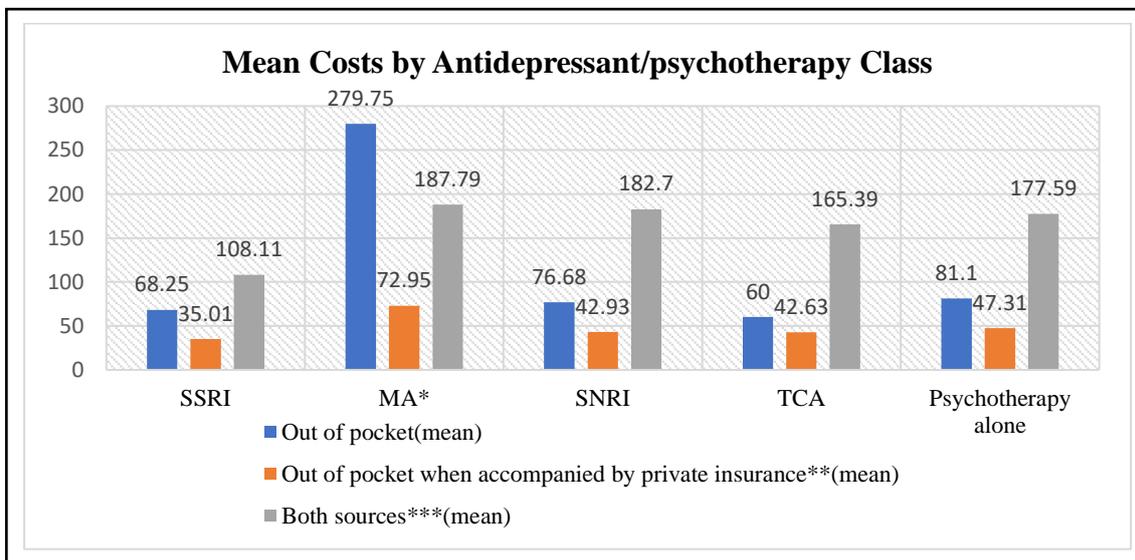
As seen from the figure above, patients receiving psychotherapy alone, also had some other office-based visits, majority of which were either for treatment or follow-up purposes. There were around 11% (n=159) patients who did not report any office-based visit other than that for psychotherapy/mental health counseling. The study sample was then restricted to patients receiving psychotherapy as an office visit only so the costs could be associated mainly with psychotherapy and reduce bias due to costs associated with other categories of visits. The total costs associated mainly with psychotherapy/counseling across the classes of antidepressants and with psychotherapy alone are reported in Table 14.

**Table 14: Total mean costs associated per visit across class of antidepressants and psychotherapy alone**

Combination with psychotherapy	Sample size	Mean (\$/visit)	Std Error of Mean	95% CL for Mean	
SSRI	713	121.42	4.8781	111.81	131.04
MA*	254	156.15	18.3303	120.03	192.28
SNRI	131	139.63	15.8467	108.40	170.87
TCA	19	131.25	36.6650	58.99	203.51
Psychotherapy alone	626	147.40	16.2409	115.33	179.48

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\*-Miscellaneous Agents

These costs did not differ significantly from each other. However, miscellaneous agents had a slightly higher cost associated with the visit followed by psychotherapy alone. Most of the share of total office-based visit costs was paid either completely out of pocket or by out of pocket and private insurance both. There were around 39.55%, 33.85%, 44.27%, 31.58% and 36.58% patients receiving SSRI, miscellaneous agents, SNRI, TCA and psychotherapy alone respectively who reported a combination of out of pocket and private insurance as sources of payment. Around 8.97%, 5.11%, 6.62%, 5.26% and 13.26% patients receiving SSRI, miscellaneous agents, SNRI, TCA and psychotherapy alone respectively reported only out of pocket, others reported state and local government insurance, Tricare, Veterans insurance or other combinations. Medicare/ Medicaid was not reported as a source of payment for psychotherapy/ counseling visits by any of the patients. The mean values (mean of positive values, excluded the patients who had non-positive costs) paid by private insurance, out of pocket and by private insurance and out of pocket both are summarized in Figure 10.



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI - Serotonin-Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* - Miscellaneous Agents

\*\* The share of out of pocket costs when the source of payment was out of pocket and private insurance both

\*\*\* The total cost paid by private insurance and out of pocket

**Figure 10: Mean costs paid out of pocket and by private insurance across classes of antidepressants/psychotherapy**

As seen from the findings above, on excluding the non-positive values, the means (both sources) for certain classes of antidepressants were slightly higher than the total mean costs reported in Table 14. All the mean costs for office-based visits were higher for those receiving miscellaneous agents. This was consistent with the findings above, where the total mean costs were the highest for miscellaneous agents. The mean cost for those paying entirely out of pocket were considerably higher for those receiving miscellaneous agents (mean = \$279.75 per visit). As expected, the out of pocket costs significantly reduced in all the groups when accompanied by private insurance. Since, out of pocket and private insurance were the major sources of payment in most of the population, the trends observed for mean costs (both sources) were similar to that obtained for total mean costs with SSRI being associated with the lowest cost and miscellaneous agents being associated with the highest costs.

Regression was conducted using total costs per visit as the outcome variable and regressing against the predictors including the demographic variables, overall health status, number and type of comorbidities. On adjusting for other factors, the class of antidepressant was not significantly associated with the visit cost. These results were similar to the unadjusted results where the cost differences were not significant across the depression therapy classes. The costs however numerically reduced the most for SSRI (estimate = -54.73, p-value = 0.0171) followed by miscellaneous agents (estimate = -25.21, p-value = 0.4075), SNRI (estimate = -11.41, p-value = 0.7461) and TCA (estimate = -0.96, p-value = 0.9895) as compared to psychotherapy alone, which was consistent with the unadjusted mean costs, where the unadjusted costs associated with psychotherapy alone were higher than the other classes. These results are summarized in Appendix Table 4. Table 15 below summarizes the adjusted costs for office-based visits, mainly psychotherapy.

**Table 15: Adjusted total mean costs associated per visit across class of antidepressants and psychotherapy alone**

Combination with psychotherapy	Sample size	Mean (\$/visit)	Std Error of Mean	95% CL for Mean	
SSRI	707	110.28	2.730	104.34	116.23
MA*	247	139.42	5.778	126.83	152.01
SNRI	129	141.20	5.755	128.66	153.74
TCA	19	165.84	17.263	128.23	203.45
Psychotherapy alone	619	166.39	3.488	144.79	169.92

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\*-Miscellaneous Agents

On controlling for other factors, the costs associated were the highest for those who received psychotherapy alone where as they were lowest for those receiving SSRI. The trends seen in these adjusted costs were thus different on controlling for other factors.

### **Section 4.3: Discussion**

It was seen from the results that the total mean prescription costs associated per month were the lowest for TCA and the highest for SNRI. The findings of SNRI being associated with highest costs were consistent with the prices reported earlier under ‘Introduction’, where SNRI had highest out of pocket price for 30 tablets.<sup>23</sup> In addition, a study conducted by Khandker et al. also suggested that the patients who switched from an SNRI to SSRI eventually had lower pharmacy and medical costs.<sup>50</sup> This study also suggested that, switching classes of antidepressants was rare and patients who made a switch had higher all-cause healthcare costs and higher depression-related costs. This study was however conducted in non-cancer patients.<sup>50</sup> In our study, the total mean adjusted prescription costs were higher when SSRI, miscellaneous agents or SNRI was prescribed as compared to prescribing any antidepressant along with psychotherapy. These results were consistent with the unadjusted analyses findings, where the costs of the above-mentioned classes were higher than that when accompanied by psychotherapy. These findings were in contrast to that obtained in a study conducted by Shen et al.<sup>51</sup> and Alwhaibi et al.,<sup>25</sup> where in, the costs associated with psychotherapy along with antidepressant or alone were higher than that associated with only antidepressant use. However, these were total expenditures per patient and not just prescription costs, also these studies were either restricted to a specific type of cancer<sup>25</sup> or were not in cancer population at all.<sup>51</sup> In our study, it was also observed that most patients reported a combination of private insurance and out of pocket both as sources of payment for prescription medicines. Some also reported Medicaid or out of pocket entirely as a source of payment. There have not been any studies prior to this looking at sources of payment for depression therapies amongst cancer patients with depression. However, American Cancer Society suggests that, most of the cancer patients report private insurance as their source of payment (44%) for the total costs that are incurred during the cancer treatment.<sup>5</sup> A study conducted by Iadeluca et al. also suggested that prescription

medications and office-based visits were the main cost drivers in their cancer population, however they were looking at cancer in general and not depression specifically.<sup>32</sup>

With respect to costs associated with office-based visits mainly psychotherapy, it was observed that miscellaneous agents had slightly higher unadjusted costs of these visits compared to other classes and psychotherapy alone. Miscellaneous agents also had the highest percentage of patients within this group requiring psychotherapy. The adjusted costs were the highest for those receiving psychotherapy only without any antidepressant, these findings were similar to the results of a study conducted by Alwhaibi et al.,<sup>25</sup> where psychotherapy higher associated costs as compared to antidepressants only. These costs for psychotherapy visits could differ slightly because of the type of credentials the therapist has, the cost of running the office, the type of practice (community mental health or private practice) or the services offered during these visits and the intensities of these.<sup>52</sup> These visit costs were paid by a combination of private insurance and out of pocket both by most of the patients. Medicare/ Medicaid was not reported as a source of payment. There have not been any studies conducted yet looking at costs associated with office-based visits mainly psychotherapy. The results were consistent with a study conducted by Chung which suggested that utilization of SSRI led to a reduction in overall outpatient visits and other prescription drugs however, this study was not restricted to cancer patients and the comparison group consisted of people only taking TCA.<sup>53</sup> There have however not been any studies comparing office-based visit costs across classes of antidepressants/ psychotherapy amongst cancer patients with depression.

Our study however, has certain limitations. In addition to the limitations stated above, certain cost specific limitations were identified. Firstly, the prescription costs associated could not be restricted completely to antidepressants only. The patients were also taking some other medicines such as painkillers, blood pressure or cholesterol medications; however, these were minimum and evenly spread across all the classes. Secondly, the prescription costs were

associated per purchase/fills per month. However, MEPS does not capture the number of fills associated per person in a month. The total costs thus per month could differ based on the number of fills that were associated with patients taking any particular medication. Thirdly, when office-based visit costs were compared, these could differ based on the therapist charges, which is subjective and could not be controlled for in the study. Finally, since the study was not prospective, any further changes in the therapy and thus the cost could not be tracked.

Despite the limitations mentioned above, the study has a lot of significance. None of the studies conducted prior with respect to depression amongst cancer patients have looked at costs associated with individual therapies. This study thus adds to the literature. There have been cost effective analysis studies of certain non-pharmacotherapy interventions such as telecare, home care, inpatient care and psycho-educational interventions; however, none of them have compared classes of antidepressants along with psychotherapy.<sup>33,34</sup> There have also been studies looking at total expenditure in cancer patients with no depression treatment versus only antidepressants versus only psychotherapy however, these have not looked at prescription costs separately or compared costs across classes of antidepressants separately.<sup>24</sup> In addition, the population in some of these studies was restricted only to specific types of cancer. There have also been no studies looking at office-based visit utilization and the costs associated with these across classes of antidepressants. This study is thus novel in producing such findings and forms the basis for future studies to be conducted with respect to cost comparisons. Total healthcare costs could be studied across classes of antidepressants. Conducting future studies addressing the limitations above would produce more robust results which could help in guiding formulary or coverage decisions based on the cost findings.

## **CHAPTER V: SPECIFIC AIM III**

**Aim 3: To compare quality of life (QOL) of cancer patients in the US with comorbid depression across different classes of antidepressants and psychotherapy**

A: To compare the physical and mental component score (PCS/MCS) across different classes in order to assess quality of life of cancer patients with comorbid depression

B: To compare Patient Health Questionnaire – 2 (PHQ-2) scores and the frequency of depression obtained from Short Form version 12 (SF-12) to assess quality of life of cancer patients with comorbid depression

### **Section 5.1: Methods**

#### **Data Source and Study Design:**

As mentioned earlier, it was a cross-sectional retrospective study conducted using MEPS. For this aim, office-based visit files were needed for identifying psychotherapy visits. All the main outcome variables were captured from the full year consolidated files. Prescription medicine files were used to identify patients in each class of antidepressant. The sample size was same as the first two aims with 17,671 patients diagnosed with cancer along with a comorbid depression condition.

#### **Variables:**

##### **Demographics and controlling factors:**

Similar to aim 2, age, gender, race, marital status, education, employment status and income were the demographic factors, overall health status (from SF-12 SAQ), comorbidities and number of comorbidities were the variables that were controlled for in the study. All these variables were obtained from full year consolidated files.

### Quality of life variables:

All quality of life variables were obtained from the full year consolidated files. Physical and Mental Component Scores (PCS and MCS) are the continuous variables captured by MEPS using SF-12 SAQ. The SF-12 measures eight constructs: physical functioning, role limitations resulting from physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitation resulting from emotional problems, and mental health. MEPS imputes these into physical and mental domains and rescales the scores with a maximum average of 50.<sup>28</sup> A higher physical/mental score indicates a better functioning and thus a better quality of life. MCS is mainly indicative of depression and mental health, however both the scores were used for this study's purposes. PCS/MCS are mainly indicative of Health Related QOL (HrQOL). These scores were compared across different classes of antidepressants and psychotherapy, the scores across the combinations of antidepressants identified in aim 1 were compared too. For aim 3b, PHQ-2 scores were used to assess quality of life. These were obtained from the patient health questionnaire. The PHQ-2 is made up of 2 items and the scores range from 0 to 6. A higher PHQ-2 score indicates a greater tendency towards depression. A lower score thus implies lower depression and hence a better quality of life. A categorical variable indicating the frequency of depression in a week was used too. This variable has 4 levels for the frequency namely: "0-Not at all", "1-Several Days", "2-More Than Half The Days" and "3-Nearly Every Day". This variable was a part of SF-12 Self-Assessment Questionnaire – 2 weeks (SAQ-2 Wks). The PHQ-2 scores and frequency of patients belonging to each category of depression frequency were compared across different classes of antidepressants, psychotherapy and combinations of antidepressants.

### **Statistical Analyses:**

Means were used to summarize the PCS, MCS and PHQ-2 scores. Frequencies/proportions were used to identify the percentages of patients in each of the categories for the depression frequency variable across the classes of antidepressants. The mean scores were

compared across individual classes, psychotherapy alone and combinations of antidepressants. The unadjusted comparison was conducted using PROC ANOVA. In order to compare the QOL outcomes of combinations of antidepressants against the individual classes, means were calculated for each group. A mean PCS/MCS/PHQ-2 score was calculated for those using any combination of antidepressants and this was compared against the mean score of those using individual classes using t-test. All these means were weighted and calculated using PROC SURVEYMEANS. Since, the scores had a normal distribution, PROC SURVEYREG was used to conduct adjusted regression analyses on PCS and MCS and PHQ-2 scores. The mean PHQ-2 scores were also compared using graphs. The model used for regression was as follows:

$$\hat{Y} = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Gender} + \beta_3 \cdot \text{Race} + \beta_4 \cdot \text{Marital Status} + \beta_5 \cdot \text{Education} + \beta_6 \cdot \text{Employment Status} + \beta_7 \cdot \text{Income} + \beta_8 \cdot \text{Overall Health Status} + \beta_9 \cdot \text{Comorbidities} + \beta_{10} \cdot \text{Number of comorbidities} + \beta_{11} \cdot \text{Antidepressant/Psychotherapy prescribed} + \epsilon^a$$

$\hat{Y}$ - PCS/MCS/PHQ-2 Score

The categorical variable for depression frequency was compared using chi-square test obtained from PROC SURVEYFREQ. Adjusted analyses was carried on the same using PROC SURVEYLOGISTIC, by using the multinomial regression approach. The model was as follows:

$$\text{Logit}(y=a^*) = \log \left\{ \frac{p(y=a^*)}{1-p(y=a^*)} \right\} = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Gender} + \beta_3 \cdot \text{Race} + \beta_4 \cdot \text{Marital Status} + \beta_5 \cdot \text{Education} + \beta_6 \cdot \text{Employment Status} + \beta_7 \cdot \text{Income} + \beta_8 \cdot \text{Overall Health Status} + \beta_9 \cdot \text{Comorbidities} + \beta_{10} \cdot \text{Number of comorbidities} + \beta_{11} \cdot \text{Antidepressant/Psychotherapy prescribed} + \epsilon^a$$

\*-Depression frequency either not at all, several days or more than half the days (Reference – Nearly every day), a-Error Term

All of the analyses were conducted first on individual therapy classes and later on combinations of antidepressants. The analyses were conducted on a patient-level file obtained by summarizing the scores from an events-level file. All the analyses were conducted at a significance level of 0.05. The hypothesis tested in this analysis was that the QOL scores and depression frequency would differ significantly across the groups. SAS v9.4 was used to conduct the analyses and MS Excel 2016 was used for plotting graphs.

## Section 5.2: Results

**Aim 3A: To compare the physical and mental component score (PCS/MCS) across different classes in order to assess quality of life of cancer patients with comorbid depression**

Quality of life of patients was compared across different class of antidepressants/psychotherapy and combinations of antidepressants using physical and mental component scores (PCS and MCS). The mean PCS and MCS associated with each class are summarized in Tables 16 and 17 respectively.

**Table 16: Mean PCS across therapy class**

Therapy class	Sample size	Mean PCS	Std Error of Mean	95% CL for Mean PCS	
No therapy	9,480	38.58	0.2129	38.16	39.03
SSRI	3,404	41.18	0.4470	40.30	42.06
MA*	1,099	40.76	0.6899	39.39	42.13
SNRI	730	41.13	0.7769	39.44	42.82
TCA	224	38.68	1.0769	38.66	39.44
Psychotherapy	1,423	36.77	0.8525	35.72	37.93
Both**	1,271	35.87	0.8333	34.56	36.78

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\* - Miscellaneous Agents

Both\*\* - Antidepressant and psychotherapy

A higher score indicates a higher QOL

**Table 17: Mean MCS across therapy class**

Therapy class	Sample Size	Mean MCS	Std Error of Mean	95% CL for Mean MCS	
No therapy	9,480	37.36	0.2126	36.94	37.77
SSRI	3,404	37.51	0.4195	36.69	38.34
MA*	1,099	36.76	0.6438	35.48	38.04
SNRI	730	38.16	0.7083	36.61	39.70
TCA	224	38.59	1.3822	36.81	39.42
Psychotherapy	1,423	31.64	0.8737	30.87	32.35
Both**	1,271	29.62	0.9095	27.21	31.34

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\* - Miscellaneous Agents

Both\*\* - Antidepressant and psychotherapy

A higher score indicates a higher QOL

The above unadjusted analyses suggested that, a higher mean PCS was obtained with SSRI, miscellaneous agents and SNRI. On comparing MCS, it was seen that a higher score was associated with SNRI and TCA. The PCS scores associated with psychotherapy with or without an antidepressant were even lower than no therapy at all. Similar results were obtained for mean MCS scores, along with miscellaneous agents also having a score below no therapy at all. On conducting unadjusted analyses using the ANOVA test, it was found that PCS and MCS for some groups differed significantly from the others. These significant ANOVA results for PCS and MCS are summarized in Appendix Figures 1 and 2 and Tables 5 and 6 respectively. Adjusted regression analyses was conducted controlling for demographic factors, their health status in general and comorbidities associated. These results are summarized in Tables 18 and 19.

**Table 18: Regression results for PCS across depression therapy classes**

<b>Predictors</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t value</b>	<b>p-value</b>
<b>Intercept*</b>	23.728416	0.93900531	25.27	<.0001
<b>Age Groups*</b>				
18-44 years	3.874257	0.31629756	11.78	<.0001
>65 years	-1.815827	0.42259368	-4.30	<.0001
45-65 years	-	-	-	-
<b>Gender</b>				
Males	0.278189	0.25408081	1.09	0.2742
Females	-	-	-	-
<b>Race</b>				
Blacks	0.099802	0.33801221	0.30	0.7679
Asians	1.559674	1.01718881	1.53	0.1259
Multiple races	-0.069454	0.59215191	-0.12	0.9067
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	-0.504700	0.45096851	-1.12	0.2637
Divorced	-0.294626	0.33787106	-0.87	0.3837
Separated	1.250402	0.82722660	1.51	0.1314
Never married	1.449368	0.31241265	4.64	<.0001
Married	-	-	-	-

<b>Education</b>				
No education	1.373198	1.07486621	1.28	0.2021
School	0.408673	0.55035149	0.74	0.4582
High school	-0.228869	0.27561317	-0.83	0.4068
5+ years college	0.623551	0.44813450	1.39	0.1648
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	3.891197	0.32932964	11.82	<.0001
Unemployed	-	-	-	-
<b>Income <sup>a</sup></b>				
Low	0.533477	0.36957637	1.44	0.1496
High	0.001782	0.37378312	0.01	0.9962
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	27.793365	0.56299920	49.37	<.0001
Very good	25.297794	0.47079079	53.73	<.0001
Good	19.034358	0.42691104	44.59	<.0001
Fair	8.211462	0.43952025	18.68	<.0001
Poor	-	-	-	-
<b>Comorbidities*</b>				
Asthma	-2.231539	0.44603500	-5.00	<.0001
Arthritis	-3.056831	0.34306491	-8.91	<.0001
Diabetes	1.611439	0.56801676	2.84	0.0048
High blood pressure	0.917330	0.44432410	2.06	0.0396
None	-	-	-	-
<b>Number of Comorbidities</b>				
2	0.677611	1.05998349	0.64	0.5230
≥ 3	-	-	-	-
<b>Antidepressant/Psychotherapy*</b>				
SSRI	2.297618	0.40744707	5.64	<.0001
MA**	2.243898	1.10656492	2.03	0.0432
SNRI	1.868457	0.62967328	2.97	0.0032
TCA	-0.280224	1.13371517	-0.25	0.8049
Psychotherapy	2.391769	1.34158557	1.78	0.0753
Both***	3.832430	1.54504948	2.48	0.0135
No therapy	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

**Table 19: Regression results for MCS across depression therapy classes**

<b>Predictors</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t value</b>	<b>p-value</b>
<b>Intercept*</b>	33.957960	1.43596729	23.65	<.0001
<b>Age Groups*</b>				
18-44 years	-2.067972	0.37344141	-5.54	<.0001
>65 years	2.921289	0.54958779	5.32	<.0001
45-65 years	-	-	-	-
<b>Gender</b>				
Males	-0.174395	0.35127254	-0.50	0.6198
Females	-	-	-	-
<b>Race</b>				
Blacks	0.798348	0.46221061	1.73	0.0849
Asians	-0.472144	1.27060925	-0.37	0.7104
Multiple races	0.732625	1.01384428	0.72	0.4703
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	-0.776112	0.63059156	-1.23	0.2191
Divorced	-1.542013	0.43718346	-3.53	0.0005
Separated	-1.725167	0.89000522	-1.94	0.0532
Never married	-2.621354	0.43058545	-6.09	<.0001
Married	-	-	-	-
<b>Education</b>				
No education	-0.450708	1.53321560	-0.29	0.7689
School	-0.138705	0.65117050	-0.21	0.8314
High school	-0.103938	0.34966929	-0.30	0.7664
5+ years college	0.621971	0.58552212	1.06	0.2887
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	1.638000	0.41961254	3.90	0.0001
Unemployed	-	-	-	-
<b>Income <sup>a</sup></b>				
Low	-0.303451	0.50914415	-0.60	0.5515
High	0.853695	0.50874153	1.68	0.0941
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	18.478604	0.76617114	24.12	<.0001
Very good	14.931983	0.64048127	23.31	<.0001
Good	11.666374	0.59302916	19.67	<.0001
Fair	6.477895	0.59607520	10.87	<.0001
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	0.434419	0.52272693	0.83	0.4064
Arthritis	0.226897	0.42508743	0.53	0.5938
Diabetes	1.673379	0.75773470	2.21	0.0278
High blood pressure	0.450593	0.65983624	0.68	0.4951
None	-	-	-	-

<b>Number of Comorbidities</b>				
2	1.558807	0.16183439	9.63	0.7764
≥ 3	-	-	-	-
<b>Antidepressant/Psychotherapy*</b>				
SSRI	-0.671898	0.57012753	-1.18	0.0259
MA**	-1.574317	1.08475602	-1.45	0.0036
SNRI	-3.037997	1.13809892	-2.67	0.0003
TCA	-2.064295	1.89204826	-1.09	0.3955
Psychotherapy	-0.409942	1.68289385	-0.24	0.2292
Both***	-1.178011	1.91372016	-0.62	0.0004
No therapy	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

The depression therapy class was significantly associated with PCS and MCS. It was observed that except TCA, PCS was higher when any kind of antidepressant/ psychotherapy was prescribed compared to no therapy. With MCS, it was observed that none of the antidepressants/ psychotherapy led to an increase in MCS as compared to no therapy at all.

PCS and MCS were now compared across combinations of antidepressants identified in aim 1A. The findings of mean PCS and MCS across these combinations are summarized in Tables 20 and 21.

**Table 20: Mean PCS across combination of antidepressants**

<b>Combinations</b>	<b>Sample size</b>	<b>Mean</b>	<b>Std Error of Mean</b>	<b>95% CL for Mean</b>	
SSRI-MA*	179	40.94	1.9131	37.18	44.70
SNRI-MA*	47	40.27	4.0428	32.32	48.22
SSRI-SNRI	42	44.25	3.2391	37.89	50.62
SSRI-TCA	34	37.52	2.6088	32.39	42.65
Other Combinations	16	42.27	5.84	30.31	53.62

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*-Miscellaneous Agents

A higher score indicates a higher QOL

**Table 21: Mean MCS across combination of antidepressants**

<b>Combination of antidepressants</b>	<b>Sample size</b>	<b>Mean</b>	<b>Std Error of Mean</b>	<b>95% CL for Mean</b>	
SSRI-MA*	179	35.74	1.6074	32.58	38.90
SNRI-MA*	47	37.28	3.8294	29.75	44.81
SSRI-SNRI	42	36.25	2.7947	30.76	41.74
SSRI-TCA	34	40.65	2.7440	35.25	46.04
Other Combinations	16	32.89	5.51	22.52	43.35

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

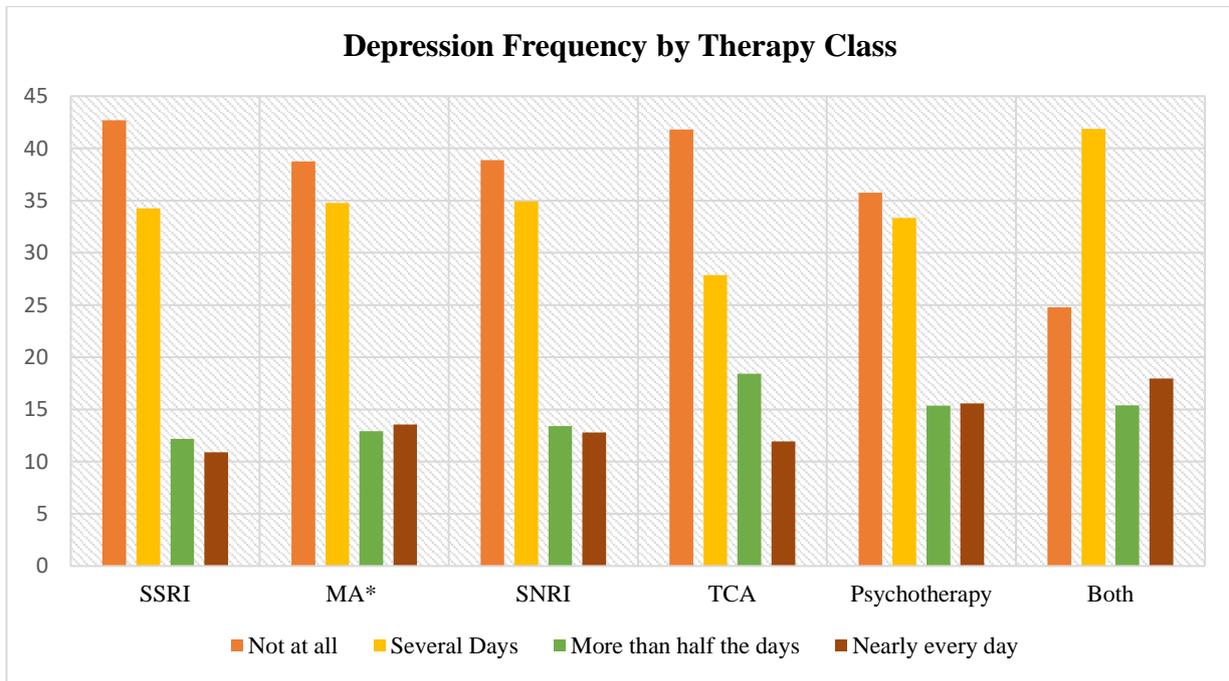
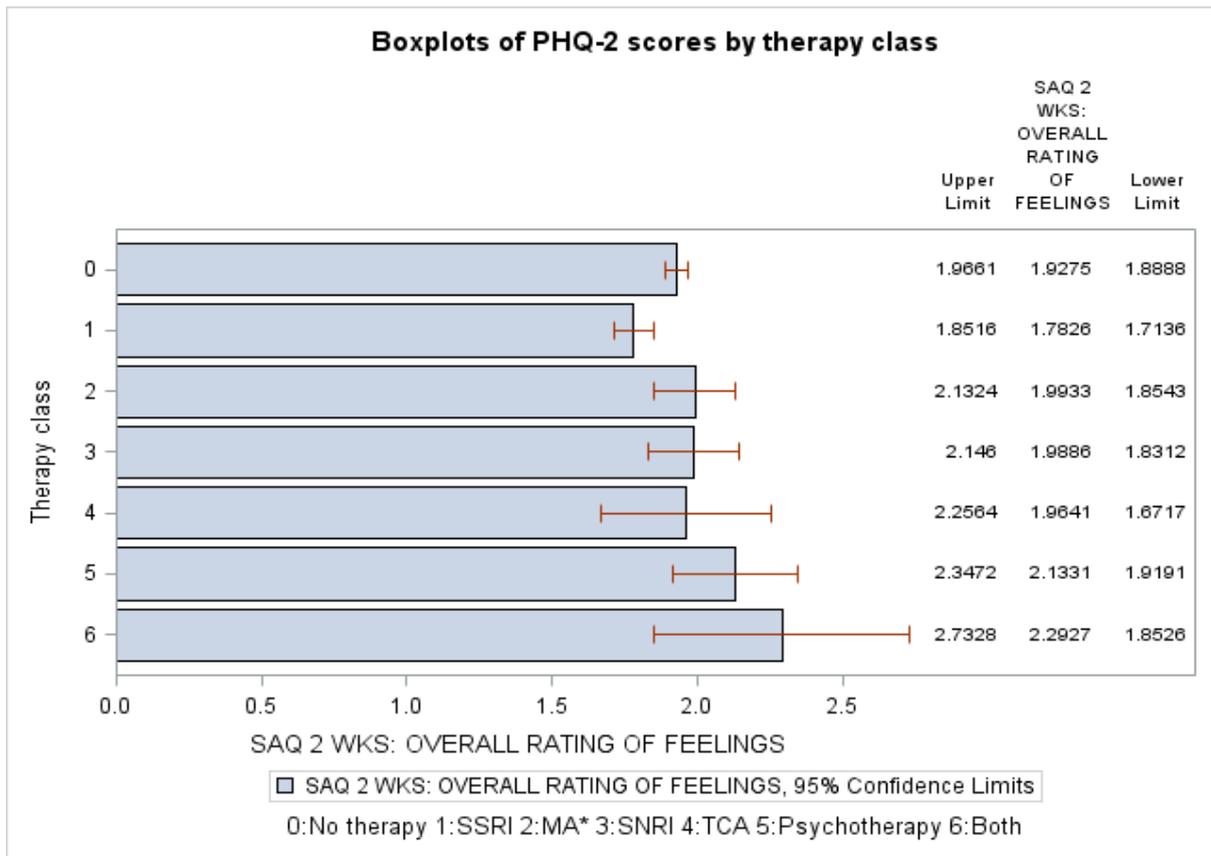
MA\*-Miscellaneous Agents

A higher score indicates a higher QOL

The findings suggest that, the PCS and MCS both were higher when antidepressants were given in combination as compared to given individually. The mean PCS was highest when SSRI was given in combination with SNRI, whereas the MCS was highest when SSRI was given in combination with TCA. On comparing the PCS and MCS of those who were on individual therapies to those who were using combinations of antidepressants, these mean scores were significantly higher for those who were on combinations of antidepressants at a p-value of 0.0352 and 0.0417 for PCS and MCS respectively. Quality of life, when measured using PCS and MCS was higher when SSRI was given in combination with either SNRI or TCA. However, the differences in PCS and MCS were not significant in unadjusted analyses conducted using the ANOVA test. Adjusted analyses was carried similarly for combinations and the results obtained suggested that, PCS increased with all the combinations as compared to getting no combination prescribed, the maximum increase in PCS was when SSRI was prescribed with a miscellaneous agent (estimate=2.47, p-value=0.0182). MCS increases only when SSRI-TCA (estimate=2.2, p-value=0.45) was the combination prescribed as compared to getting no combination prescribed. The combination of antidepressants was significantly associated with the PCS whereas it was associated with the MCS at the significance level of 0.1. These regression results are summarized in Appendix Tables 7 and 8.

**Aim 3B: To compare Patient Health Questionnaire – 2 (PHQ-2) scores and the frequency of depression obtained from Short Form version 12 (SF-12) to assess quality of life of cancer patients with comorbid depression**

In order to compare quality of life of patients across classes of antidepressants and psychotherapy, PHQ-2 scores and a categorical variable indicating depression frequency from the SF version 12 were used. Mean PHQ-2 scores across the depression therapy classes and proportions of patients belonging to each category of depression frequency across the classes are summarized in Figure 11. SSRI were associated with the lowest PHQ-2 scores (mean = 1.7826) indicating lesser tendency towards depression. The frequency of feeling depressed was the lowest with SSRI too (highest percentage of patients reporting “Not at all” – 42%). Patients receiving antidepressant and psychotherapy both had the highest PHQ-2 scores (mean = 2.29) and highest percentage (17.94%) of patients reporting “Nearly every day” for depression frequency. These findings thus suggest that, the highest quality of life and lowest tendency towards depression is associated with SSRI and the highest tendency towards depression when antidepressant is given along with psychotherapy. These unadjusted findings are summarized in figure 11. On conducting ANOVA test for PHQ-2 scores, SSRI scores differed significantly from psychotherapy and no therapy both. These significant results are summarized in Appendix Figure 3 and Appendix Table 9. Unadjusted analyses carried out for depression frequency using chi square was significant at a p-value of 0.0056. Adjusted regression analyses was thus conducted on PHQ scores (surveyreg), these results are summarized in Table 22, and depression frequency (multinomial logistic regression) these results are summarized in Table 23. Multinomial logistic regression was conducted using “3: Nearly every day” as the reference group for the outcome variable.



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* - Miscellaneous Agents  
 Both – Antidepressants and Psychotherapy

A higher PHQ-2 score indicates higher tendency towards depression

**Figure 11 – Mean PHQ-2 scores and depression frequency across therapy class**

**Table 22: Regression results for PHQ-2 scores across depression therapy classes**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	3.8262809	0.42733705	8.95	<.0001
<b>Age Groups*</b>				
18-44 years	0.1758891	0.05330577	3.30	0.0011
>65 years	-0.2965855	0.08613440	-3.44	0.0006
45-65 years	-	-	-	-
<b>Gender*</b>				
Males	0.1137426	0.04907728	2.32	0.0209
Females	-	-	-	-
<b>Race</b>				
Blacks	-0.0171856	0.07168833	-0.24	0.8107
Asians	-0.0236067	0.14913997	-0.16	0.8743
Multiple races	0.0815454	0.16004197	0.51	0.6107
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	0.1488145	0.09208217	1.62	0.1068
Divorced	0.2530129	0.06095075	4.15	<.0001
Separated	0.2978353	0.12228318	2.44	0.0153
Never married	0.2739648	0.06652892	4.12	<.0001
Married	-	-	-	-
<b>Education*</b>				
No education	-0.1088568	0.29883598	-0.36	0.7158
School	0.1389425	0.11449242	1.21	0.2256
High school	0.1137930	0.05271159	2.16	0.0314
5+ years college	-0.1395697	0.08117844	-1.72	0.0863
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	-0.3578200	0.06237240	-5.74	<.0001
Unemployed	-	-	-	-

<b>Income a*</b>				
Low	0.1865571	0.07900060	2.36	0.0187
High	-0.1139192	0.06636350	-1.72	0.0868
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	-3.1065494	0.11563765	-26.86	<.0001
Very good	-2.7051892	0.10574756	-25.58	<.0001
Good	-2.1801921	0.09885237	-22.06	<.0001
Fair	-1.2064063	0.10037303	-12.02	<.0001
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	-0.0654268	0.08188706	-0.80	0.4247
Arthritis	0.0802863	0.06562501	1.22	0.2219
Diabetes	-0.1317421	0.11799824	-1.12	0.2649
High blood pressure	0.0221986	0.08542314	0.26	0.7951
None	-	-	-	-
<b>Number of Comorbidities</b>				
2	0.0043501	0.21438471	0.02	0.9838
≥ 3	-	-	-	-
<b>Antidepressant/Psychotherapy*</b>				
SSRI	-0.0103671	0.05130837	-0.20	0.8400
MA**	0.2050913	0.10252836	2.00	0.0461
SNRI	0.3253804	0.11778651	2.76	0.0060
TCA	-0.0988881	0.18589890	-0.53	0.5950
Psychotherapy	0.1499525	0.16325672	0.92	0.3589
Both***	0.2697418	0.24444909	1.10	0.2705
No therapy	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

<sup>a</sup> - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

Thus, as seen from the adjusted regression results, the depression therapy class was significantly associated with the PHQ-2 scores at the significance level of 0.05. The PHQ-2 scores were lower with the utilization of SSRI and TCA as compared to no therapy at all. The adjusted results were consistent for SSRI with unadjusted analyses where the mean PHQ-2 score for SSRI was lower than no therapy at all.

**Table 23: Multinomial regression results for depression frequency**

Predictor	Depression frequency (OR, Confidence Intervals) <sup>a</sup>		
	0: Not at all	1: Several Days	2: More Than Half the Days
<b>Age**</b>			
18-44 years	<b>0.686**</b> <b>(0.540, 0.871)</b>	0.851 (0.664, 1.092)	1.116 (0.864, 1.443)
> 65 years	<b>1.845**</b> <b>(1.269, 2.682)</b>	1.297 (0.910, 1.848)	1.170 (0.778, 1.759)
45-65 years	Reference	Reference	Reference
<b>Gender</b>			
Males	0.712 (0.505, 1.003)	0.741 (0.520, 1.055)	0.948 (0.640, 1.420)
Females	Reference	Reference	Reference
<b>Race</b>			
Blacks	0.985 (0.554,1.752)	0.957 (0.527,1.736)	<b>2.291**</b> <b>(1.364,3.847)</b>
Asians	1.774 (0.572,5.500)	1.110 (0.309,3.989)	1.158 (0.291,4.613)
Multiple Races	2.120 (0.647,6.948)	1.308 (0.425,4.019)	2.870 (0.896,9.190)
Whites	Reference	Reference	Reference
<b>Marital Status**</b>			
Widowed	<b>0.478**</b> <b>(0.244,0.939)</b>	<b>0.420**</b> <b>(0.220,0.804)</b>	0.657 (0.287,1.503)
Divorced	<b>0.513**</b> <b>(0.321,0.819)</b>	<b>0.529**</b> <b>(0.339,0.827)</b>	0.879 (0.519,1.491)
Separated	0.400 (0.152,1.052)	0.725 (0.315,1.667)	0.775 (0.294,2.044)
Never Married	<b>0.535**</b> <b>(0.331,0.867)</b>	0.693 (0.420,1.144)	1.188 (0.174,4.029)
Married	Reference	Reference	Reference

<b>Education</b>			
No education	0.836 (0.174,4.029)	0.604 (0.098,3.700)	1.050 (0.082,13.420)
Elem/ Mid School	0.819 (0.358,1.876)	0.695 (0.333,1.450)	1.321 (0.603,2.893)
High school	0.831 (0.558,1.239)	0.698 (0.485,1.005)	0.972 (0.625,1.510)
5+ Years College	1.206 (0.576,2.526)	1.048 (0.504,2.180)	0.965 (0.404,2.308)
≤ 4 years college	Reference	Reference	Reference
<b>Employment Status**</b>			
Employed	<b>1.959**</b> <b>(1.255, 3.060)</b>	<b>1.793**</b> <b>(1.144, 2812)</b>	<b>1.816**</b> <b>(1.102, 2.993)</b>
Unemployed	Reference	Reference	Reference
<b>Income<sup>b**</sup></b>			
Low income	<b>0.716**</b> <b>(0.535, 0.958)</b>	<b>0.750**</b> <b>(0.575, 0.978)</b>	0.936 (0.711, 1.233)
High income	1.176 (0.806, 1.715))	1.009 (0.689, 1.478)	0.965 (0.620, 1.501)
Middle class income	Reference	Reference	Reference
<b>Overall Health Status**</b>			
Excellent	<b>228.761**</b> <b>(68.720, 761.51)</b>	<b>28.251**</b> <b>(8.520, 93.683)</b>	<b>4.842**</b> <b>(1.179, 19.894)</b>
Very good	<b>101.589**</b> <b>(45.245, 228.098)</b>	<b>24.818**</b> <b>(11.797, 52.210)</b>	<b>5.649**</b> <b>(2.577, 12.385)</b>
Good	<b>24.931**</b> <b>(12.851, 48.365)</b>	<b>10.740**</b> <b>(6.001, 19.22)</b>	<b>2.670**</b> <b>(1.493, 4.77)</b>
Fair	<b>4.562**</b> <b>(2.407, 8.649)</b>	<b>4.316**</b> <b>(2.491, 7.479)</b>	<b>1.949**</b> <b>(1.118, 3.396)</b>
Poor	Reference	Reference	Reference
<b>Comorbidities</b>			
Asthma	0.810 (0.477, 1.374)	0.708 (0.410, 1.223)	0.552 (0.279, 1.092)
Arthritis	1.206 (0.721, 2.018)	0.971 (0.597,1.577)	0.871 (0.490, 1.549)
Diabetes	2.709 (0.162, 6.314)	1.655 (0.737, 3.718)	1.705 (0.636, 4.572)
High blood pressure	1.031 (0.544, 1.953)	0.765 (0.391, 1.498)	0.899 (0.423, 1.912)
None	Reference	Reference	Reference
<b>Number of Comorbidities</b>			
2	0.244 (0.041, 1.468)	0.221 (0.049, 1.003)	0.182 (0.029, 1.133)
≥ 3	Reference	Reference	Reference

<b>Antidepressant/ Psychotherapy</b>			
SSRI	2.318 (0.654, 8.224)	0.752 (0.236, 2.399)	1.824 (0.532, 6.257)
MA*	1.547 (0.403, 5.935)	0.688 (0.204, 2.321)	1.641 (0.439, 6.129)
SNRI	1.371 (0.350, 5.371)	0.596 (0.168, 2.107)	1.758 (0.431, 7.161)
TCA	2.365 (0.507, 11.044)	0.695 (0.163, 2.969)	1.568 (0.371, 6.618)
Psychotherapy	1.580 (0.368, 6.788)	0.774 (0.210, 2.847)	1.122 (0.273, 4.605)
Both***	Reference	Reference	Reference

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

\*MA = Miscellaneous Agents

<sup>a</sup> The reference class for depression frequency was 3: Nearly every day

\*\* - Significant results

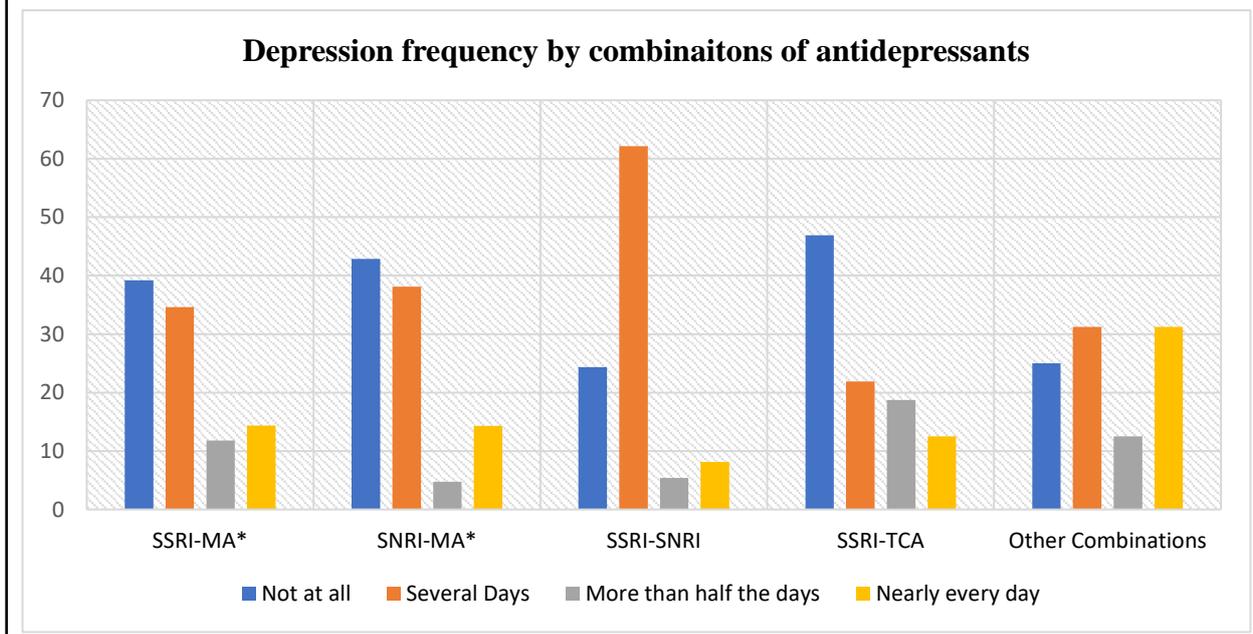
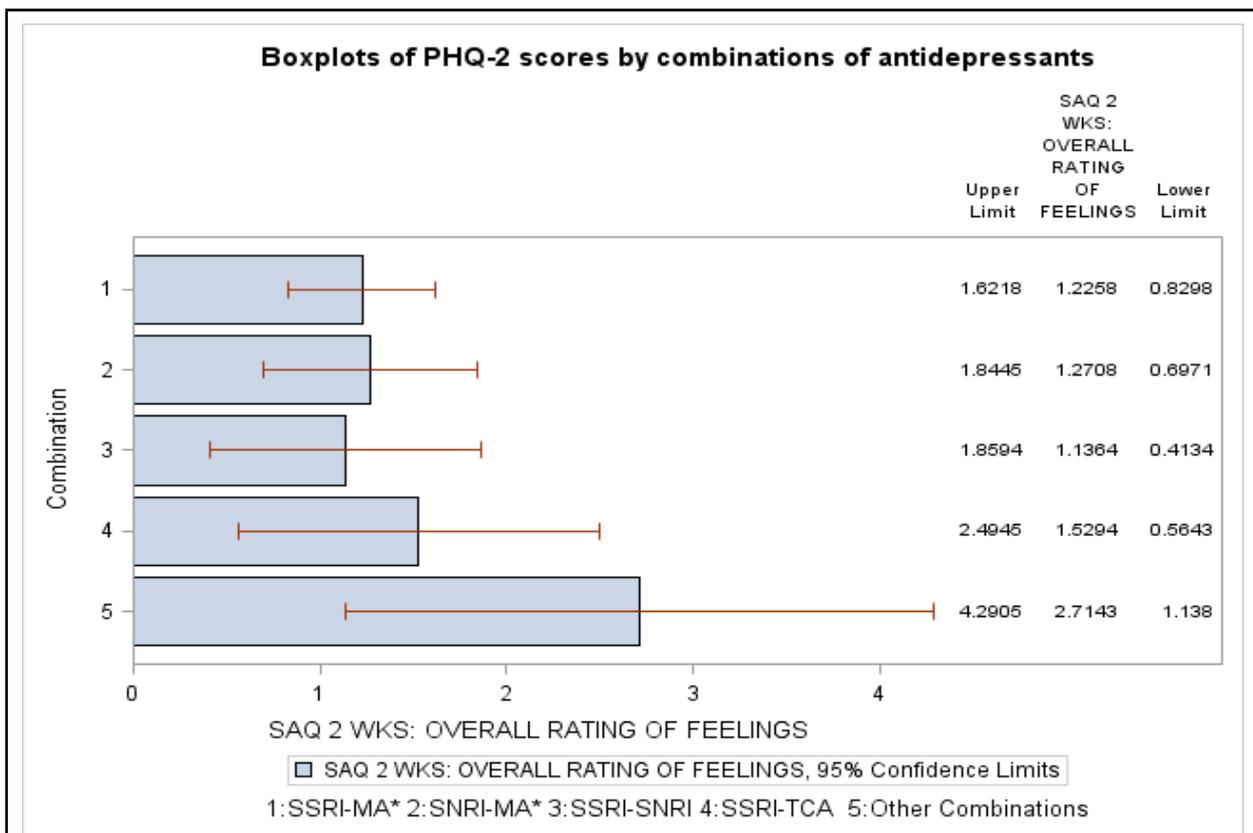
Both\*\*\* - Antidepressant and Psychotherapy

<sup>b</sup> - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

Thus, as seen from the multinomial regression results, on adjusting for other factors, antidepressant/ psychotherapy class was not significantly associated with the frequency of depression. However, numerically it was found that, as compared to both the therapies (antidepressant and psychotherapy) being prescribed, all the classes had a higher likelihood of reporting either “not at all” or “more than half days” of depression (OR>1).

Mean PHQ-2 scores and depression frequency were then compared across combinations of antidepressants, since, PCS and MCS suggested that a better quality of life was associated with combinations. SSRI with SNRI was the combination associated with the lowest PHQ-2 scores (mean = 1.13) indicating lesser tendency towards depression. The findings of significantly lower PHQ-2 scores (p-value = 0.0214) being associated with combinations of antidepressants as compared to individual classes were consistent with the results suggested by PCS and MCS. The frequency of feeling depressed was the lowest with SSRI and TCA as a combination (highest percentage of patients reporting “Not at all” – 46.87%) with SSRI-SNRI

combination having the lowest percentage (8.10%) of patients reporting “Nearly every day” depression. These findings thus suggest that, the highest quality of life and lowest tendency towards depression is associated with SSRI – SNRI or SSRI - TCA. These unadjusted findings are reported in Figure 12. ANOVA results for unadjusted analyses suggested that the differences in PHQ-2 scores across the combination groups were not significant. Chi-square test for depression frequency could not be conducted since one of the categories had a sample size of less than 5, hence Fisher’s exact test was conducted which suggested that, the depression therapy class was not significantly associated with the depression frequency (p-value=0.713).



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 MA\* - Miscellaneous Agents  
 Both – Antidepressants and Psychotherapy  
 A higher PHQ-2 score indicates higher tendency towards depression

**Figure 12 – Mean PHQ-2 scores and depression frequency across combinations of antidepressants**

Adjusted analyses was then conducted to evaluate if the combinations of antidepressants were associated with PHQ-2 scores (surveyreg) or depression frequency (multinomial logistic regression) on accounting for other factors. Results for these are summarized under Appendix Tables 10 and 11 respectively. On controlling for other factors, the combinations of antidepressant were not significantly associated with the PHQ-2 score at a p-value of 0.7665. Numerically, all the combinations except SNRI - Miscellaneous Agents (estimate = 0.5534, p-value = 0.2659) and SSRI-SNRI (estimate = 0.0905, p-value = 0.8032) reduced PHQ-2 scores as compared to not getting any combination of antidepressant prescribed. The combinations were however significantly associated with the depression frequency on controlling for other factors. Patients receiving 'other combinations' (TCA either with a miscellaneous agent or SNRI) were less likely to report more than half days of depression as compared to no combinations prescribed.

### **Section 5.3: Discussion**

The study thus suggested that individually SSRI, miscellaneous agents and SNRI were associated with a higher mean PCS whereas SNRI and TCA were associated with a higher mean MCS. Psychotherapy with or without an antidepressant was associated with lower scores. These findings were consistent with the study findings in the literature that suggested pharmacotherapy had higher effectiveness than psychotherapy. A study conducted by Siddique et al. suggested that amongst depressed women with moderate baseline depression, pharmacotherapy was superior to psychotherapy.<sup>54</sup> In women with severe depression, psychotherapy was superior, however after 12 months. This study was however not restricted to cancer population, also, the psychotherapy that they looked at was cognitive-behavioral therapy or community mental health service and not necessarily an office-based physician visit.<sup>54</sup> A study conducted by Vyas et al. suggested that amongst cancer patients with depression, the mean MCS score was lowest among those who received psychotherapy with or without antidepressants compared to those receiving antidepressants only and those with no reported use of either.<sup>30</sup> Similar results were replicated in our study. The study conducted by Vyas et al. however, did not look at classes of antidepressants or combinations of antidepressants separately. Adjusted regression analyses in our study suggested that, PCS was higher with any kind of antidepressant/psychotherapy except TCA compared to no treatment at all. MCS however was not higher for any of therapy classes as compared to no treatment at all. It was also found that PCS and MCS both were even higher when the antidepressants were used in combination with each other, with SSRI-SNRI producing the highest PCS and SSRI-TCA producing the highest MCS. It was thus suggested that, using SSRI either in combination with SNRI or TCA or individually produced the highest quality of life. The results of SSRI being associated with a higher QOL were consistent with a study that compared pharmacotherapy involved in treating depression. However, this study did not include psychotherapy and only included monotherapy, excluding combinations of antidepressants. The

study was also not restricted to cancer population.<sup>55</sup> There have been studies comparing the effectiveness and suggesting that pharmacotherapy is more effective than psychotherapy.<sup>55,56</sup> These were however, not necessarily amongst cancer patients<sup>55</sup> or necessarily did not look at quality of life as an outcome measure for effectiveness.<sup>56</sup>

On comparing the PHQ-2 scores and depression frequency from SF-12, it was observed that, SSRI had the lowest PHQ-2 score indicating lesser tendency towards depression, the depression frequency was also reported to be low by maximum patients in the SSRI group. In addition, combinations of antidepressants had even lower PHQ-2 scores, with SSRI-SNRI having the lowest score. The frequency of depression was reported to be low with most of the patients in the SSRI-TCA group. Thus, similar results were obtained for quality of life by both these methods, where SSRI was suggested to be superior to others, individually or in combination with either an SNRI or a TCA. These findings were consistent with the literature, where a study conducted by Mills et al. suggested that the PHQ scores and depression frequency improved after antidepressant initiation.<sup>57</sup> However, in this study, antidepressants were not compared against psychotherapy. In addition, this study was not restricted to cancer patients. The results of SSRI being associated with the highest QOL and relatively lower prescription and office-based visit costs (from specific aim 2) also align with the results of a study that has already been conducted which suggests that a lower financial burden usually leads to a higher QOL and lower tendency towards depression.<sup>6</sup>

In addition to the limitations stated above, there were certain QOL limitations identified. One of the major limitation of the study is selection bias. The reason for lower MCS with the treatment groups or the lower PCS/MCS and higher PHQ-2 scores with psychotherapy could be due to the difference in population across classes of antidepressants and the baseline scores being worse to begin with as compared to others. Presence of such selection bias affects the validity of the results obtained above. Secondly, quality of life is a subjective term and the

scores/frequency of depression could vary based on personal preferences. Thirdly, the quality of life could be associated with the cancer condition and not depression, which is a common limitation of studies looking at comorbidities. However certain cancer characteristics such as, the type of cancer, remission state and other comorbidities associated were looked at in the study which would help in reducing the bias but due to maximum missing values this effect would be minimum. Certain types of cancers have higher survival rates and depression levels in these patients could be different as compared to those with lower survival rates.<sup>58</sup> Also, some cancers have certain effects on the endocrine and hormonal system which would present depression differently in these.<sup>59</sup> Due to the missing values, these effects of type of cancer could not be studied. Moreover, the data being cross-sectional, it was not possible to track the patients. Depression treatment could have long-term effects and could improve quality of life after a long duration; however, this could not be tracked due to data limitations and the study being cross-sectional. In addition, certain antidepressants were reported to have interactions with certain chemotherapeutic drugs which could lower the quality of life of certain specific cancer patients mainly breast cancer patients.<sup>60</sup> However, this could not be tracked because of the lack of available data. Finally, the stage of cancer could also have some effect on the quality of life; however, this is not captured by MEPS and hence was not controlled for in the study.

Despite of these limitations, the findings add a lot to the literature. None of the studies so far have looked at quality of life associated with separate classes of antidepressants or combinations of antidepressants. Studies so far have compared antidepressants as a whole with psychotherapy or no treatment at all; however, none of them have looked at individual classes. This is the first study that also compares the quality of life associated with combinations of antidepressants and suggests that higher quality of life scores are associated with combinations of antidepressants as compared to using antidepressants individually. These findings form the basis for future studies to explore the combinations even further, since these were associated

with a higher QOL. However, a higher QOL could also be associated with higher side effects which could be explored in future studies. As stated above, our study has limitations due to selection bias involved, future studies could address this limitation by using a longitudinal dataset or matching the patients and produce more robust findings. Our study is hypothesis generating for such future studies. On achieving more robust results, the patient-reported QOL findings could also provide certain guidance to clinicians to manage depression amongst cancer patients more efficiently.

## **CHAPTER VI: CONCLUSIONS AND FUTURE RESEARCH**

### **Section 6.1: Conclusions**

Our study examined the patterns of use, sociodemographic characteristics, prescription medicine costs, office-based visit costs and QOL associated with the utilization of antidepressants and psychotherapy amongst cancer patients with a comorbid depression condition. These factors were studied across all the classes of antidepressants/ psychotherapy and were compared against each other. It was found that in a majority of patients had untreated depression (53.64%). Amongst those receiving antidepressants, SSRI was the most commonly prescribed antidepressant with or without psychotherapy. Psychotherapy was also prescribed to many patients with or without any antidepressant. The patterns of use were similar across all the classes of antidepressants. As suggested by the trends observed throughout the study period, the use of psychotherapy and miscellaneous agents has eventually increased with SSRI still being the most frequently prescribed antidepressant class. On identifying the sociodemographic characteristics, age, employment status and education were found to be the most significantly associated predictors of receiving any particular class of antidepressant/psychotherapy. Age and employment status were significant even in most of the adjusted analyses, where people below 65 years of age and who were employed had a higher PCS and a lower PHQ score. MCS was however higher in those above 65 years of age and employed. These were not significantly associated with total prescription medicine or office-based visit costs.

Comparing the total prescription medicine and office-based visit costs, it was found that, the adjusted mean prescription costs per purchase were the highest for SNRI (\$112.92 per fill/purchase) with out of pocket and private insurance being the sources of payments in majority of the patients. The adjusted office-based visit costs mainly associated with psychotherapy were the highest for those receiving psychotherapy only without any antidepressant (mean = \$166.39/visit). The sources of payment were similar to those of prescription medicine costs.

Some other major office-based visits identified along with psychotherapy were general checkup, treatment and follow-up visit.

Quality of Life as measured by PCS was the highest for SSRI (mean = 41.18), whereas MCS was the highest for TCA (mean = 38.59). Psychotherapy with or without any antidepressants was associated with a lower PCS and MCS. Both the PCS and MCS were higher when the antidepressants were prescribed in combination with one another, with SSRI-SNRI associated with the highest PCS (mean = 44.25) and SSRI-TCA associated with the highest MCS (mean = 40.65). The PHQ-2 scores and depression frequency also suggested using antidepressants in combinations. SSRI-SNRI was associated with the lowest PHQ-2 score (mean = 1.13) indicating a lower tendency towards depression. It was thus suggested that the QOL was the highest when SSRI was given in combination with either SNRI or TCA by all the measures. As mentioned above, these results could however involve selection bias since the groups were not randomized and were non uniform.

As stated above, these results would further help policy makers and clinicians in guiding their decision regarding depression management amongst cancer patients. It also provides a framework for further studies to be conducted which could explore the outcomes associated with SSRI more, since as identified in this study, it is associated with a lower cost and higher QOL. Finally, it is one of the first studies looking at patterns of use, costs and QOL across classes of antidepressants/ psychotherapy amongst cancer patients with depression in the US in a nationally representative population and hence has high generalizability.

## **Section 6.2: Future Research**

Based on the results obtained in our study, further hypotheses can be generated in order to carry out a cost-effective or a cost-benefit analysis study comparing antidepressant (identified in our study that they have higher costs and higher QOL) to psychotherapy. The current study was cross-sectional and there were certain other data limitations to it as mentioned above, which can be overcome by using a longitudinal database like SEER. Family history of depression was identified as one of the predictors for antidepressant use by a study.<sup>18</sup> This could not be studied using MEPS due to data limitation but can be explored further using another dataset or conducting a primary research study. In addition, costs/outcomes associated with combinations of antidepressants can be explored further, since as suggested by this research, they are associated with a higher QOL. Although, combinations of antidepressants could also be associated with higher side effects resulting into higher hospital visits and utilization, which could also be studied further. Since, antidepressants can have long-term effects, future studies, with the help of an appropriate dataset or by collecting data primarily can look at some of the long-term effects and costs associated with these.

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## APPENDIX

**Table 1: Names of antidepressants under each class included by MEPS**

<b>Class of Antidepressant</b>	<b>Specific Names</b>
SSRI	Fluoxetine, Paroxetine, Citalopram, Escitalopram, Sertraline
MA*	Bupropion, Vilazodone, Trazodone
SNRI	Duloxetine, Venlafaxine, Milnacipran
TCA	Amitriptyline, Imipramine, Desipramine, Clomipramine, Doxepin

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\* - Miscellaneous Agents

**Table 2: Regression results for out of pocket mean**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	24.89205222	8.74675731	2.85	0.0044
<b>Age Groups</b>				
18-44 years	-1.50047886	1.30243726	-1.15	0.2493
> 65 years	1.00642186	1.77273562	0.57	0.5702
45-65 years	-	-	-	-
<b>Gender</b>				
Males	2.09221651	1.18641357	1.76	0.0779
Females	-	-	-	-
<b>Race*</b>				
Blacks	-5.00697489	1.62160864	-3.09	0.0020
Asians	-10.01955001	4.83803174	-2.07	0.0384
Multiple Races	-6.01595753	3.40774864	-1.77	0.0775
Whites	-	-	-	-
<b>Marital Status</b>				
Widowed	3.24869167	2.07868341	1.56	0.1181
Divorced	-1.17190603	1.45237018	-0.81	0.4198
Separated	-0.97394564	2.68520613	-0.36	0.7168
Never married	-0.40774070	1.50994369	-0.27	0.7871
Married	-	-	-	-
<b>Education</b>				
No education	-1.43296923	7.49235072	-0.19	0.8483
Elem/ Mid School	-4.67678411	2.13444176	-2.19	0.0285
High school	-3.00020914	1.22495556	-2.45	0.0143
5+ years college	-0.64547227	2.20276081	-0.29	0.7695
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	1.17311514	1.36332519	3.06	0.0022
Unemployed	-	-	-	-

<b>Income<sup>a</sup></b>				
Low	2.24144739	1.72693686	1.30	0.1944
High	1.40480556	1.74631474	0.80	0.4212
Middle class	-	-	-	-
<b>Overall Health Status</b>				
Excellent	-3.91695499	2.91685784	-0.66	0.5111
Very good	-1.01249562	2.19795533	-0.46	0.6451
Good	-1.76607286	2.00820408	-0.38	0.7029
Fair	-1.95592030	1.99388251	-0.98	0.3266
Poor	-	-	-	-
<b>Comorbidities*</b>				
Asthma	-3.93870068	1.82370555	-2.16	0.0308
Arthritis	-7.49776796	1.39887361	-5.36	<.0001
Diabetes	-5.92353195	3.00399085	-1.97	0.0487
High blood pressure	-5.98537545	2.01492051	-2.97	0.0030
None	-	-	-	-
<b>Number of Comorbidities</b>				
2	13.12443039	4.62407154	0.68	0.4993
≥ 3	-	-	-	-
<b>Antidepressant/ Psychotherapy*</b>				
SSRI	3.56660851	7.03681896	0.51	0.6123
MA**	-1.76813682	7.29705630	-0.11	0.9162
SNRI	10.44893516	7.34510560	1.42	0.01549
TCA	-9.41596457	8.23746390	-0.78	0.04361
Both***	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

**Table 3: Regression results for private insurance mean**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	6.92742626	15.34217368	0.45	0.6516
<b>Age Groups*</b>				
18-44 years	-10.69437442	2.28452877	-4.68	<.0001
> 65 years	-13.09469435	3.10945151	-4.21	<.0001
45-65 years	-	-	-	-
<b>Gender*</b>				
Males	-2.05571531	2.08101841	-0.99	0.03233
Females	-	-	-	-
<b>Race</b>				
Blacks	-1.40114029	2.84436855	-0.49	0.6223
Asians	-4.26155647	8.48610755	-0.50	0.6156
Multiple Races	-5.24204676	5.97733190	-0.88	0.3805
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	-9.99602554	3.64609658	-2.74	0.0061
Divorced	-18.60734786	2.54751730	-7.30	<.0001
Separated	-10.89525996	4.70996249	-2.31	0.0207
Never married	-11.06275973	2.64850362	-4.18	<.0001
Married	-	-	-	-
<b>Education*</b>				
No education	-16.51308617	13.14189269	-1.26	0.2090
School	-14.22990611	3.74389902	-3.80	0.0001
High school	-3.88944507	2.14862266	-1.81	0.0703
5+ years college	4.55515847	3.86373346	1.18	0.2385
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	-10.52912219	2.39132871	-5.24	<.0001
Unemployed	-	-	-	-

<b>Income<sup>a*</sup></b>				
Low	0.03531818	3.02911860	0.01	0.9907
High	12.75315004	3.06310819	4.16	<.0001
Middle class	-		-	-
<b>Overall Health Status*</b>				
Excellent	3.57859162	5.11628916	0.70	0.4843
Very good	-4.53679795	3.85530444	-1.95	0.0506
Good	9.06168072	3.52247292	1.15	0.02489
Fair	7.35823912	3.49735230	0.39	0.6978
Poor	-		-	-
<b>Comorbidities</b>				
Asthma	1.52376768	3.19885487	0.16	0.8699
Arthritis	-3.48482396	2.45368210	-0.20	0.8434
Diabetes	-19.48482396	5.26912405	-0.19	0.8434
High blood pressure	-3.33090645	3.53425381	-0.94	0.3460
None	-		-	-
<b>Number of Comorbidities</b>				
2	13.10729660	8.11081251	0.88	0.3809
≥ 3	-		-	-
<b>Antidepressant/Psychotherapy*</b>				
SSRI	31.40857817	12.34287116	1.41	0.01585
MA**	36.42555682	16.42555682	1.28	0.01994
SNRI	54.34920142	12.88361866	2.67	0.0077
TCA	5.15450675	14.44885198	0.36	0.7213
Both***	-		-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

Both\*\*\* - Antidepressant and psychotherapy

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

**Table 4: Regression results for total mean costs associated with office-based visits across the depression therapy classes**

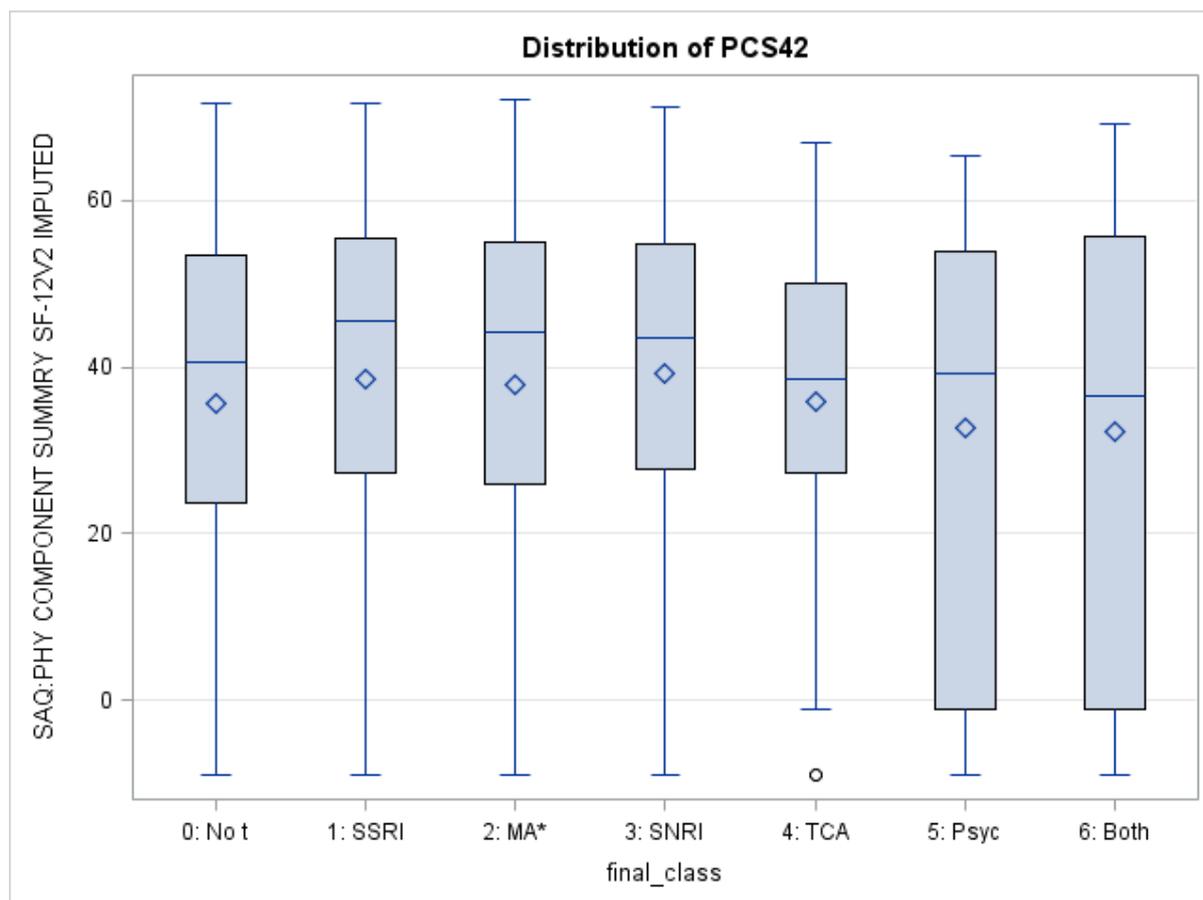
<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept</b>	53.6476569	187.3324928	0.29	0.7747
<b>Age groups</b>				
18-44 years	-1.9655426	22.2586973	-0.09	0.9297
> 65 years	-17.5375943	47.5225233	-0.37	0.7122
45-65 years	-	-	-	-
<b>Gender</b>				
Males	11.8761283	20.6516483	0.58	0.5655
Females	-	-	-	-
<b>Race</b>				
Blacks	26.7029490	28.7576662	0.93	0.3535
Asians	-29.5338169	94.3807429	-0.31	0.7544
Multiple Races	29.9604617	64.3155627	0.47	0.6415
Whites	-	-	-	-
<b>Marital Status</b>				
Widowed	-45.9267711	50.7617867	-0.90	0.3659
Divorced	-26.7392134	26.5802324	-1.01	0.3148
Separated	-38.5364169	46.1481697	-0.84	0.4040
Never married	-3.6898327	25.4342062	-0.15	0.8847
Married	-	-	-	-
<b>Education*</b>				
No education	348.5230548	126.7031474	2.75	0.0061
School	-1.2809766	48.4710790	-0.03	0.9789
High school	-7.9406433	22.1071736	-0.36	0.7196
5+ years college	79.3119381	36.6317060	2.17	0.0308
≤4 years college	-	-	-	-
<b>Employment Status</b>				
Employed	31.5660583	23.7834408	1.33	0.1849
Unemployed	-	-	-	-

<b>Income <sup>a</sup></b>				
Low	2.3544166	29.9792873	0.08	0.9374
High	-18.1456907	31.2543869	-0.58	0.5617
Middle class	-	-	-	-
<b>Overall Health Status</b>				
Excellent	-30.1133732	52.4238654	-0.57	0.5659
Very good	-2.0131863	42.3824247	-0.05	0.9621
Good	-17.1224176	40.0574044	-0.43	0.6692
Fair	-17.4989455	39.4296601	-0.44	0.6573
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	-3.5462970	30.7966528	-0.12	0.9084
Arthritis	-26.0213489	29.3743990	-0.89	0.3760
Diabetes	-0.1337772	62.6870647	-0.00	0.9983
High blood pressure	42.1564507	37.0422598	1.14	0.2555
None	-	-	-	-
<b>Number of comorbidities</b>				
2	72.8539973	175.3242383	0.42	0.6779
≥ 3	-	-	-	-
<b>Antidepressant along with psychotherapy</b>				
SSRI	-54.7345382	22.8998066	-2.39	0.0171
MA**	-25.2182136	30.4261791	-0.83	0.4075
SNRI	-11.4613521	35.3772990	-0.32	0.7461
TCA	-0.9686245	73.6722672	-0.01	0.9895
Psychotherapy alone	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\*\* - Miscellaneous Agents

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

No t – No therapy

MA\* - Miscellaneous Agents

Both- Antidepressant and Psychotherapy both

**Figure 1: Distribution of PCS across depression therapy classes**

**Table 5 – Significant ANOVA results for PCS comparison across depression therapy classes**

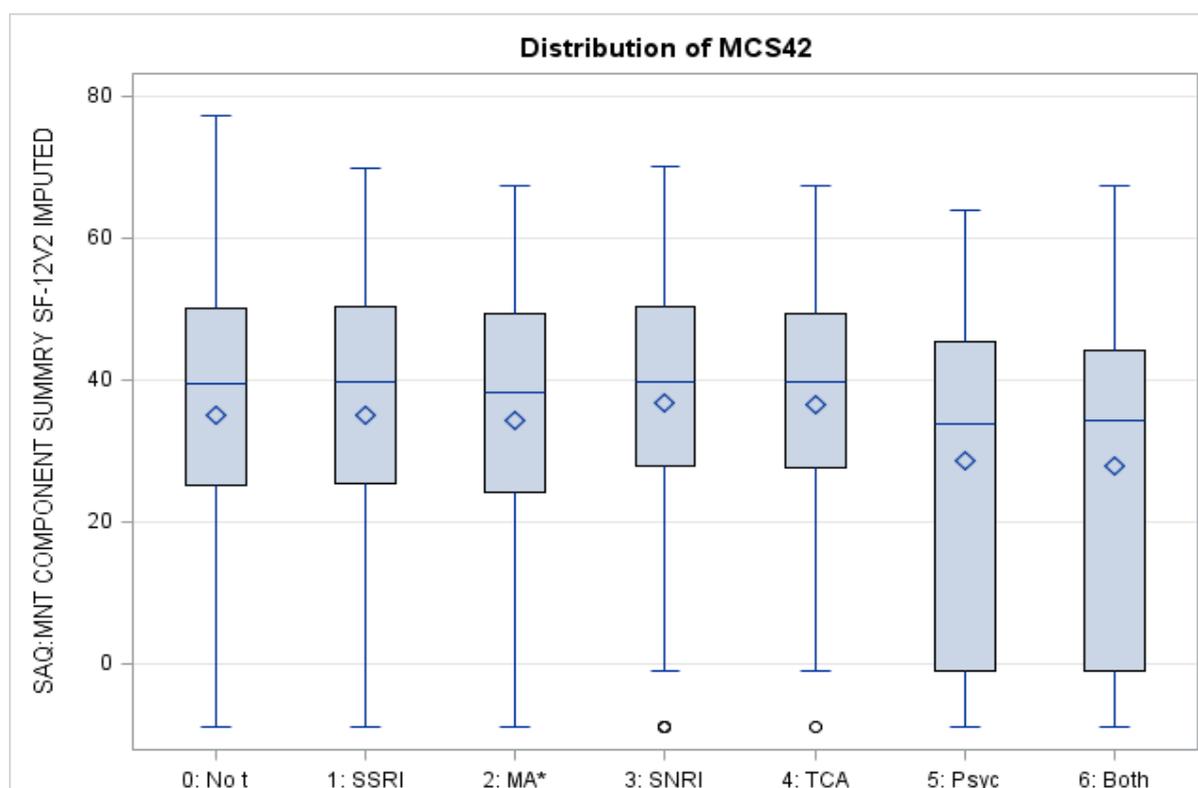
Comparisons significant at the 0.05 level are indicated by ***.				
Therapy class	Difference Between Means	Simultaneous 95% Confidence Limits		
3: SNRI - 0: No t <sup>a</sup>	3.6162	1.2188	6.0137	***
3: SNRI - 5: Psysc	6.6499	2.9946	10.3051	***
3: SNRI - 6: Both <sup>b</sup>	6.9709	0.7615	13.1803	***
1: SSRI - 0: No t	2.8004	1.6221	3.9786	***
1: SSRI - 5: Psysc	5.8340	2.8338	8.8342	***
1: SSRI - 6: Both	6.1550	0.3072	12.0028	***
2: TCA - 0: No t	2.1614	0.0380	4.2847	***

2: TCA - 5: Psyc	5.1950	1.7134	8.6766	***
0: No t - 3: SNRI	-3.6162	-6.0137	-1.2188	***
0: No t - 1: SSRI	-2.8004	-3.9786	-1.6221	***
0: No t - 2: TCA	-2.1614	-4.2847	-0.0380	***
0: No t - 5: Psyc	3.0336	0.1603	5.9069	***
5: Psyc - 3: SNRI	-6.6499	-10.3051	-2.9946	***
5: Psyc - 1: SSRI	-5.8340	-8.8342	-2.8338	***
5: Psyc - 2: TCA	-5.1950	-8.6766	-1.7134	***
5: Psyc - 0: No t	-3.0336	-5.9069	-0.1603	***
6: Both - 3: SNRI	-6.9709	-13.1803	-0.7615	***
6: Both - 1: SSRI	-6.1550	-12.0028	-0.3072	***

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

a-No therapy

b-Antidepressant and Psychotherapy Both



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

No t – No therapy

MA\* - Miscellaneous Agents

Both- Antidepressant and Psychotherapy both

**Figure 2: Distribution of MCS across depression therapy classes**

**Table 6 – Significant ANOVA results for MCS comparison across depression therapy classes**

Comparisons significant at the 0.05 level are indicated by ***.				
Therapy Class	Difference Between Means	Simultaneous 95% Confidence Limits		
3: SNRI - 5: Psyc	8.1075	4.6311	11.5839	***
3: SNRI - 6: Both <sup>a</sup>	8.9740	3.0684	14.8795	***
4: TCA - 5: Psyc	7.9680	2.9894	12.9466	***
4: TCA - 6: Both	8.8345	1.9369	15.7320	***
1: SSRI - 5: Psyc	6.3814	3.5280	9.2349	***
1: SSRI - 6: Both	7.2479	1.6862	12.8096	***
0: No t <sup>b</sup> - 5: Psyc	6.3029	3.5702	9.0356	***
0: No t - 6: Both	7.1694	1.6686	12.6701	***
2: MA* - 5: Psyc	5.6476	2.3364	8.9589	***
2: MA* - 6: Both	6.5141	0.7042	12.3239	***
5: Psyc - 3: SNRI	-8.1075	-11.5839	-4.6311	***
5: Psyc - 4: TCA	-7.9680	-12.9466	-2.9894	***
5: Psyc - 1: SSRI	-6.3814	-9.2349	-3.5280	***
5: Psyc - 0: No t	-6.3029	-9.0356	-3.5702	***
5: Psyc - 2: MA*	-5.6476	-8.9589	-2.3364	***
6: Both - 3: SNRI	-8.9740	-14.8795	-3.0684	***
6: Both - 4: TCA	-8.8345	-15.7320	-1.9369	***
6: Both - 1: SSRI	-7.2479	-12.8096	-1.6862	***
6: Both - 0: No t	-7.1694	-12.6701	-1.6686	***
6: Both - 2: MA*	-6.5141	-12.3239	-0.7042	***

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

a- Antidepressant and Psychotherapy Both

b-No therapy

MA\* - Miscellaneous Agents

**Table 7: Regression results for Physical Component Scores for combinations of antidepressants**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	23.737071	0.93949108	25.27	<.0001
<b>Age groups*</b>				
18-44 years	3.544700	0.32190941	11.01	<.0001
> 65 years	-1.531427	0.41001011	-3.74	0.0002
45-65 years	-	-	-	-
<b>Gender</b>				
Males	0.327339	0.25427629	1.29	0.1987
Females	-	-	-	-
<b>Race</b>				
Blacks	-0.073475	0.33992723	-0.22	0.8290
Asians	1.399997	1.02685030	1.36	0.1735
Multiple Races	-0.087833	0.57709360	-0.15	0.8791
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	-0.526873	0.44996723	-1.17	0.2423
Divorced	-0.305923	0.33941	-0.9	0.3679
Separated	1.25079	0.83265	1.5	0.1338
Never married	1.43798	0.31128	4.62	<.0001
Married	-	-	-	-
<b>Education</b>				
No education	1.14764	1.05989	1.08	0.2795
Elem/ Mid School	0.30336	0.54825	0.55	0.5803
High school	-0.2583	0.27664	-0.93	0.351
5+ years college	0.64182	0.44502	1.44	0.15
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	3.950119	0.32796056	12.04	<.0001
Unemployed	-	-	-	-

<b>Income <sup>a</sup></b>				
Low	0.509209	0.36687368	1.39	0.1659
High	0.026453	0.37817921	0.07	0.9443
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	28.062420	0.55912130	50.19	<.0001
Very good	25.481147	0.47509790	53.63	<.0001
Good	19.138884	0.43428593	44.07	<.0001
Fair	8.267454	0.44576231	18.55	<.0001
Poor	-	-	-	-
<b>Comorbidities*</b>				
Asthma	-2.236821	0.44825096	-4.99	<.0001
Arthritis	-3.043042	0.34248529	-8.89	<.0001
Diabetes	1.694565	0.58220957	2.91	0.0038
High blood pressure	0.997117	0.45210909	2.21	0.0280
None	-	-	-	-
<b>Number of comorbidities</b>				
2	0.779260	1.07477781	0.73	0.4688
≥ 3	-	-	-	-
<b>Combination of antidepressants*</b>				
SSRI-MA**	2.479085	1.04549570	2.37	0.0182
SNRI-MA**	1.337592	1.46930357	0.91	0.3632
SSRI-SNRI	0.079626	2.37666638	0.03	0.9733
SSRI-TCA	0.112497	1.43652840	0.08	0.9376
Other combinations	0.403784	3.08942656	0.13	0.8961
None	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

**Table 8: Regression results for Mental Component Scores for combinations of antidepressants**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	34.089138	1.43485949	23.76	<.0001
<b>Age Groups*</b>				
18-44 years	-2.076411	0.38279452	-5.42	<.0001
> 65 years	3.147859	0.54721375	5.75	<.0001
45-65 years	-	-	-	-
<b>Gender</b>				
Males	-0.185170	0.35308193	-0.52	0.6002
Females	-	-	-	-
<b>Race</b>				
Blacks	1.008868	0.46058275	2.19	0.0290
Asians	-0.254178	1.25548987	-0.20	0.8397
Multiple Races	0.754341	1.01934443	0.74	0.4597
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	-0.741	0.63211	-1.17	0.2417
Divorced	-1.6109	0.44247	-3.64	0.0003
Separated	-1.7505	0.89523	-1.96	0.0512
Never married	-2.7223	0.43057	-6.32	<.0001
Married	-	-	-	-
<b>Education</b>				
No education	-0.2248	1.55815	-0.14	0.8854
Elem/ Mid School	0.01862	0.65138	0.03	0.9772
High school	-0.0222	0.35052	-0.06	0.9496
5+ years college	0.60689	0.58198	1.04	0.2976
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	1.618264	0.41601700	3.89	0.0001
Unemployed	-	-	-	-

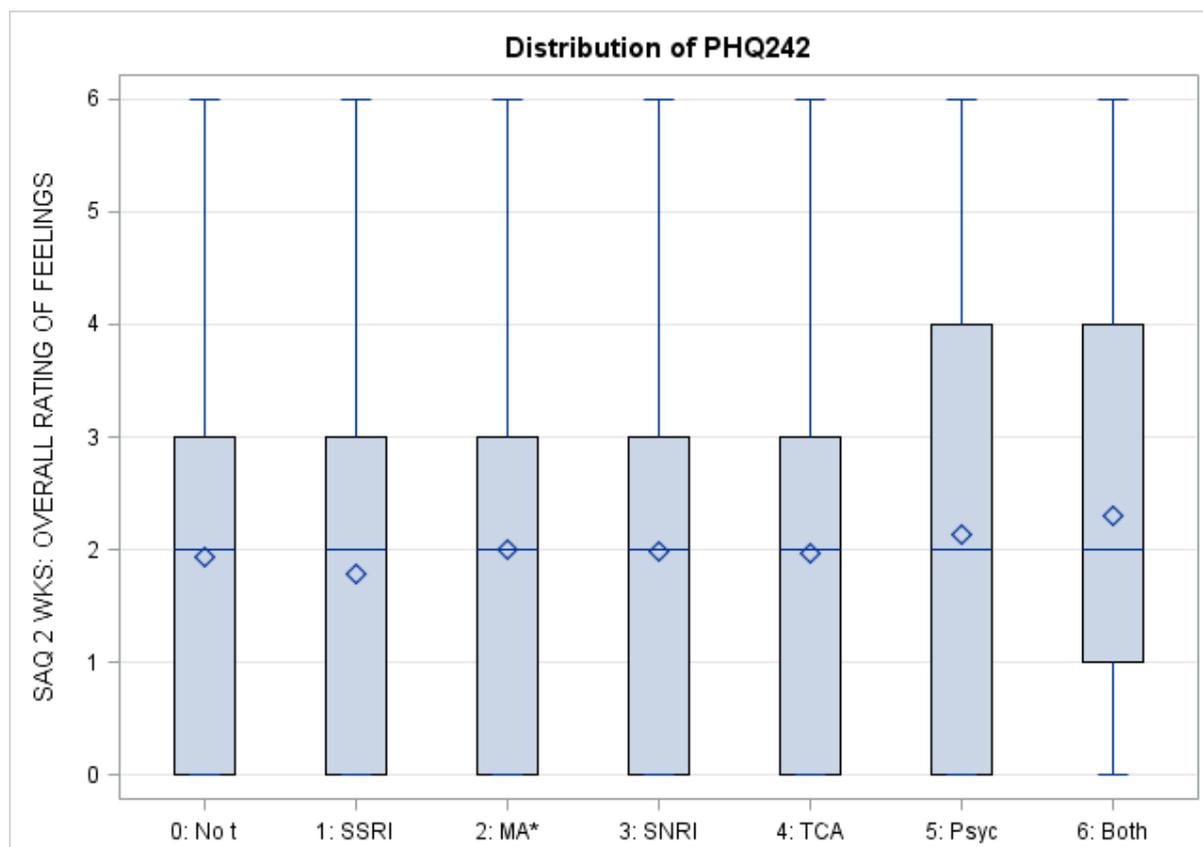
<b>Income <sup>a</sup></b>				
Low	-0.181734	0.50670403	-0.36	0.7200
High	0.756142	0.51285046	1.47	0.1411
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	18.376139	0.77668778	23.66	<.0001
Very good	14.833277	0.64242942	23.09	<.0001
Good	11.581959	0.59187438	19.57	<.0001
Fair	6.417728	0.59524026	10.78	<.0001
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	0.350122	0.52871868	0.66	0.5082
Arthritis	0.170229	0.42819455	0.40	0.6912
Diabetes	1.503815	0.76608830	1.96	0.0503
High blood pressure	0.404819	0.65851149	0.61	0.5391
None	-	-	-	-
<b>Number of comorbidities</b>				
2	0.323815	1.13879645	0.28	0.7763
≥ 3	-	-	-	-
<b>Combinations of antidepressants***</b>				
SSRI-MA**	-1.5584	1.35104	-1.15	0.2494
SNRI-MA**	-5.4855	3.90132	-1.41	0.1604
SSRI-SNRI	-2.0289	3.15032	-0.64	0.5199
SSRI-TCA	2.20433	2.9153	0.76	0.45
Other combinations	-1.6377	2.51062	-0.65	0.5145
None	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

MA\*\* - Miscellaneous Agents

\*Significant predictors, \*\*\*-Significant at  $\alpha=0.1$

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)



Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 No t – No therapy  
 MA\* - Miscellaneous Agents  
 Both- Antidepressant and Psychotherapy both

**Figure 3: Distribution of PHQ-2 scores across depression therapy classes**

**Table 9: Significant ANOVA results for PHQ-2 scores comparison across depression therapy classes**

Comparisons significant at the 0.05 level are indicated by ***.				
Therapy Class	Difference Between Means	Simultaneous 95% Confidence Limits		
5: Psyc - 1: SSRI	0.35053	0.02424	0.67681	***
0: No t* - 1: SSRI	0.14484	0.02447	0.26521	***
1: SSRI - 5: Psyc	-0.35053	-0.67681	-0.02424	***
1: SSRI - 0: No t	-0.14484	-0.26521	-0.02447	***

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
 No t\* - No therapy

**Table 10: Regression results for PHQ-2 Scores for combinations of antidepressants**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>t Value</b>	<b>Pr &gt;  t </b>
<b>Intercept*</b>	2.694124	0.48879317	5.51	<.0001
<b>Age Groups*</b>				
18-44 years	0.217255	0.07258875	2.99	0.0029
> 65 years	-0.400896	0.11087437	-3.62	0.0003
45-65 years	-	-	-	-
<b>Gender</b>				
Males	0.087150	0.06934299	1.26	0.2095
Females	-	-	-	-
<b>Race*</b>				
Blacks	-0.183707	0.10973178	-1.67	0.0948
Asians	-0.151575	0.29001387	-0.52	0.6015
Multiple Races	-0.035496	0.24603147	-0.14	0.8854
Whites	-	-	-	-
<b>Marital Status*</b>				
Widowed	0.02015	0.13274	0.15	0.8794
Divorced	0.23396	0.08047	2.91	0.0038
Separated	0.10532	0.21016	0.5	0.6165
Never married	0.15652	0.08804	1.78	0.0762
Married	-	-	-	-
<b>Education</b>				
No education	-0.1324	0.27974	-0.47	0.6362
Elem/ Mid School	-0.1372	0.16398	-0.84	0.4034
High school	0.0792	0.07231	1.1	0.274
5+ years college	-0.1419	0.11152	-1.27	0.2039
≤4 years college	-	-	-	-
<b>Employment Status*</b>				
Employed	-0.342392	0.08228428	-4.16	<.0001
Unemployed	-	-	-	-

<b>Income <sup>a</sup></b>				
Low	0.160173	0.10910055	1.47	0.1428
High	-0.073283	0.08796945	-0.83	0.4053
Middle class	-	-	-	-
<b>Overall Health Status*</b>				
Excellent	-2.870641	0.15753074	-18.22	<.0001
Very good	-2.540560	0.15289902	-16.62	<.0001
Good	-1.976290	0.14120859	-14.00	<.0001
Fair	-0.989290	0.14615247	-6.77	<.0001
Poor	-	-	-	-
<b>Comorbidities</b>				
Asthma	0.023763	0.11088139	0.21	0.8304
Arthritis	0.033420	0.08681256	0.38	0.7005
Diabetes	-0.011586	0.14908447	-0.08	0.9381
High blood pressure	0.084496	0.10383440	0.81	0.4162
None	-	-	-	-
<b>Number of comorbidities</b>				
2	0.305076	0.36284854	0.84	0.4009
≥ 3	-	-	-	-
<b>Combinations of antidepressants</b>				
SSRI-MA**	-0.465199	0.36555129	-1.27	0.2039
SNRI-MA**	0.553461	0.49684260	1.11	0.2659
SSRI-SNRI	0.090573	0.36314474	0.25	0.8032
SSRI-TCA	-0.448151	0.80005073	-0.56	0.5757
Other combinations	-0.051863	0.20586987	-0.25	0.8012
None	-	-	-	-

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin - Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants  
MA\*\* - Miscellaneous Agents

\*Significant predictors

a - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

**Table 11: Multinomial regression results for depression frequency for combinations of antidepressants**

Predictor	Depression frequency (OR, Confidence Intervals) <sup>a</sup>		
	0: Not at all	1: Several Days	2: More Than Half the Days
<b>Age**</b>			
18-44 years	<b>0.656**</b> <b>(0.517, 0.833)</b>	0.836 (0.653, 1.069)	1.112 (0.863, 1.434)
> 65 years	<b>2.000**</b> <b>(1.384, 2.889)</b>	1.361 (0.963, 1.924)	1.201 (0.805, 1.793)
45-65 years	Reference	Reference	Reference
<b>Gender</b>			
Males	0.866 (0.702, 1.069)	0.886 (0.724, 1.085)	1.048 (0.828, 1.328)
Females	Reference	Reference	Reference
<b>Race **</b>			
Blacks	<b>1.394**</b> <b>(1.029,1.889)</b>	1.111 (0.842,1.467)	<b>1.572**</b> <b>(1.167,2.119)</b>
Asians	1.055 (0.557,2.001)	1.188 (0.661,2.138)	0.839 (0.357,1.972)
Multiple races	1.187 (0.580,2.432)	1.166 (0.632,2.151)	1.427 (0.746,2.731)
Whites	Reference	Reference	Reference
<b>Marital Status**</b>			
Widowed	0.682 (0.463,1.003)	0.786 (0.542,1.140)	0.775 (0.503,1.193)
Divorced	<b>0.622**</b> <b>(0.477,0.812)</b>	<b>0.698**</b> <b>(0.545,0.894)</b>	0.921 (0.701,1.208)
Separated	<b>0.531**</b> <b>(0.318,0.887)</b>	0.709 (0.438,1.150)	1.031 (0.599,1.775)
Never Married	<b>0.574**</b> <b>(0.422,0.782)</b>	<b>0.655**</b> <b>(0.493,0.871)</b>	0.821 (0.601,1.124)
Married	Reference	Reference	Reference
<b>Education**</b>			
No education	0.989 (0.303,3.222)	0.945 (0.308,2.897)	1.210 (0.348,4.209)
Elem/ Mid school	0.660 (0.431,1.011)	<b>0.568**</b> <b>(0.391,0.825)</b>	0.716 (0.462,1.108)
High school	<b>0.726**</b> <b>(0.569,0.927)</b>	<b>0.722**</b> <b>(0.572,0.912)</b>	0.796 (0.615,1.030)
5+ years college	1.127 (0.700,1.813)	0.989 (0.625,1.565)	0.733 (0.407,1.320)
≤ 4 years college	Reference	Reference	Reference
<b>Employment Status**</b>			
Employed	<b>1.847**</b> <b>(1.413, 2.415)</b>	<b>1.599**</b> <b>(1.251, 2.045)</b>	<b>1.430**</b> <b>(1.09, 1.895)</b>
Unemployed	Reference	Reference	Reference
<b>Income<sup>b</sup></b>			
Low	<b>0.752**</b>	0.773	0.951

	<b>(0.566,0.999)</b>	(0.595, 1.003)	(0.722, 1.251)
High	1.147 (0.786, 1.676)	0.995 (0.678, 1.461)	0.947 (0.608, 1.474)
Middle class	Reference	Reference	Reference
<b>Overall Health Status</b>			
Excellent	<b>119.049**</b> <b>(59.58, 237.87)</b>	<b>11.451**</b> <b>(5.772, 22.717)</b>	1.613 (0.703, 3.702)
Very good	<b>69.674**</b> <b>(42.688, 113.720)</b>	<b>12.815**</b> <b>(8.477, 19.372)</b>	<b>2.610**</b> <b>(1.612, 4.228)</b>
Good	<b>23.542**</b> <b>(15.703, 35.292)</b>	<b>7.477**</b> <b>(5.520, 10.129)</b>	<b>1.966**</b> <b>(1.402, 2.757)</b>
Fair	<b>5.512**</b> <b>(3.724, 8.159)</b>	<b>2.917**</b> <b>(2.204, 3.860)</b>	<b>1.521**</b> <b>(1.116, 2.073)</b>
Poor	Reference	Reference	Reference
<b>Comorbidities</b>			
Asthma	1.111 (0.803, 1.538)	1.053 (0.774, 1.432)	0.877 (0.626, 1.230)
Arthritis	0.877 (0.664, 1.158)	0.976 (0.752, 1.266)	0.953 (0.726, 1.252)
Diabetes	1.330 (0.794, 2.228)	1.355 (0.814, 2.255)	1.042 (0.585, 1.856)
High blood pressure	1.082 (0.745, 1.572)	0.848 (0.583, 1.233)	1.158 (0.733, 1.829)
None	Reference	Reference	Reference
<b>Number of Comorbidities</b>			
2	0.712 (0.310, 1.637)	0.874 (0.420, 1.819)	0.682 (0.312, 1.491)
≥3	Reference	Reference	Reference
<b>Combinations of antidepressants**</b>			
SSRI-MA**	1.072 (0.351, 3.276)	1.227 (0.438, 3.435)	0.673 (0.193, 2.351)
SNRI-MA**	0.288 (0.040, 2.073)	0.863 (0.131, 5.687)	0.285 (0.021, 3.808)
SSRI-SNRI	0.542 (0.135, 2.177)	0.723 (0.192, 2.731)	N/A <sup>c</sup>
SSRI-TCA	1.482 (0.174, 12.650)	0.304 (0.032, 2.885)	0.287 (0.028, 2.940)
Other combinations	0.951 (0.258, 3.498)	0.329 (0.051, 2.104)	<b>0.052**</b> <b>(0.004, 0.622)</b>
None	Reference	Reference	Reference

Abbreviations: SSRI – Selective Serotonin Reuptake Inhibitors, SNRI – Serotonin -Norepinephrine Reuptake Inhibitor, TCA – Tricyclic antidepressants

\*MA = Miscellaneous Agents

<sup>a</sup>The reference class for depression frequency was 3: Nearly every day

\*\* - Significant results

<sup>b</sup> - Low defined as income <100% FPL (<\$12,060), middle class defined as income between the range of 100-400% FPL (\$12,060-\$48,240) and high defined as income over 400% FPL (>\$48,240)

<sup>c</sup> - N/A – Not applicable, since there were almost no patients in that group and the sample size for that cell was < 5, the OR obtained for that particular group were absurd