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Assessment of health-related quality of life, patient-reported mental health status and psychological distress based on the type of pharmacotherapy used among patients with depression

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A Thesis

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Assessment of Health-Related Quality of Life, Patient-Reported Mental Health Status and Psychological Distress based on the Type of Pharmacotherapy used Among Patients with Depression

by

Drishti Shah

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Masters of Science Degree in

Pharmaceutical Science

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An Abstract of

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Background: Pharmacotherapy with antidepressants and/ or anti-psychotics helps to relieve depression and improve the mental health and overall quality of life of individuals suffering from this disease. There is sufficient data from clinical trials that show the safety and efficacy of these medications. However there is lack of clear guidelines for prescribing these medications and there is a gap in literature on studies which determine the effect of these medications on the overall wellbeing of individuals.

Objective: 1. To compare the effect of the specific class of antidepressants on the health-related quality of life, psychological distress and patient reported mental health status (PR-MHS) of individuals suffering from depression who are on monotherapy.2. To compare the above mentioned outcomes in patients on monotherapy and those who add-on/switch therapies.

Methods: This retrospective, observational study used the Medical Expenditure Panel Survey database. Individuals suffering from depression (ICD-9-CM: 296, 300, and 311) and those taking antidepressants and/or antipsychotics since the beginning of the panel

were identified. Difference in SF-12 scores, K6 scores and PR-MHS over a year's time was categorized into "improve", "unchanged scores" and "decline" in scores. A multinomial logistic regression model was built to examine the association between the class of medications and HRQOL, psychological distress and mental health status.

Results: A total of 804 patients met the study inclusion criteria, among which 688 patients were on monotherapy and 116 on add-on/switch therapy. Among patients only on monotherapy, no significant difference was observed in their tendency to show improvement or decline on PCS-12, K6 and PR-MHS scores based on the class of antidepressants. However patients on SNRIs (OR 0.361, 95% CI 0.114– 0.950) and TCAs (OR 0.337, 95% CI 0.155–0.730) were significantly less likely to show improvement on MCS-12 scores as compared to those on SSRIs. Further, no significant differences were observed in patients on monotherapy and add-on/switch therapy in their likelihood to show improvement or decline on SF-12, K6 and PR-MHS scores.

Conclusion: The results of the study may imply that further research needs to be done to determine the reason for SSRIs to show greater improvement on mental health as compared to SNRIs. Similar results in patients on monotherapy and add-on/switch therapy can suggest that their therapy may keep depressive symptoms under control, which can indicate a good clinical decision by the patients' health care providers.

I dedicate this thesis to my mom, dad and sister, Bhoomi Shah

for their love and support.

They have been a constant source of motivation

and have inspired me to do my very best.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

AAPs.....Atypical Antipsychotics
AHRQ ……...Agency for Healthcare Research and Quality

CBT ……..Cognitive-Behavioral Therapy
CDC…….. .Centers of Disease Control and Prevention

HRQOL.....Health- Related Quality of Life

K6.....Kessler-6 Psychological Distress Scale

MDD……..Major Depressive Disorder

OR……..Odds Ratio

PROs……..Patient Reported Outcomes
PR-MHS.....Patient Reported Mental Health Status

SNRIs.....Serotonin Norepinephrine Reuptake Inhibitors
SSRIs.....Selective Serotonin Reuptake Inhibitors
STAR*D……Sequenced Treatment Alternatives to Relieve Depression

TCAs.....Tricyclic Antidepressants
TRD……....Treatment Resistant Depression

U.S……. United States

Chapter 1

Introduction

1.1 Background

Depression is a mental illness that can be both debilitating and costly to sufferers. It can adversely affect the course and outcome of common chronic conditions, such as asthma, cardiovascular disease, cancer, diabetes, arthritis and obesity.[1] Depression is associated with decrease in functioning and well-being of an individual and increase in number of disability days, utilization of healthcare services and cost.[2-4] Approximately 1 in 10 adults in the United States is affected by depression according to the Centers of Disease Control and Prevention (CDC).[1]Depression is expected to be the second leading cause of disability in the world by the year 2020.[5]As per World Health Organization, unipolar depression was the third cause of disease burden worldwide in 2004.[6]

Diagnosis and treatment of depression has increased over the past few years among both men and women. A total of $ 22.8 billion was spent to treat depression in the year 2009 as compared to $18.0 billion in the year 1999.Prescription medication expenditures to cure depression nearly doubled from 28.8 percent of the total expenditures in 2009 to 52.8 percent of the total

expenditures in 2009[7]. As more individuals are getting diagnosed with depression, and with the advent of newer medications to treat depression, the total expenditures associated with depression are increasing drastically.

Treatment options for depression include medication, primarily antidepressants, psychotherapy which includes cognitive-behavioral therapy (CBT), interpersonal therapy (IPT) and electroconvulsive therapy. Most common treatments are medications and psychotherapy.[8] This paper will focus on medications, chiefly antidepressants and other atypical antipsychotics which are used for treating depression. According to the Centers for Disease Control and Prevention, during the last 20 years the use of antidepressants has grown significantly making them one of the most costly and the third most commonly prescribed class of medications in the U. S.[9] The rate of antidepressant use in United States from 1988-1994 through 2005-2008 increased nearly 400% among all ages. [9]It has been found that more than 60 percent of Americans take antidepressants medications for 2 years or longer and among these 14 percent take the medication for over 10 years.[10] This suggests that there has been a substantial increase in use of antidepressants over the years in depressed individuals.

Several different classes of antidepressants are available for treating depression. These include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). There are also other antidepressants that do not fall into any of these classes.[11] Effectiveness of antidepressants is generally comparable between and within classes. Selection of appropriate antidepressants will largely be based on side effects, safety or tolerability for individual

patients.[12] The SSRIs and other newer antidepressants (e.g. nefazodone, venlafaxine etc.) have comparable clinical efficacy and lower side effects in comparison to the tricyclic antidepressants and other older antidepressants.[13-18] Also despite of comparable efficacy, lower treatment discontinuation rates were found for SSRIs in comparison to TCAs.[19] A study by Simon et al suggests that patient and physician preferences are the most important for treatment decision.[20] However the available data does not indicate whether SSRIs, which are the most frequently prescribed antidepressants and the newer antidepressants, outweigh the higher purchase cost and show improved outcomes such as better quality of life, lesser psychological distress and better mental health status.

It has been reported that as many as 40% patients suffering from depression fail to respond to conventional therapy, which consists of mainly using a single antidepressant agent at an adequate dose and duration.[21-23] This is along the lines of the findings of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial's findings, which is regarded as the gold standard for non-psychotic depressive disorders.[24] It is hence recommended by the American Psychiatric Association practice guidelines that a patient who fails to show adequate response to a certain antidepressant should be switched to different antidepressants. [25]In case the patient shows partially response to a certain antidepressant, physicians can either titer up the dose or add another antidepressant to the patients' medication regimen.[24-26] However patients who do not show response to one or more antidepressants become candidates for adjuvant drug therapies which may include use of atypical antipsychotics, which are not originally indicated for treatment of depression.[27] Several randomized controlled trials have shown superiority of these atypical antipsychotics over placebo for patients having treatment-resistant depression

(TRD).[26,28-31]These drugs have hence been included by the American Psychiatric Association in the treatment guidelines for non-psychotic depressive disorders as adjuvant therapy for TRD. [25]Only some atypical antipsychotics, which include aripiprazole, olanzapine/fluoxetine combination (OFC) and quetiapine have been approved by FDA for the treatment of Major Depressive Disorder (MDD).[32,33]

While there is enough data available on the clinical efficacy of antidepressants used for the treatment of depression, both as monotherapy or in form of combination therapy, there is lack of information regarding their impact on patient reported outcomes (PROs). This study evaluated the effect of medications used to treat depression on health- related quality of life, patient-reported mental health status and psychological distress.

Health-related quality of life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning of an individual.[34,35] Quality of life is found to have a significant association with validated measures of depressive symptoms such as Hamilton Rating Scale for Depression and the Beck Depression Inventory. [36]Also the severity of depression is found to have an inverse correlation with the HRQOL of a patient. [36]The significance of measuring the HRQOL in depression has greatly increased after the Medical Outcomes Study, wherein the social wellbeing and physical functioning of depressed patients were compared with those of other chronic conditions such as hypertension, arthritis and diabetes.[2] This study also showed that as compared to other chronic medical conditions, depression has the greatest negative impact on a patients' HRQOL. [2]Hence many researchers believe that it is valuable to evaluate any medical intervention or treatment to control any chronic

medical condition such as depression in terms of its ability to improve the patients' HRQOL.[37] The treatment with antidepressants and /or psychotherapy has shown to improve the HRQOL of multiple patient populations suffering from depression.[38] However there is a gap in literature that evaluates the effect of various classes of antidepressants and other medications used to treat depression when taken as a single medication or in combination on the patients' HRQOL.

This study also assessed the mental health as patient- reported mental health status (PR-MHS) and psychological distress score in individuals suffering from depression. Patients with depressive disorder tend to have worse physical and mental health, role functioning and perceived current health as compared to patients having no chronic conditions. [39]The self-reported mental health status measure is a good predictor of psychological distress, depressed mood and functioning. [40]It is also related to psychiatric symptoms and diagnosed mental illness. [41]Moreover , perceived mental health status has been shown to be a strong predictor of the mental health treatment used.[40] Psychological distress measured using Kessler 6 scale (K6) appears to be a useful screener for current depression as examined by CIDI in population-based studies. [42]Both these measures have been used to evaluate mental health of an individual in the present study.

1.2 Need for study

Accumulating evidence suggests that the use of the number of available antidepressant medications is increasing. According to data from the Centers for Disease Control and Prevention (CDC), the rate of antidepressant use in the United States nearly increased by 400% over the last two decades.[43] Nevertheless the available evidence for the treatment of depression is

limited. Also, most participants in clinical trials are recruited by advertisement rather than from representative practices, and they are often selected to have few comorbid disorders, either medical or psychiatric.[42,44] Furthermore the protocols used in these trials do not represent usual real world clinical practice. There is sufficient data from clinical trials that show the safety and efficacy of these medications. However unlike many other chronic conditions such as diabetes, hypertension, etc there is a lack of clear guidelines for prescribing medications for depression. The goal for treatment of mental disorders is now shifting from mere remission from symptoms to complete recovery of the individual. Recovery from illness focuses on restoring the overall well being of an individual. There is hence need for evidence on treatments that can improve the overall well being of an individual. There is a gap in the literature on antidepressants and their impact on patient reported outcomes such as quality of life, mental health status and psychological distress. Also, no previous research was found to have determined the class of antidepressants that leads to greater improvement in the above mentioned patient reported outcomes using a nationally representative sample. As per the authors' knowledge, one previous study has shown the comparative effectiveness of antidepressants and adjuvant atypical antipsychotics used to treat depression using a nationally representative sample. However this was a cross-sectional study, whereas the present study will look into the change in patient reported mental health status, psychological distress and quality of life over a year for patients on who are on monotherapy and those taking a combination of medications.

1.3 Significance of the study

A study by Simon et al suggests that patient and physician preferences are the most important factors that influence treatment decisions for depression. There is a lack of clear guidelines in

prescribing medications used to treat depression. The current study will not only examine the effect of monotherapy and those who use combination therapy or switch medications on patient-reported outcomes such as mental health and HRQOL, but will also assess the effect of various classes of antidepressants on the same. This can be supported by further research in similar area to provide some cue to clinicians prescribing these medications.

1.4 Goal

To determine the effect of antidepressants and other atypical antipsychotics used to treat depression on the health-related quality of life, psychological distress and patient- reported mental health status of individuals suffering from depression.

1.5 Objectives

1. To establish criteria to determine improvement and decline in HRQOL scores, psychological distress scores and PR-MHS of individuals suffering from depression.

2. To compare HRQOL scores, psychological distress scores and PR-MHS of individuals suffering from depression who are on monotherapy based on specific class of antidepressants.

Null hypothesis: There is no significant difference in HRQOL, psychological distress scores and PR-MHS based on the class of medication.

Alternate hypothesis: There is a significant difference in HRQOL, psychological distress scores and patient- reported mental health status based on the class of medication.

3. To compare the HRQOL scores, psychological distress and PR-MHS in individuals suffering from depression who are on monotherapy (one antidepressant) and those on add-on /switch

therapy (those on any combination of antidepressants and/or AAPs or those who switch medications).

Null hypothesis: There is no significant difference in the HRQOL, psychological distress scores and PR-MHS between patients on monotherapy and add-on/switch therapy.

Alternate hypothesis: There is a significant difference in the HRQOL, psychological distress scores and PR-MHS between patients on monotherapy and add-on/switch therapy.

Chapter 2

Literature Review

This chapter gives an overview of the existing literature of relevant topics related to the study.

2.1 Depression

Depression is a condition that is characterized by depressed or sad mood, diminished interest in activities which used to be pleasurable, weight gain or loss, psychomotor agitation or retardation, fatigue, inappropriate guilt, difficulties concentrating, as well as recurrent thoughts of death. The American Psychiatric Association has established the diagnostic criteria for depression as five or more of the above symptoms present for a continuous period of at least two weeks. Depression, as an illness, falls within the spectrum of affective disorders. [45,46] It is mostly caused by a combination of biological, genetic, environmental, and psychological factors.[8]

2.1.1 Types of depression

Several forms of depressive disorders include:

Major depression: This is commonly unrecognized and if untreated, may foster tragic consequences, such as suicide and impaired interpersonal relationships at work and at home. A person with major depressive disorder will experience severe symptoms that interfere with their

ability to work, sleep, study, eat, and enjoy life. The use of medications and/or specific psychotherapeutic techniques has proven to be effective in the treatment of major depression, but this disorder is still misconstrued as a sign of weakness, rather than being recognized as an illness.[8,46]

Persistent depressive disorder: This includes depressed mood that lasts for at least two years. A person having persistent depressive disorder may have episodes of major depression along with periods of less severe symptoms.[8]

Some types of depression are somewhat different and may develop under certain circumstances. They include:

Psychotic depression: This occurs when a person has severe depression in addition to some form of psychosis, such as delusions, or hallucinations. [8]

Postpartum depression: This occurs in women soon after giving birth. This includes symptoms such as sadness and hopelessness.[8]

2.1.2 Signs and Symptoms:

People with depression do not all experience the same symptoms. The severity, frequency, and duration of symptoms vary from patient to patient based on the individual and his or her particular illness. The signs and symptoms include:

- Persistent sad, anxious, or "empty" feelings
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness, or helplessness
- Irritability, restlessness
- Loss of interest in activities or hobbies once pleasurable, including sex

- Fatigue and decreased energy
- Difficulty concentrating, remembering details, and making decisions
- Insomnia, early-morning wakefulness, or excessive sleeping
- Overeating or appetite loss
- Thoughts of suicide, suicide attempts
- Aches or pains, headaches, cramps, or digestive problems that do not ease even with treatment.

Source: National Institute of Mental Health [8]

2.1.3 Risk factors:

Major depressive disorder (MDD) is one of the most common mental disorders in the U.S. About 6.7 percent of US adults each year may experience major depressive disorder. Women are 70 percent more likely to experience depression during their lifetime than men. Non- Hispanic blacks are 40% less likely to experience depression during their lifetime as compared to Non – Hispanic Whites. The average age of onset of depression is 32 years. Furthermore 3.3 percent of 13 to 18 year olds have also experienced serious debilitating depressive disorder.[8,46] Studies suggest that four factors have been consistently associated with MDD, and there is some evidence which suggests that at least some of the association is causal. These factors include gender, stressful life events, adverse childhood experiences, and certain personality traits. As per the National Comorbidity Study, the lifetime prevalence of MDD in the U.S. population was estimated to be 21.3% in women and 12.7% in men.[47] Also, environmental adversities such as job loss, marital difficulties, loss of close personal relationships and major health problems are associated with increase in risk for the onset of MDD.[48] In addition to these, adverse health

behaviors such as smoking, alcohol consumption, physical inactivity and sleep disturbance appears to be associated with depression. In most studies, it is difficult to establish whether depression is a result of an unhealthy behavior or whether depression causes the behavior.[46,49-52]

2.1.4 Epidemiology

According to Centers of Disease Control and Prevention (CDC), in 2011 approximately 1 in 10 adults in the United States is affected by depression.[1] As per the World Health Organization (WHO), major depression also carries the heaviest burden of disability among mental and behavioral disorders in 2010. Specifically, major depression accounts for nearly 3.7 percent of all U.S. disability-adjusted life years (DALYs) and 8.3 percent of all U.S. years lived with disability (YLDS).[53] The 12-month prevalence data for MDD from the National Survey on Drug Use and Health showed that in 2012, an estimated 16 million adults aged 18 or older in the U.S. had at least one major depressive episode in the past year. This was equivalent to 6.9 percent of all U.S. adults.[53]

2.1.5 Economic burden

Cost- of- illness studies on depression has show that it is associated with an enormous economic burden, in the order of tens of billions of dollars each year in the U.S. alone. The largest component of this economic burden comes from the loss of productivity at work due to depression.[54] A systematic review of cost-of -illness studies of depression in the year 2003 revealed that the average annual cost per case ranged from $1000 to $2500 for direct costs, from $2000 to $3700 for morbidity costs and from $200 to $400 for mortality costs.[55] As per AHRQ (Agency for Healthcare Research and Quality), medical spending to treat depression totaled $22.8 billion in 2009 as compared to $18.0 billion in 1999.Also, mean annual prescription drug

expenditures for depression increased from $574 per person in 1999 (in 2009 dollars) to $742 per person in 2009.[7]

2.1.6 Reducing the burden of depression

The urgency of rate of depression to public health is compounded by the recognition that if it is not treated effectively, it is likely to lapse into a chronic disease. Experiencing just one episode of depression places the individual at a 50% risk for experiencing another, with subsequent episodes raising the likelihood of experiencing more episodes in the future.[56] While the global burden of depression poses a considerable public health challenge both at social ,economic as well as clinical level, a number of well-defined and evidence based strategies can be effectively used to address this issue.[57]

2.2 Treatment options

Treatment in the acute phase of major depressive disorder is aimed in inducing remission from major depressive episode and achieving a full return to the patient's baseline level of functioning. Treatment options may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and light therapy. Selection of an appropriate initial treatment modality should be influenced by clinical factors such as severity of symptoms, presence of co-occurring disorders or psychosocial stressors and other factors such as patient preference, prior treatment experiences etc.[58] For the purpose of this study, our discussion will be limited to pharmacotherapy.

2.3 Pharmacotherapy

2.3.1 Antidepressants:

Antidepressants are recommended as an initial choice of treatment for patients with mild to moderate major depressive disorder.[59] Antidepressants mainly work on chemicals in the brain called neurotransmitters, especially serotonin and norepinephrine. Other antidepressants work on dopamine neurotransmitter. It has been found that these particular chemicals are involved in regulating mood, but they are unsure of the exact ways that they work.[8]

Antidepressant medications have been classified as follows: 1) TCAs which include amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine; 2) SSRIs, which include fluoxetine, paroxetine, sertaline, fluvoxamine, citalopram, and escitalopram; 3) SNRIs, that include venlafaxine, desvenlafaxine, and duloxetine; 4) MAOIs, which include phenelzine, isocarboxazid, tranylcypromine and the transdermal formulation of selegiline 5) other antidepressants, which include buproprion, nefazodone, trazodone, and mirtazapine. There are some studies that have suggested superiority of the mechanism of action of one class over another; however there are no robust findings that establish a clinically meaningful difference. For a majority of patients the effectiveness of these medications is commonly comparable between classes and within classes of medications.[60-62] But, antidepressants differ in their potential to cause side effects such as adverse sexual effects, sedation, or weight gain. Hence, the initial selection of these medications will chiefly depend on the tolerability, safety, cost of medication, patient preference and history of prior medication treatment. Selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal for most patients. Ordinarily, the use of

monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments.[59]

1. Selective serotonin reuptake inhibitors (SSRIs)

The currently available SSRIs include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. [59]There is a large amount of literature that supports the superiority of SSRIs compared with placebo in the treatment of major depressive disorder. The effectiveness of SSRIs has been compared with that of other antidepressant medications, mainly TCAs in more than 10 systematic reviews and meta-analyses. As far as efficacy is concerned SSRIs show comparable efficacy to TCAs.[63,64] [65,66]Most studies show that SSRIs are often better tolerated than TCAs because they cause fewer troublesome anticolinergic effects and less sedation.[67-70] Furthermore, there are a few analyses that suggest some superiority of SNRIs over SSRIs in rates of remission, however a large amount of the data finds no significant evidence of the superiority of any other class or agents over SSRIs.[63,71,72]

2. Serotonin norepinephrine reuptake inhibitors (SNRIs)

The currently available SNRIs are venlafaxine, desvenlafaxine which is a principal metabolite of venlafaxine, and duloxetine.[59] Each of these medications has been proved to be efficacious and have found to be superior to placebo in controlled studies and meta-analysis.[73,74] A meta-analysis by Nemeroff et al and Thase et al. showed that venlafaxine and duloxetine are generally as effective as SSRIs.[75,76] Some studies have pooled datasets that have suggested a relatively small advantage of SNRIs over SSRIs, which might lead to clinically modest benefits for patients with more severe depression or for patients who have not responded to prior treatment with SSRIs.[71] [76,77]However other meta-analysis have shown similar efficacy of both SSRIs and SNRIs. Some

studies have shown superiority of individual medications but no clear-cut medication class effects.[63,73]

3. Tricyclic antidepressants (TCAs)

TCAs include amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine. These can be compared in efficacy to other class of antidepressants such as SSRIs, SNRIs, and MAOIs for the treatment of major depressive disorder.[64,78] TCAs are very effective but they are not used as much today because their potential side effects are more serious. [8]TCAs may be chiefly effective in certain populations, such as in hospitalized patients.[79,80]

4. Monoamine oxidase inhibitors (MAOIs)

MAOIs are the oldest class of antidepressants and they include phenelzine, tranylcypromine, isocarboxazid, moclobemide, and the transdermally delivered formulation of selegiline. [59]MAOIs have similar efficacy in treating outpatients with major depressive disorder when compared to other classes of antidepressants. Also, these are more appropriate for patients with major depressive disorder who have not responded to safer and easily used treatments.[81,82] In fact, the use of MAOIs in treating major depressive disorder is now almost exclusively reserved for patients who have not responded to at least several other pharmacotherapies. [81]There are studies which have shown the effectiveness of MAOIs in patients who have not responded to other antidepressants, mainly TCAs.[81] They can be especially effective in cases of "atypical" depression, so clinicians should consider using these medications for patients with symptoms such as reactive moods, increased appetite and need for more sleep.[8,81,82]

5. Other antidepressant medications

There are other antidepressant medications that differ in their structure and pharmacological action from medications in the categories just described above. These include bupropion, mirtazapine, trazodone, and nefazodone.

Even though bupropion (Wellbutrin) is a norepinephrine and dopamine reuptake inhibitor, the latter effect is comparatively weak, and its mechanism of action remains unclear.[83] It tends to have side effects that are similar to SSRIs and SNRIs, but it is less likely to cause sexual side effects.[8] A meta-analysis by Papakostas et al. showed that SSRIs were relatively superior to bupropion for a subset of patients with major depressive disorder and anxiety. However the same meta-analysis showed that the efficacy of bupropion is almost the same as SSRIs for treating low to moderate levels of anxiety and depression.[84] Bupropion may also be a good choice of drug for patients who have a goal of quitting smoking and it has been approved by the U.S. Food and Drug Administration (FDA) for the same.[85]

Mirtazapine is not a reuptake inhibitor but is thought to work through noradrenergic and serotonergic mechanisms.[86] It has similar efficacy as that of SSRIs.[87]

Trazodone, on the other hand, is the oldest medication from this group and is widely used for the treatment of depression. Trazodone has been proved to be an effective antidepressant as compared to placebo.[78,88] However in contemporary practice it is much more likely to be used in lower doses as a sedative-hypnotic than as an antidepressant.[59]

Nefazodone has a structure which is analogous to trazodone but has somewhat different pharmacological properties. Nefazodone has been proved to show comparable efficacy and overall tolerability as SSRIs.[89]

2.3.2 Atypical antipsychotics

Three atypical antipsychotic agents have been approved by Food and Drug Administration (FDA) as adjunct, which includes aripiprazole and quetiapine or in combination with antidepressant therapy (olanzapine-fluoxetine combination [OFC]). [31] A meta-analysis by Spielmans et al. And Nelson and Papakostas showed that adjunctive atypical anti- psychotics are significantly more effective than placebo with approximately two-fold higher odds of achieving remission. [28,31]However atypical antipsychotics have higher odds for discontinuation when compared to placebo probably due to akathisia caused by aripiprazole, sedation caused by quetiapine and abnormal metabolic laboratory results and weight gain caused by quetiapine and OFC.[90] Taken together atypical antipsychotics are the most widely studied adjunctive agents to SSRIs and SNRIs in the treatment of patients with MDD, although a double blind recurrence prevention data is largely unavailable. Furthermore side effect profile of these drugs which include weight gain, metabolic disruption and sedation remain significant limitations for some of these agents.[90]

2.3.3 Need for augmenting and combining treatments

The overarching aim in treating major depressive disorder is to achieve remission ,a return to full functioning and improved quality of life. Remission is defined as absence of both sad mood and reduced interest and no more than three remaining symptoms of the major depressive episode for at least 3 weeks.[91] Available evidence indicates that majority of patients with MDD who are receiving acute phase treatment do not achieve and sustain a fully remitted state with index antidepressant treatment. Results from the STAR-D study, which is regarded as the gold standard for non-psychotic depressive disorders suggests that as the remission rates decreases

subsequent relapse rates increases.[92] Hence, it is important not to conclude the acute phase of treatment prematurely for partially responsive patients.[93] Furthermore there may be patients who may not respond to two or more adequate antidepressant trials. Such patients may have treatment –resistant depression.[94]

2.3.4 Strategies to address non-response: Augmenting and combining treatments

A number of strategies can be used when a change of treatment seems necessary. For patients treated with an antidepressant, optimizing the dose till the side-effect burden is tolerable and till the upper limit of dose has not been reached is a reasonable first step.[59] Other options include augmenting the antidepressant with depression focused psychotherapy or with other agents, mainly another non-MAOI antidepressant or with other non-antidepressant agents or changing to another non-MAOI antidepressant. The addition of another non-MAOI antidepressant may be helpful, particularly in patients who have had a partial response to antidepressant monotherapy. [95]Also, a second non-MAOI antidepressant medication can be added from a different pharmacological class, taking care to avoid drug-drug interactions. Another option is to add an adjunctive, such as a non-antidepressant medication like lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or an atypical antipsychotic. [27]Some clinical experience and limited evidence also support the addition of bupropion to an SSRI.[96] Another commonly used approach is the combination of mirtazapine and an SSRI .[97] Atypical antipsychotics can increase the rates of response or remission of depressive symptoms in individuals who have not responded to more than two medication trials, even when psychotic symptoms are absent.[21,28] A rarely used approach is the combination of TCA or trazodone and an MAOI, however there is a risk of drug-drug interactions and it necessitates careful monitoring.[81,98]

2.4 Patient –reported outcomes (PRO)

According to US-FDA, a PRO is any report of the status of a patient's health condition that comes directly from the patient, without any form of interpretation of the patient's response by a clinician or anyone else.[99] A PRO instrument is a questionnaire plus the information and documentation that support its use, that is used to capture PRO data to measure treatment benefit or risk involved in medical product and clinical trials.[99] Through a PRO, various types of outcomes such as physical functions, symptoms, global judgments of health, psychological well-being, social well-being, cognitive functioning, role activities, personal constructs, satisfaction with care, health- related quality of life ,adherence to medical regimens and clinical trial outcomes can be measured.[100] This study will look into patient-reported mental health status, HRQOL (measured using SF-12v2 questionnaire) and psychological distress (measured using the K6, a 6-item Kessler Psychological Distress Scale).

2.4.1 Health- related quality of life (HRQOL) and its measures

According to Healthy people 2020, HRQOL is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. [34]The concept of HRQOL and its determinants have evolved since the 1980s in order to include those aspects of quality of life that can be clearly shown to affect the health, either physical or mental.[35] The questions about perceived physical and mental health function which are used to measure HRQOL have become an important component of health surveillance and are usually considered valid indicators of service needs and intervention outcomes. Several recent federal policy changes have emphasized the need to measure HRQOL to supplement public health's traditional

measures of mortality and morbidity. Healthy People 2000, 2010 and 2020 have identified improvement in quality of life as a central public health goal. HRQOL is related both to self-reported chronic diseases as well as their risk factors. [35]

Several measures used to assess HRQOL and related concepts of functional status include the Medical Outcomes Study Short Forms (SF-12 and SF-36), the Sickness Impact Profile, and the Quality of Well-Being Scale.[35]

The SF-12v2 is derived from SF-36 health-related quality of life measure and is the most recent subset scale of the SF-36. [101]It has 12 items, measures 8 domains of health and is used to calculate two component scores, the Mental Component Summary Score (MCS-12) and the Physical Component Summary Score (PCS-12).[102]Version 2 was released in 2002 and is thought to be an improvement over the previous version (SF-12vl). [102,103]A study by Ware and colleagues which measured the reliability and validity of SF-12v2 showed that it has high reliability (Cronbach's alpha of .89 for PCS-12 and .86 for MCS-12). Validity of PCS-12 measures was high, however validity of MCS-12 measures resulted in weaker correlations as compared to PCS-12, but were similar to validity measured conducted on SF-36.[103]

2.4.2 Health related quality of life and depression

A study done by Pyne and colleagues showed that the severity of depression negatively affects the HRQOL of a patient.[36] A number of previous studies on HRQOL in MDD have restricted their objectives to only some components of HRQOL like social functioning and have showed that acute or depressive phase of MDD have a high impact on HRQOL.[38,39,104] Another study which compared the HRQOL in patients with depression and a control group found that HRQOL was largely reduced in depressive outpatients as compared to control group. The significance of

measuring the HRQOL in depression has greatly increased after the Medical Outcomes Study, wherein the social wellbeing and physical functioning of depressed patients were compared with those of other chronic conditions such as hypertension, arthritis and diabetes.[39] This study showed that when compared to other chronic conditions, depression has the greatest negative impact on HRQOL of patients. [39,105] It is therefore believed by researchers that it is important to evaluate a treatment or medical intervention in terms of its ability to improve the HRQOL of patients suffering from chronic conditions such as depression. [37]A study by Shi and colleagues comparing the effect of olanzapine alone and OFC on HRQOL found that OFC was associated with greater improvement in HRQOL than olanzapine alone. [106]

2.4.3 Mental health status and depression

Mental health in MEPS database can be evaluated in multiple ways, which includes the Kessler 6 scale for psychological distress, two item Patient Health Questionnaire (PHQ-2), mental health component (MCS-12) of SF-12v2 and patient self reported mental health status (PR-MHS). PR-MHS is predictive of psychological distress, depressed mood and functioning.[107] A study by Helen *et al*. Showed that depression symptoms are a significant predictor of mental health functioning. It has also been found that patients with depressive disorder tend to have worse physical, social, mental health, role functioning and worse perceived current health as compared to patients having no chronic conditions. [39]

2.5 Factors affecting HRQOL and mental health in depression

The STAR*D report evaluating the socio-demographic and clinical factors associated with the physical and mental health components of SF-12 suggest that African Americans reported worse physical function on the SF-12 when compared to Caucasians. Other factors associated with

worse physical function include unemployment, having public insurance, being of Hispanic ethnicity and higher depression severity. As opposed to this, higher level of education was associated with better physical function. Males were more likely to have better mental health when compared to females. Also, African American race and employment status were associated with better mental function, with unemployed participants reporting better mental function than those who were employed. Worse mental health was found to be associated with greater severity of depression, having higher education and being married or divorced. [108]Most of these findings are in line with the data obtained from the sample of patients with depression in the Medical Outcomes Study.[109] A study by Stewart *et al.* and Ormel *et al* found that chronic conditions have a negative impact on overall functioning and well-being of a person as a result of adverse events which lead to increased hospitalizations and elevation of psychological distress.[4,109]

Chapter 3

Methods

This chapter provides an overview of the methodology used to conduct the study. The following topics will be discussed in this chapter: (1) study design, (2) data source, (3) data collection, (4) inclusion- exclusion criteria, (5) study measures (6) theoretical framework and (7) data analysis.

3.1 Study Design

This was a retrospective, longitudinal observational study conducted using a secondary database. A two- year longitudinal panel covering years 2008 to 2011 (Panel 13 to 16) of the Medical Expenditure Panel Survey (MEPS), a publically available dataset, was used for the purpose of this study. This study was approved by the University of Toledo Biomedical Institutional Review Board.

3.2 Data Source

The data for this study comes from year 2008 to 2011 Medical Expenditure Panel Survey Household Component (MEPS-HC). It includes surveys of families from a nationally representative sample of the civilian, non-institutionalized U.S. population and is sponsored by the Agency for Healthcare Research and Quality.[110] It provides nationally representative estimates of health care use, expenditures, sources of payment, health insurance coverage,

respondents' health status, demographic and socio-economic characteristics, employment, access to care, and satisfaction with health care. Information about each household member is collected using computer assisted personal interviewing (CAPI) technology. All the data collected for a sampled household is reported by a single household respondent. Patients' reports are further verified by surveying their health-care providers as well as contacting the pharmacies where they reported filling the medications prescribed to them. Approximately 13,000 households and 35,000 individuals are surveyed each year.[111]

The panel design of the survey includes five rounds of interviews covering two full calendar years, providing data for examining person level changes in selected variables such as expenditures, health insurance coverage, and health status. The MEPS- HC sample is drawn from the households participating in the previous year's National Health Interview Survey (NHIS) conducted by the National Center for Health Statistics. The NHIS uses a stratified, multistage probability cluster sampling design which provides a nationally representative sample of the U.S. civilian non-institutionalized population. It oversamples Hispanics, African Americans, Asians and those in low-income families.

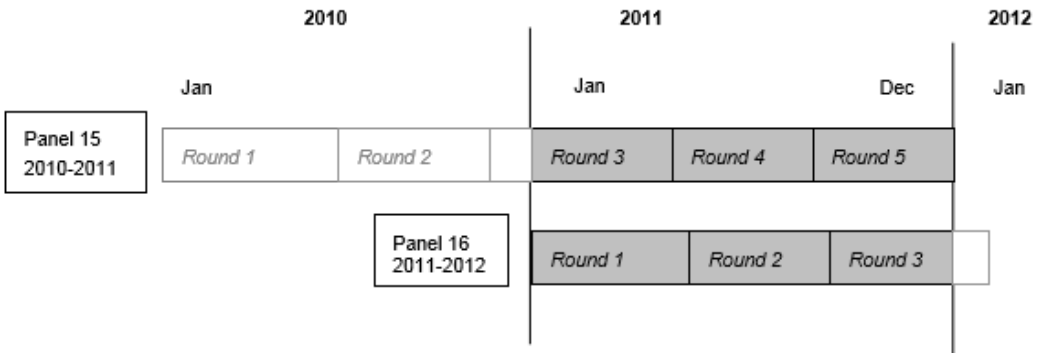

Figure1: Rotating panel design

3.3 Data Collection

3.3.1 Identification of patients with depression

Individuals having depression were identified using the MEPS HC medical conditions file. This file contains information on observation of each self-reported medical conditions that a MEPS respondent experienced during the data collection year. The participants are asked to report the medical condition that they experienced during the last four to five months since the previous interview in each round of interviews. Medical conditions reported by participants were recorded by interviewers as verbatim text, and were coded by professional coders to fully specified three digits ICD-9-CM codes.[112] According to AHRQ, conditions with ICD-9 codes 296, 300 and 311 were classified as depression.[7] These three ICD-9 codes were used to identify patients with depression.

3.3.2 Medications used to treat depression

Patients taking antidepressants and those who were concomitant users of atypical antipsychotics were identified using the Prescribed Medicines Files. In this study, first the psychotherapeutic agents were identified using the therapeutic classification variable number 242(TC1), which is one of the Multum Lexicon Drug Database variables. [113] The therapeutic sub-classification variable (TC1S1) number 249 and 251were then used to identify antidepressants and antipsychotics respectively. Furthermore the therapeutic sub- sub classification variable (TC1S1_1) number 76(miscellaneous antidepressants), 208 (SSRI antidepressants), 209 (tricyclic antidepressants), 306 (phenylpiperazine antidepressants), 307(tetracyclic antidepressants) and 308 (SNRI antidepressants) were used to identify specific classes of antidepressants. Only those patients who were taking antidepressants and/or AAPs since the beginning of a panel were

included in the study (using RXBEGYRX variable).Patients starting medications in the 3rd,4th and 5th round of a panel were also excluded (using PURCHRD and RXBEGMM variable) as their HRQOL, PRMHS and K6 scores were seen in rounds 2 and 4.

The drugs that were classified as antidepressants included citalopram, escitalopram, amitriptyline, clomipramine, desipramine, amoxapine, buproprion, doxepine, venlafaxine, desvenlafaxine, paroxetine, imipramine, trimipramine, trazodone, tranylcypromine, sertraline, protriptyline, phenelzine, nortriptyline, nefazodone, mirtazapine, maprotiline, isocarboxazid, fluvoxamine, fluoxetine, doxepin, and desipramine. AAPs included ziprasidone, quetiapine, risperidone, olanzapine and aripiprazole as they have been approved by the FDA for treatment of major depressive disorder or supported with evidence. [31]

3.4 Inclusion-Exclusion Criteria

3.4.1 Inclusion criteria

All respondents identified with depression in the 2008-2011 MEPS database files, above the age of 18 years and taking one or more antidepressants and/or antipsychotics were included in the study. Only those respondents who started taking antidepressants and/or AAPs since the beginning of the panel were included in the study.

3.4.2 Exclusion criteria

Patients who purchased medications in the 3rd, 4th and 5th round of a panel for the first time were excluded. Patients taking AAPs alone were excluded, as they are generally prescribed as monotherapy in patients with bipolar disorder and schizophrenia. Respondents with missing responses on either of the questions of SF-12, K6 and PR-MHS were also excluded.

3.5 Study definitions

Monotherapy: Patients on monotherapy were defined as those taking only one antidepressant.

Add-on/Switch therapy: Patients on add-on/switch therapy were defined as those patients who switch from one antidepressant to another or those who take a combination of antidepressants and/or AAPs.

3.6 Study measures

3.6.1 Classes of medications used to treat depression

For Objective 2, the effect of specific class of medications on change in PR-MHS, K6 and SF-12 scores was compared. For this study, the classes of antidepressants that were evaluated included, Selective serotonin reuptake inhibitors (SSRIs), Seretonin norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCAs) and other antidepressants (which included buproprion, mirtazapine, trazodone, and nefazodone). MAOIs was not evaluated as a separate class, as preliminary analysis found less than 5 patients on MAOIs. These patients were excluded from final data analysis.

3.6.2 Dependent variable measures

Effect of medications on three dependent variables, namely health-related quality of life, patient-reported mental health status and psychological distress was assessed. A criterion was established to determine change in these outcomes over a period of one year.

3.6.3 Health –related quality of life (HRQOL)

HRQOL of MEPS participants have been assessed by AHRQ using the Short Form Health Survey-12 version two (SF-12v2). [114]It has two component summary scales, namely the Physical

Component Summary(PCS-12) and Mental Component Summary(MCS-12) and their scores range from 0 to 100 where a higher score is indicative of a better HRQOL.[102](Refer Appendix A) The longitudinal data files in MEPS contain variables for both the PCS-12 and the MCS-12 scores of participants. These scores are measured in rounds 2 and 4 of a panel and are roughly a year apart. In this study, the change in scores of both PCS-12 and MCS-12 in one year's time, based on the class of medications and scores between those on monotherapy and add-on/switch therapy were evaluated.

In order to establish criteria to assess change in these scores, three categories were created. These include, "improve", "decline" and "unchanged" scores. If the difference in scores in round 4 and round 2 was ≥6 then the change in scores was defined as improved. Similarly if the difference in between the two rounds was ≤6 then it was defined as decline in scores. If the difference was between ≥6 and ≤ 6 in between the round 4 and 2, then the scores were said to remain unchanged. We chose the 6 point difference as response definition, because it represented half SD difference in HRQOL in our study. A half SD difference is considered a clinically significant change in HRQOL in a patient.[115]

3.6.4 Psychological distress measure

The Kessler Index (K6) scores measure the individuals' non-specific psychological distress in the past 30 days. The scores are based on six mental health related questions (refer Appendix B) that measure the individuals' nervousness, hopelessness, sadness, restlessness, worthlessness, and effortlessness in the past 30 days on a scale of 0 to 4, with 0 being none of the time and 4 being all the time. The values on all these questions give the overall K6 scores. The higher the K6 scores, the more is the person's tendency towards mental disability. The internal consistency

and reliability of K6 scores is high (Cronbach's alpha of 0.89).[116]The longitudinal data files in MEPS contain K6 scores. These scores are measured in rounds 2 and 4 of a panel and are roughly a year apart.

In order to establish criteria to define change in scores in between rounds 2 and 4, K6 scores were first categorized into no/low psychological distress, mild or moderate and severe distress. We used previously reported cut off-points in the literature to stratify K6 scores into no/low psychological distress (0–6), mild-moderate psychological distress (7– 12), and severe distress (13–24).[116] If a person moved from a lower category in round 2 to a higher category in round 4, for example, from high distress to moderate or low distress then it was defined as improvement. If a person moved from a higher category in round 4 to a lower category in round 2 then it was defined as decline in K6 scores. In case the category remained the same in both the rounds, then psychological distress was defined to remain unchanged.

3.6.5 Patient self- reported mental health status (PR-MHS)

Perceived mental health was assessed using questions that asked the participant of MEPS-HC: "In general, compared with other people of the same age, would you say that your mental health is excellent, very good, good, fair, or poor?" It is scored on a likert scale of 1 to 5, where 1 is excellent, 2 is very good, 3 is good, 4 is fair and 5 is poor. Change in scores between rounds 2 and 4 were assessed in this study. All perceived health responses were reverse coded in MEPS so as to match the scaling of the MCS-12 and PCS-12 and to aid in interpretation.

Similar to the classification in K-6 scores, PR-MHS scores were further classified into very good (if PR-MHS is excellent and very good), fair (if PR-MHS is good and fair) and poor. The criteria to evaluate change in scores were similar to K6.

3.3.6 Other independent variables (covariates)

The information on covariates, which include, demographic factors, socio-economic factors, health-related factors and resources available was obtained from the MEPS longitudinal data files. In the present study we controlled for demographic variables such as age, gender, race, ethnicity and marital status. Socio-economic factors included education level, annual total person income, insurance type (private, public and no insurance) and employment status (employed vs. unemployed).Health-related factor included the number of co-morbid health conditions that a patient may have in addition to depression. These were counted as the sum of priority chronic conditions that are present in the longitudinal full -year consolidated files of MEPS. MEPS collects information about a selected group of medical conditions that have been specified by the Agency for Healthcare Research and Quality as "priority conditions". Resources available included the variables "satisfaction with quality of care", "access to healthcare" and "health state stopped social activity". To determine the satisfaction with quality of care, the respondents were asked to rate their overall healthcare from 0 (worst possible healthcare to 10 (best possible healthcare). This was dichotomized into low satisfaction (scored from 0 to 6) and high satisfaction (scored from 7 to 10). "Access to healthcare" was further dichotomized into "never got access to medical care" and "always got access to medical care". "Health stopped social activity" was also used as a covariate in the study. This was further categorized into health stopped social activity all the time, sometime and none of the time.

3.7 Theoretical framework

In the present study, the theoretical framework depicts the relationship between depression characteristics, mainly the type of pharmacotherapy and patient-reported outcomes such as

HRQOL, PR-MHS and non-specific psychological distress. This model is based on Pearlin's Stress Process Model and the "Biopsychosocial" model of health. In the Stress Process Model, the primary stressors namely conditions, experiences, or life events may cause psychological distress and anxiety that can affect an individual's well-being or physical and/or mental health.[117] The Biopsychosocial model of health puts emphasis on the social, behavioral factors and psychological factors, in addition to biological factors which may influence an individual's health.[118]

Studies by Pyne et al, Kennedy et al and Wells et al have found that depression is negatively associated with the quality of life[36], patients' physical, social and psychological status[105] and overall functioning. In this theoretical framework, diagnosis of depression is hence a factor which may affect the mental health status and HRQOL of an individual. Therefore, depression diagnosis might act as a stressor and have a negative impact on the mental health status and HRQOL Depression diagnosis and its effect on HRQOL and mental health may be influenced by various demographic characteristics, socio-economic characteristics, general health characteristics, and social support available to them. Moreover, a study by Papakostas and colleagues showed that the treatment with antidepressants and /or psychotherapy has shown to improve the physical and mental health of multiple patient populations suffering from depression. This study evaluated the effect of pharmacotherapy used to treat depression on HRQOL, PR-MHS and psychological distress after controlling for the various demographic, socio-economic, general health characteristics and resources available to individuals suffering from depression.

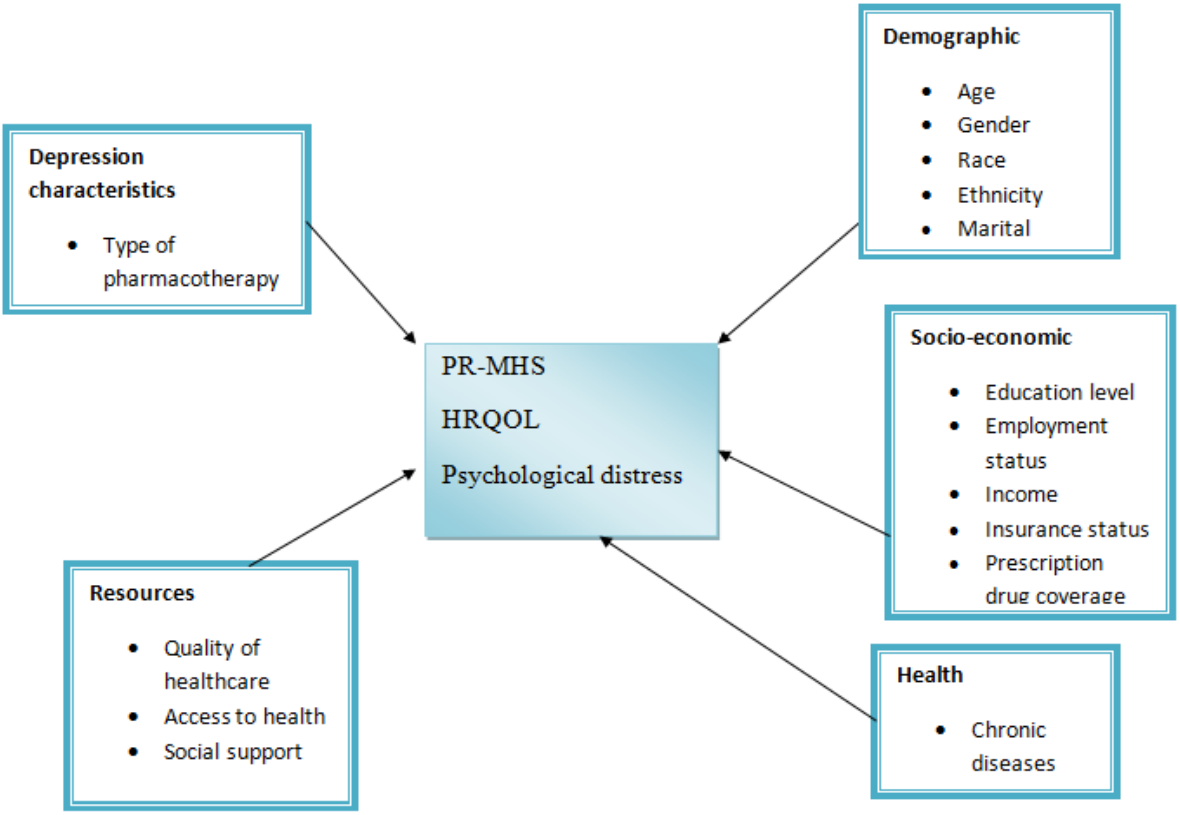

Figure 2 -Theoretical framework for HRQOL, perceived mental health status and psychological distress.

3.8 Data analysis

Descriptive statistics were used to describe the population according to their socio-demographic characteristics. The characteristics of patients taking different classes of medications and those who are on monotherapy, combination therapy and those who switch from monotherapy to combination therapy were analyzed for differences using t-tests for continuous variables and chi-square tests for categorical variables. All statistical values were considered significant at a level of significance of $p \leq 0.05$. The dependent variables, namely the change in HRQOL, K6 scores and PR-MHS, were categorized into "improve", "decline" and "unchanged". A multinomial logistic regression model was built to determine the effect of independent variables on the above

mentioned dependent variables. Demographic variables, (race, gender, ethnicity, marital status) socioeconomic status (education level, employment status, income and insurance status), co-morbidities, and resources available (quality of healthcare, access to healthcare, socio-economic support) were controlled in the regression analysis. Statistical analysis was conducted using SAS software (version 9.3 SAS Institute Inc., Cary, NC, USA).

Chapter 4

Results

This chapter a description of the patient population under study, the statistical analysis carried out on the data and the results obtained from the study.

4.1 Patient Population for study

A total of 804 patients met the study criteria and were included in the data analysis. The selection of the patient population for the study is described in Figure 3.

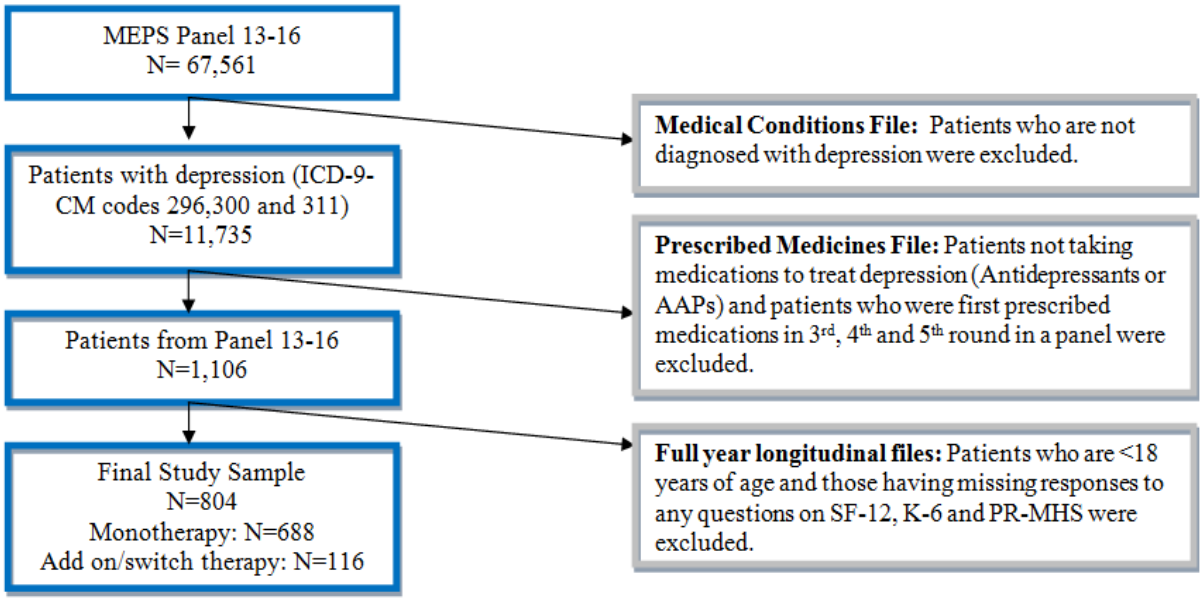

Figure 3: Selection process for the final study sample.

There were 67,561 respondents in panels 13 to 16 (years 2008-2012). Among them, 11,735 patients were identified to have depression. Only those patients who were either taking one or more antidepressant or a combination of antidepressant and atypical antipsychotics were included in the study. Furthermore, patients who were prescribed medications since the beginning of a panel were included in the study. Patients who were prescribed medications in the 3rd, 4th, and 5th round of a panel for the first time were excluded .This gave a total of 1,106 patients who met the inclusion criteria. Out of these, 302 patients who were below the age of 18 years and who had one or more missing responses on the self administered questionnaire of MEPS (SAQ) were excluded. This gave a final sample of 804 patients. Among these, 688 patients were found to be on monotherapy (patients taking only one antidepressant) and 116 patients were found to take more than one antidepressant or a combination of antidepressant and AAPs. This group included all the patients who either switched from one medication therapy to another and those who were asked to take another medication in addition to the previously prescribed medication.

4.2 Demographic characteristics:

The socio-demographic characteristics of the sample are summarized in Table 1. As shown in Table 1, assigning weights gave a number of 17,199,715 which represented a national cohort of patients with depression who are prescribed one or more medications to treat depression. A vast majority of the study sample were females (N=579, 68%), whites (N=487, 70%) and Non Hispanics (N=681, 91%). Most of the patients fell within the age category of 18-45 years (N=376, 47%). Patients who were married (N=351, 44%), had low income (N=429, 53%) and had an education level of greater than high school (N=365, 45.5%) represented a majority of the

population. Most of the patients had private insurance (N=443, 55%) and had high satisfaction with health care (N=659, 81.97). Furthermore, access to medical care was easy for a majority of the patients (N=520, 65%) and very few patients had greater than six co-morbidities in addition to depression (N=16, 2%).

Table 1: Socio-demographic characteristics of study population

Selected Characteristics	N=804(%)	Weighted (%) N=17,199,715
Gender		
Males	225(27.99)	31.37
Age		
18-45	376(46.77)	45.38
45-64	322(40.05)	41.73
>64	106(13.18)	12.88
Race		
White	487(60.57)	69.73
African American	75(9.33)	4.85
Other	242(30.10)	25.41
Ethnicity		
Hispanic	123(15.30)	8.21
Education Level		
Less than high school	139(17.29)	12.35
High School	300(37.31)	35.04
More than high school	365(45.50)	52.59
Marital Status		
Married	351(43.66)	46.91
Divorced, widowed, separated	263(32.71)	29.27
Never married	190(23.63)	23.80
Person's total income		
No income	83(10.32)	8.70
Less than $25,000	429(53.36)	49.79
$25000-$50,000	181(22.51)	24.78
>$50,000	111(13.81)	16.70
Employment Status		
Employed	406(50.37)	55.21
Insurance		
Any private	443(55.10)	63.91
Public only	268(33.33)	25.69
Uninsured	93(11.57)	10.39
Prescription drug insurance coverage		
Yes	363(45.15)	52.62

Quality of health care rating		
High	659(81.97)	51.90
Ease of access to medical care		
Never/sometimes	91(11.32)	11.18
Always	520(64.68)	66.30
Unknown	193(24.00)	22.50
Health stopped social activity		
Most of the time	236(29.35)	27.03
Sometime	360(44.78)	44.50
None of the time	208(25.87)	28.19
No. of comorbidities		
1-2	364(45.27)	47.26
3-4	307(38.18)	36.56
4-5	117(14.55)	14.44
>6	16(1.99)	1.72

Table 2 shows results from chi-square tests which were run to determine significant differences between patients on monotherapy and add-on/switch therapy. No statistically significant difference was found between patients who were on monotherapy and those who were on add-on or switch therapy based on their gender, race, ethnicity, education level, number of co-morbidities, type of insurance, satisfaction with heath care and ease of receiving medical care ($P \geq 0.05$). When compared according to marital status, married individuals were significantly higher in the monotherapy group as compared to those who switch medications or take more than one medication.($P=0.0039$).On an average, patients who had a lower income were significantly higher in the add-on/switch group as compared to monotherapy group($P=0.0413$). The proportion of patients who were employed was significantly higher in those on monotherapy ($P=<0.0001$). Also, the proportion of individuals having prescription drug coverage was significantly higher in the monotherapy group when compared to those who were in the add-on/switch group. ($P=0.0126$). Patients who were on add-on switch therapy were significantly

more likely to report that their health condition stopped their social activity most of the times as compared to patients who were on monotherapy (P= 0.0004).

Table 2: Patient characteristics stratified by type of pharmacotherapy(Monotherapy or Add-on/Switch therapy)

Selected Characteristics	Monotherapy (N=688)	Add on/Switch therapy(N=116)	P value
	N(%)	N(%)	
Gender			
Males	195 (28.34)	30(25.86))	0.58199
Age			
18-45	316 (45.93)	60(51.72)	0.2394
45-64	276(40.12)	46(39.66)	
>64	96(13.95)	10(8.62)	
Race			
White	422(61.34)	65(56.03)	0.4276
African American	61(8.87)	14(12.07)	
Other	205(29.80)	37(31.90)	
Ethnicity			
Hispanic	106(15.41)	17(14.66)	0.8352
Education Level			
Less than high school	121(17.59)	18(15.52)	0.7642
High School	258(37.50)	42(36.21)	
More than high school	309(44.91)	56(48.28)	
Marital Status			
Married	314(45.64)	37(31.90)	**0.0039**
Divorced, widowed, separated	224(32.56)	39(33.62)	
Never married	150(21.80)	40(34.48)	
Person's total income			
No income	64(9.30)	19(16.38)	**0.0413**
Less than $25,000	364(52.91	65(56.03)	
$25000-$50,000	163(23.69)	18(15.52)	
>$50,000	97(14.10)	14(12.07)	
Employment Status			
Employed	368(53.49)	37(31.90)	**<0.0001**
Insurance			
Any private	391(56.83)	52(44.83)	0.0548
Public only	220(31.98)	48(41.38)	
Uninsured	77(11.19)	16(13.79)	
Prescription drug insurance			

Yes	323(46.95)	40(34.48)	**0.0126**
Quality of health care rating			
High	569(82.70)	90(77.59)	0.1848
Ease of access to medical care			
Never/sometimes	75(10.90)	16(13.79)	0.4107
Always	443(64.93)	77(66.38)	
Unknown	170(24.71)	23(19.83)	
Health stopped social activity			
Most of the time	188(27.33)	48(41.38)	**0.0004**
Sometime	307(44.62)	53(45.69)	
None of the time	193(28.05)	15(12.93)	
No. Of comorbidities			
1-2	314(45.64)	50(43.10)	0.5350
3-4	263(38.23)	44(37.93)	
4-5	96(13.95)	21(18.10)	
>6	15(2.18)	1(6.25)	

Statistically significant p-values are presented in bold.

4.3 Descriptive statistics

Table 3 shows the percentage of patients on monotherapy and add-on/switch therapy who show improvement, no change or decline in SF-12, K6 and PR-MHS scores. Table 3 shows that a vast majority of the patients were found to remain in the "unchanged" category in both the monotherapy and add-on switch therapy group. These patients neither showed improvement nor decline in their outcomes. A greater percentage of individuals were found to show decline in PCS-12 scores in both the groups (23.4 % and 27.59%) as compared to showing improvement (18.6% and 19.83%). On the contrary, the percentage of individuals showing improvement was higher in both the groups on MCS-12 scores (31% in monotherapy and 31.90% in add-on/switch group) in comparison to individuals showing decline (24.27% and 23.28% respectively). Approximately 20% of individuals were found to show improvement on PR-MHS in the monotherapy group as compared to 18.97% individuals in add-on/switch group. The number of people showing improvement and declines in PR-MHS scores was almost the same in the add-

on/switch group. (18%). A greater number of patients on monotherapy showed improvement on K6 scores (21.80%) as compared to decline (17.88%). Similarly a greater number of patients on add-on/switch therapy showed improved K6 scores (26.72%) as compared to decline (16.38%).

Table 3: Percentage of individuals showing change in SF- 12, K6 and PR-MHS scores based on monotherapy and add on/switch therapy

Category	Monotherapy			Add on/Switch therapy		
	Improve N(%)	Unchanged N(%)	Decline N(%)	Improve N(%)	Unchanged N(%)	Decline N(%)
SF-12:PCS	128(18.60)	399(57.99)	161(23.40)	23(19.83)	61(52.59)	32(27.59)
SF-12:MCS	213(30.96)	308(44.77)	167(24.27)	37(31.90)	52(44.83)	27(23.28)
PR-MHS	139(20.20)	436(63.37)	113(16.42)	22(18.97)	73(62.93)	21(18.10)
K6 scores	150 (21.80)	415(60.32)	123(17.88)	31(26.72)	66(56.90)	19(16.38)

The study also determined differences in the scores of outcome variables for patients who are only on monotherapy based on the class of antidepressants prescribed to them. Of the total of 668 patients on monotherapy, a majority of the patients reported taking SSRIs to treat depression (N=421). Minimum numbers of individuals were found to be taking TCAs to manage depression (N=40). SNRIs were found to be taken by 109 individuals. Other antidepressants, which include bupropion, nefazodone, trazodone and mirtazapine was prescribed to 118 individuals with depression. Table 4 shows the percentage of patients showing improvement, decline and those individuals whose scores remained the same in 2nd and 4th rounds of the panel. Similar to results in Table 3, a vast majority of patients on either of the four classes of antidepressants showed no change in the scores of the outcome variables. Also, more patients were found to show decline in PCS-12 scores as compared to improvement in either of the four classes of antidepressants. Among those on SSRIs there were a greater percentage of patients showing improvement in

MCS-12 scores (35.62%) as compared to decline (18.05%). Similar results were obtained for those on other antidepressants on MCS-12 scores (34% compared to 24.6%). On the contrary, more patients on SNRIs showed decline (31%) in MCS-12 scores as compared to improvement (23%). Higher percentage of patients on SSRIs, TCAs and SNRIs were found to show improvement on the PR-MHS scale as compared to decline. The percentage of patients on other antidepressants, showing improvement and decline in PR-MHS were the same. (17.80%).Likewise, the percentage of patients on SSRIs and TCAs that showed improvement on K6 scores were higher as compared to those showing decline.

Table 4: Percentage of individuals on monotherapy showing change in SF- 12, K6 and PR-MHS scores based on the class of antidepressants prescribed.

Category	SSRIs (N=421)			TCAs(N=40)			SNRIs(N=109)			Other Antidepressants(N=118)		
	Improve N (%)	Remains same N (%)	Decline N (%)	Improve N (%)	Remains same N (%)	Decline N (%)	Improve N (%)	Remains same N (%)	Decline N (%)	Improve N (%)	Remains same N (%)	Decline N (%)
SF-12:PCS	71 (16.86)	256 (60.81)	94 (22.33)	13 (32.50)	19 (47.50)	8 (20.00)	24 (22.02)	59 (54.13)	26 (23.85)	20 (16.95)	65 (55.08)	33 (27.97)
SF-12: MCS	150 (35.62)	195 (46.32)	76 (18.05)	15 (37.50)	14 (35.00)	11 (27.50)	25 (22.94)	50 (45.87)	34 (31.19)	40 (33.90)	49 (41.53)	29 (24.58)
PR-MHS	91 (21.62)	260 (61.76)	70 (16.63)	9 (22.50)	24 (60.00)	7 (17.50)	18 (16.51)	76 (69.72)	15 (13.76)	21 (17.80)	76 (64.41)	21 (17.80)
K6 scores	93 (22.09)	256 (60.81)	72 (17.10)	12 (30.00)	22 (55.00)	6 (15.00)	23 (21.10)	64 (58.72)	22 (20.18)	22 (18.64)	73 (61.86)	23 (19.49)

4.4 Multinomial Logistic Regression Results:

Table 5 shows multinomial logistic regression results for the physical component summary score and mental component summary scores for patients only on monotherapy. Decline in these scores was treated as the reference category for comparison. Among antidepressants, SSRIs was treated as the reference as it is the most frequently prescribed antidepressant class. No significant differences were observed in the PCS-12 scores among patients on monotherapy based on the class of antidepressant used. Nonetheless, the odds of users of TCAs were found to be 64% lower in showing improvement on MCS-12 scores as compared to users of SSRIs (95% CI, 0.114– 0.950). Those on SNRIs were 66.3% less likely than those on SSRIs to show improvement on MCS-12 scores as opposed to decline (95% CI, 0.155–0.730). In addition to this, the study findings also reveal that age, race, gender, type of insurance, income and number of co-morbidities are significant predictors of improvement in PCS-12 scores. On the other hand social activity, ethnicity and income were found to be significant predictors of change in MCS-

12 scores. Blacks were 2.2 times more likely to show improvement in PCS-12 scores as compared to whites (95% CI, 1.006–5.007). Patients who were older than 65 years were 64% less likely to show improvement in PCS-12 scores as compared to patients of age 18-45 years (95% CI, 0.134-0.978). Also, females were 54% less likely to show improvement in PCS-12 scores as compared to males (95% CI, 0.24-0.91).Likewise, those having an income of $25,000 to $50,000 and those having an income of >$50,000 had lesser odds of showing improvement in PCS-12 scores when compared to patients having no income. Patients having public insurance had 3 times higher odds of showing improved PCS-12 scores when compared to those having private insurance.(95% CI, 1.188- 7.707). Patients who responded that their health state "sometimes" and "none of the times" stopped their social activity were less likely to show improved MCS-12 scores as compared to those who responded "all the time." Non-Hispanics were 2 times more likely to show improvement in MCS-12 scores as opposed to decline when compared to Hispanics.

Table 5: Multinomial logistic regression to predict improvement in SF-12 scores among patients on monotherapy.

Category	PCS-12		MCS-12	
	Odds Ratio (95 % CI) Ref: Decline		Odds Ratio (95 % CI) Ref: Decline	
	Improve	Unchanged	Improve	Unchanged
Drug Class (Ref:SSRIs)				
TCAs	1.919 (0.656-5.609)	0.757 (0.310-1.850)	**0.361 (0.114- 0.950)**	0.417 (0.129 - 1.352)
SNRIs	1.002 (0.508-1.976)	0.787 (0.425-1.460)	**0.337 (0.155–0.730)**	0.685 (0.367–1.278)
Other Antidepressants	0.543 (0.284-1.038)	0.724 (0.387-1.354)	0.823 (0.423–1.600)	0.804 (0.411–1.573)
Race (ref: white)				
Black	**2.244 (1.006–5.007)**	1.000 (0.440–2.272)	0.879 (0.346 –2.233)	1.063 (0.461 –2.449)
Others	1.615 (0.798 – 3.268)	1.275 (0.745 2.184)	0.893 (0.486 –1.643)	0.839 (0.523 -1.347)
Age (Ref: 18-45)				
45-65	0.647 (0.306-1.366)	1.067 (0.595-1.913)	1.232 (0.581 –2.616)	1.232 (0.684 -2.216)
>64	**0.362 (0.134-0.978)**	0.492 (0.206-1.177)	0.392 (0.147 –1.042)	0.787 (0.364 -1.703)
Years of education (Ref: <9 years)				
9-11 years	1.265 (0.487-3.284)	0.585 (0.305-1.121)	1.163 (0.552–2.454)	0.898 (0.448 -1.803)
12-17 years	1.568 (0.653-3.765)	0.747 (0.403-1.383)	1.647 (0.798 –3.397)	1.019 (0.506 -2.051)
Marital Status(Ref: Married)				
Divorced / Separated	0.760 (0.389-1.483)	1.016 (0.570 1.811)	0.834 (0.462 –1.505)	0.754 (0.447 -1.274)
Never married	0.917 (0.410-2.051)	1.481 (0.780-2.813)	0.595 (0.306 –1.159)	0.884 (0.454 -1.721)
Quality of health care rating (Ref: Low)				
High	1.206 (0.524 – 2.777)	1.185 (0.615-2.284)	0.865(0.373 – 2.006)	0.704 (0.347 -1.430)
Ease of access to care (Ref: Never / sometimes)				
Always	1.841 (0.724 – 4.686)	1.322 (0.610-2.862)	0.605 (0.235 –1.559)	1.969 (0.804 -4.822)
Unknown	0.738 (0.251 – 1.943)	0.809 (0.336-1.943)	0.767 (0.293– 2.005)	1.955 (0.775 -4.740)
Health stopped social activity (Ref: Most of the time)				
Sometimes	1.179 (0.591 – 2.349)	1.171 (0.651-2.109)	**0.295 (0.148 –0.587)**	0.825 (0.418 –1.632)
None of the time	0.892 (0.373-2.135)	1.520 (0.789-2.928)	**0.077 (0.035 –0.168)**	0.946 (0.455 -1.967)
Prescription drug insurance (Ref: Yes)				
No	0.846 (0.453-1.580)	0.579 (0.255-1.314)	0.522 (0.240 –1.133)	0.550 (0.267 -1.134)
Ethnicity (Ref: Hispanic)				
Non-Hispanic	0.579 (0.255-1.314)	1.185 (0.623-2.254)	**2.053 (1.069 –3.941)**	1.351 (0.724 -2.521)
Gender (Ref: Males)				
Females	**0.467 (0.240-0.912)**	0.688 (0.390-1.211)	1.124 (0.637 – 1.983)	0.974 (0.582 -1.629)
Insurance (Ref: Any Private)				
Public only	**3.026 (1.188- 7.707)**	2.024 (0.907 4.520)	0.820 (0.388 –1.730)	0.978 (0.430– 2.225)
Uninsured	2.599 (0.810 – 8.339)	2.324 (0.860-6.280)	0.878 (0.313 – 2.463)	1.379 (0.553 – 3.439)
Income(Ref: No income)				
$ 0 - $25,000	**0.381 (0.146 - 0.996)**	0.713 (0.292-1.742)	**3.850 (1.727 –8.585)**	2.105 (0.990 -4.475)
$25,000 - $50,000	**0.296 (0.097 – 0.904)**	0.747 (0.269-2.704)	2.459 (0.752 –8.038)	1.580 (0.583 -4.278)
> $50,000	0.393 (0.099 –1.567)	1.255 (0.361 4.367)	2.451 (0.771 –7.788)	2.761 (0.992 -7.688)
Employment status (Ref: Employed)				
Unemployed	0.595 (0.296 – 1.193)	0.935 (0.515-1.696)	1.317 (0.704 –2.464)	1.342 (0.751 -2.396)
No. of comorbidities(Ref:1-2)				
3-4	**2.817 (1.553 – 5.110)**	1.001 (0.596-1.680)	0.891 (0.467 –1.699)	1.595 (0.977 -2.604)
4-5	1.715 (0.572 -5.142)	1.118 (0.514-2.431)	0.900 (0.364 –2.331)	1.164 (0.581 -2.331)
>6	**165.4 (11.27- >999.9)**	39.93 (2.92-546.85)	1.012 (0.188 –5.448)	0.978 (0.237 -4.040)

Statistically significant values are presented in bold.

The reference categories used in Table 6 are the same as those in Table 5. As seen in Table 6, no significant association was found between the classes of antidepressants used among patients with depression and the tendency to show improvement, decline or no change in PR-MHS and K6 scores. Furthermore, only health stopped social activity was found to be a significant predictor of both changes in PR-MHS and K6 scores. The odds ratio of improvement in PR-MHS and K6 scores of patients reporting that their "health never stopped their social activity" was 0.354 (95% CI, 0.162 -0.774) and 0.083 (95% CI, 0.033 – 0.207) respectively as compared to patients whose "health always stopped their social activity". This means that these patients had lower tendency to show improvement as opposed to decline in PR-MHS and K-6 scores.

Table 6: Multinomial logistic regression to predict improvement in PR-MHS and K6 scores among patients on monotherapy.

Category	PR-MHS		K6	
	Odds Ratio (95 % CI) Ref: Decline		Odds Ratio (95 % CI) Ref: Decline	
	Improve	Unchanged	Improve	Unchanged
Drug Class (Ref:SSRIs)				
TCAs	0.939 (0.290–3.033)	0.625 (0.274–1.583)	0.742 (0.266– 2.702)	0.654 (0.302 – 1.414)
SNRIs	0.942 (0.407–2.179)	1.010 (0.462–2.179)	0.935 (0.434–2.015)	0.955 (0.507–1.798)
Other Antidepressants	0.617 (0.277–1.376)	0.706 (0.354–1.407)	0.484 (0.210–1.113)	0.925 (0.493–1.737)
Race (Ref: white)				
Black	0.749 (0.247 – 2.277)	0.772 (0.339 1.754)	1.049 (0.431 – 2.554)	0.685 (0.316 -1.487)
Others	1.003 (0.491 – 2.051)	1.221 (0.600 2.484)	0.685 (0.555 – 2.238)	1.360 (0.748 -2.473)
Age (Ref: 18-45)				
45-65	1.415 (0.647–3.093)	1.320 (0.711–2.452)	0.800 (0.374 – 1.709)	0.974 (0.547 -1.734)
>64	1.662 (0.675 – 4.091)	1.011 (0.417–2.452)	1.113 (0.394 – 3.146)	0.937 (0.384 -2.286)
Years of education (Ref: <9 years)				
9-11 years	2.503 (0.945– 6.631)	2.128 (0.866 –5.229)	1.121 (0.424 – 2.963)	0.957 (0.428 – 2.141)
12-17 years	1.815 (0.732 – 4.504)	2.215 (0.929–4.859)	2.113 (0.813 – 5.493)	1.910 (0.859 – 4.243)
Marital Status(Ref: Married)				
Divorced / Separated	1.331 (0.581 – 3.048)	1.093 (0.536 – 2.229)	0.966 (0.450 – 2.075)	1.208 (0.738 -1.977)
Never married	1.235 (0.491 – 3.107)	0.690 (0.312 –1.528)	1.182 (0.478 – 2.919)	1.178 (0.574 -2.420)
Quality of health care rating (Ref: Low)				
High	1.530 (0.514 – 4.555)	1.118 (0.555 -2.251)	0.523 (0.201 – 1.361)	0.734 (0.318 –1.694)
Ease of access to care (Ref: Never / sometimes)				
Always	0.922 (0.296 – 2.875)	1.739 (0.759 -3.987)	0.450 (0.134 - 1.509)	0.500 (0.174 – 1.441)
Health stopped social activity(Ref: All the time)				
Sometimes	**0.350 (0.149 – 0.821)**	0.442 (0.226 –0.865)	**0.292 (0.130 – 0.656)**	0.621 (0.302 – 1.277)
None of the time	0.394 (0.153 – 1.017)	0.354 (0.162 -0.774)	**0.083 (0.033 – 0.207)**	1.182 (0.537 – 2.603)
Prescription drug insurance (Ref: Yes)				
No	1.124 (0.414 – 3.052)	0.726 (0.330 –1.600)	0.653 (0.291 – 1.466)	0.608 (0.284 – 1.300)
Ethnicity(Ref: Hispanic)				
Non-Hispanic	1.135 (0.550 – 3.145)	1.090 (0.588 –2.020)	0.659 (0.306 – 1.420)	0.835 (0.477 – 1.463)
Gender(Ref: Males)				
Females	0.779 (0.440 – 1.382)	0.796 (0.440 –1.382)	0.570 (0.271 – 1.200)	0.772 (0.427 – 1.395)
Insurance (Ref: Any Private)				
Public only	1.300 (0.463 – 3.649)	1.617 (0.684 -3.821)	0.992 (0.438 – 2.245)	1.813 (0.760 –4.326)
Uninsured	0.813 (0.248 – 2.672)	1.039 (0.387 -2.672)	1.805 (0.334 -3.528)	1.754 (0.732 – 4.200)
Income(Ref: No income)				
$ 0 - $25,000	2.761 (0.766 – 9.952)	1.268 (0.488– 3.292)	1.520 (0.657 – 3.516)	1.618 (0.725 – 3.608)
$25,000 - $50,000	0.696 (0.160 – 3.021)	0.641 (0.231 –1.778)	1.743 (0.622 – 4.887)	1.861 (0.718 – 4.825)
> $50,000	1.745 (0.371 – 8.219)	1.309 (0.415 –4.125)	3.052 (0.736 – 12.65)	2.678 (0.877 – 8.174)
Employment status (Ref: Employed)				
Unemployed	0.467 (0.202 – 1.077)	0.775 (0.404 -1.486)	1.354 (0.699 – 2.258)	1.547 (0.898 – 2.666)
No. of comorbidities(Ref:1-2)				
3-4	1.597 (0.786 – 3.124)	1.156 (0.786 -3.124)	1.002 (0.465 – 2.162)	1.187 (0.634 – 2.224)
4-5	1.159 (0.419 – 3.203)	1.025 (0.395 -2.664)	0.768 (0.279 – 2.115)	1.016 (0.445 – 2.318)
>6	5.736 (0.557 – 59.12)	3.400 (0.442 -26.14)	1.563 (0.148– 16.54)	1.152 (0.194 – 6.828)

Statistically significant values are presented in bold.

As seen in Table 7, there was no statistically significant difference observed between patients on monotherapy and add-on/switch therapy to show improvement or decline in both the PCS-12 and MCS-12 scores of SF-12.In addition to this, the results suggest that patients whose age was >64 years were 58% less likely to show no change in their PCS-12 when compared to patients of age 18-45 years (95% CI, 0.18-0.94). Patients having private insurance were 2.6 times more likely than patients having public insurance to show improved scores on PCS-12. Also, patients with greater than two co-morbidities had higher odds of improvement on PCS-12 when compared to those having 1-2 co-morbidities. On the other hand, patients who did not have prescription drug insurance were 52% less likely to show improvement in MCS-12 as scores as opposed to showing decline, when compared to patients having a prescription drug insurance (95% CI, 1.131- 6.251).Those whose health stopped social activity "sometimes" and "none of the times" were significantly less likely to show improvement in MCS-12 scores as compared to those whose health "always" stopped their social activity (OR 0.453 ,95% CI 0.243 – 0.846 and OR 0.146, 95% CI 0.073 – 0.290).

Table 7: Multinomial logistic regression to predict improvement in SF-12 scores among patients on monotherapy and Add-on/switch therapy.

Category	PCS-12		MCS-12	
	Odds Ratio (95 % CI) Ref: Decline		Odds Ratio (95 % CI) Ref: Decline	
	Improve	Unchanged	Improve	Unchanged
Add on / Switch therapy (Ref: Monotherapy)	1.294 (0.584 – 2.868)	0.914 (0.516- 1.617)	0.911 (0.466 – 1.779)	0.870 (0.482 – 1.573)
Race (ref: white)				
Black	1.541 (0.736 – 3.228)	0.794 (0.395 –0.596)	0.979 (0.400 – 2.395)	1.021 (0.467 -2.231)
Others	1.172 (0.620 – 2.218)	1.029 (0.652 –1.625)	0.993 (0.585 – 1.684)	0.924 (0.616 -1.388)
Age (Ref: 18-45)				
45-65	0.756 (0.384 – 1.488)	0.944 (0.550 -1.620)	1.473 (0.766 – 2.834)	1.309 (0.790 -2.167)
>64	0.577 (0.228 – 1.459)	**0.420 (0.187 -0.940)**	0.451 (0.181 – 1.126)	0.760 (0.354 -1.629)
Years of education (Ref: <9 years)				
9-11 years	1.423 (0.602 – 3.362)	0.723 (0.400 -1.305)	0.960 (0.509 – 1.809)	0.954 (0.473 -1.924)
12-17 years	2.096 (0.948 – 4.633)	0.800 (0.439 -1.458)	1.214 (0.644 – 2.287)	0.968 (0.456 -2.053)
Marital Status (Ref: Married)				
Divorced / Separated	0.932 (0.482 – 1.799)	1.118 (0.643 -1.946)	0.893 (0.518 – 1.541)	0.772 (0.472 -1.265)
Never married	1.048 (0.494 -2.225)	1.344 (0.758 -2.381)	0.745 (0.393 – 1.415)	0.833 (0.450 -1.541)
Quality of health care rating (Ref: Low)				
High	1.156 (0.525 – 2.542)	1.351 (0.756 -2.414)	0.917 (0.432 – 1.947)	0.870 (0.458 -1.652)
Ease of access to care (Ref: Never / sometimes)				
Always	1.969 (0.744 – 5.212)	1.099 (0.534 –2.263)	0.512 (0.199 – 1.320)	1.627 (0.691 -3.831)
Health stopped social activity(Ref: All the time)				
Sometimes	0.898 (0.478 – 1.688)	0.988 (0.596 -1.637)	**0.453 (0.243 – 0.846)**	1.019 (0.537 -1.935)
None of the time	0.772 (0.346 – 1.723)	1.370 (0.743 -2.526)	**0.146 (0.073 – 0.290)**	1.196 (0.620 -2.306)
Prescription drug insurance (Ref: Yes)				
No	1.264 (0.545 – 2.934)	1.058 (0.581 -1.926)	0.478 (0.242 – 0.944)	0.526 (0.276 -1.003)
Ethnicity (Ref: Hispanic)				
Non-Hispanic	0.631 (0.301 – 1.322)	1.380 (0.758 -2.511)	1.648 (0.894 – 3.038)	1.316 (0.721 -2.402)
Gender (Ref: Males)				
Females	0.573 (0.295 – 1.111)	0.757 (0.459 -1.246)	1.384 (0.847 – 2.263)	0.976 (0.634 -1.503)
Insurance (Ref: Any Private)				
Public only	**2.659 (1.131- 6.251)**	1.553 (0.759 -3.175)	0.994 (0.485 – 2.039)	1.371 (0.641 -2.930)
Uninsured	2.188 (0.776 – 6.168)	1.628 (0.638 -4.153)	1.295 (0.531 – 3.155)	1.645 (0.713 -3.795)
Income (Ref: No income)				
$ 0 - $25,000	0.520 (0.216 – 1.249)	0.963 (0.436 -2.130)	**2.996 (1.368 – 6.559)**	1.746 (0.844 -3.610)
$25,000 - $50,000	0.440 (0.145 – 1.331)	1.190 (0.480 -2.949)	2.079 (0.735 – 5.883)	1.360 (0.552 -3.354)
> $50,000	0.597 (0.169 – 2.107)	1.666 (0.548 -5.062)	2.191 (0.754 – 6.364)	2.142 (0.798 -5.749)
Employment status (Ref: Employed)				
Unemployed	0.550 (0.273 – 1.107)	1.054 (0.604 -1.840)	1.264 (0.680 – 2.355)	1.229 (0.725 -2.081)
No. Of comorbidities (Ref: 1-2)				
3-4	**1.982 (1.156 – 3.400)**	1.067 (0.676 -1.684)	0.711 (0.427 – 1.392)	1.362 (0.857 -2.164)
4-5	1.133 (0.414 – 3.100)	1.277 (0.620 -2.632)	0.599 (0.257 – 1.398)	0.872 (0.434 -1.751)
>6	**128.42(10.663->999.99)**	71.78 (5.906 -872.499)	0.251 (0.030 – 2.087)	0.411 (0.087 -1.956)

Statistically significant values are presented in bold.

Table 8 shows that among patients on monotherapy and add-on/switch therapy there was no significant difference in scores on PR-MHS and K6. Patients in neither of the groups were more or less likely than the other to show improvement, no change or decline in the scores. In addition to this, employment status was found to be a significant predictor of change in PR-MHS scores. Patients who were unemployed had odds of 0.424 to show improvement in PR-MHS when compared to patients who were employed (95% CI, 0.2-0.897). This means that unemployed individuals were significantly less likely to show improvement in PR-MHS as compared to those who were employed. The results on health stopped social activity are similar to those in Table 6.

Table 8: Multinomial logistic regression to predict improvement in PR-MHS and K6 scores among patients on monotherapy and add-on/switch therapy.

Category	PR-MHS		K6	
	Odds Ratio (95 % CI) Ref: Decline		Odds Ratio (95 % CI) Ref: Decline	
	Improve	Unchanged	Improve	Unchanged
Add on / Switch therapy (Ref: Monotherapy)	1.039 (0.436 – 2.476)	0.748 (0.377 -1.482)	1.307 (0.577 – 2.963)	1.226 (0.610 -2.462)
Race (ref: white)				
Black	0.699 (0.228 – 2.148)	0.925 (0.404 -2.114)	1.013 (0.441 – 2.327)	0.655 (0.322 -1.330)
Others	0.918 (0.477 – 1.767)	1.158 (0.614 -2.182)	1.059 (0.561 – 1.998)	1.363 (0.790 -2.350)
Age (Ref: 18-45)				
45-65	1.495 (0.745 -3.000)	1.454 (0.827 -2.554)	0.756 (0.366 – 1.562)	0.938 (0.549 -1.601)
>64	1.675 (0.734 – 3.823)	1.017 (0.438 -2.362)	0.937 (0.320 – 2.739)	0.853 (0.356 -2.045)
Years of education (Ref: <9 years)				
9-11 years	2.063 (0.741 – 5.743)	1.880 (0.830 -4.259)	0.825 (0.329 – 2.066)	0.923 (0.448 -1.901)
12-17 years	1.315 (0.519 – 3.333)	1.623 (0.738 -3.568)	1.439 (0.549 – 3.772)	1.818 (0.856 -3.858)
Marital Status(Ref: Married)				
Divorced / Separated	1.136 (0.540 – 2.389)	0.996 (0.542 –1.828)	0.860 (0.402 – 1.838)	1.139 (0.719 -1.804)
Never married	1.313 (0.576 – 2.992)	0.920 (0.444 -1.908)	1.293 (0.565 – 2.958)	1.024 (0.517 -2.027)
Quality of health care rating (Ref: Low)				
High	1.482 (0.570 – 3.853)	0.939 (0.485 -1.819)	0.448 (0.196 – 1.022)	0.788 (0.382 –1.625)
Ease of access to care (Ref: Never / sometimes)				
Always	0.826 (0.280 – 2.436)	1.628 (0.756 -3.506)	0.429 (0.134 - 1.366)	0.480 (0.184 -1.251)
Health stopped social activity(Ref: All the time)				
Sometimes	**0.287 (0.135 – 0.610)**	**0.442 (0.240 -0.814)**	**0.272 (0.130 – 0.568)**	0.531 (0.270 -1.046)
None of the time	**0.395 (0.171 – 0.914)**	**0.375 (0.180 -0.781)**	**0.097 (0.040 – 0.234)**	0.898 (0.421 -1.197)
Prescription drug insurance (Ref: Yes)				
No	1.080 (0.447 – 2.611)	0.733 (0.348 -1.545)	0.575 (0.240 – 1.380)	0.674 (0.323 – 1.405)
Ethnicity (Ref: Hispanic)				
Non-Hispanic	1.149 (0.532 – 2.483)	0.962 (0.536 -1.725)	0.718 (0.352 – 1.468)	1.044 (0.597 – 1.827)
Gender(Ref: Males)				
Females	0.860 (0.509 – 1.452)	0.892 (0.551 –1.444)	0.747 (0.381 – 1.468)	0.850 (0.483 -1.495)
Insurance (Ref: Any Private)				
Public only	1.367 (0.535 – 3.493)	1.594 (0.696 -3.651)	1.182 (0.522 – 2.674)	1.803 (0.809 -4.016)
Uninsured	0.760 (0.240 – 2.409)	1.143 (0.462 -2.830)	1.068 (0.362 -3.148)	1.883 (0.810 -4.374)
Income (Ref: No income)				
$ 0 - $25,000	1.133 (0.365 – 3.518)	0.868 (0.369 -2.039)	1.631 (0.652 – 4.082)	1.682 (0.806 -3.509)
$25,000 - $50,000	0.346 (0.093 – 1.292)	0.545 (0.211 -1.407)	1.829 (0.644 – 5.196)	1.806 (0.740 – 4.404)
> $50,000	0.926 (0.240 – 3.575)	1.345 (0.442 -4.096)	3.495 (0.911- 13.412)	**2.973 (1.057 -8.359)**
Employment status (Ref: Employed)				
Unemployed	**0.424 (0.200 – 0.897)**	0.805 (0.444 -1.462)	1.224 (0.610 – 2.459)	1.340 (0.766 – 2.342)
No. Of comorbidities (Ref: 1-2)				
3-4	1.023 (0.568 – 1.843)	1.012 (0.572 -1.790)	1.021 (0.535 – 1.950)	1.208 (0.686 -2.126)
4-5	0.775 (0.304 – 1.973)	0.894 (0.393 -2.033)	0.827 (0.324 – 2.109)	1.104 (0.512 -2.380)
>6	6.846 (0.713 – 65.68)	2.760 (0.328 -23.25)	0.969 (0.074- 12.692)	1.811 (0.251 -13.091)

Statistically significant values are presented in bold.

Chapter 5

Discussion

This chapter discusses the findings of this study, its implications, limitations and future research.

Patients with depressive disorder tend to have worse physical, social, mental health and role functioning as compared to patients having no chronic conditions. [39]After the Medical Outcomes Study, the health-related quality of life (HRQOL) should be the ultimate measure of any kind of intervention in the treatment of depression.[39] Depression, being a mental illness, has a profound impact on the mental health of an individual. [41]Moreover , perceived mental health status has been shown to be a strong predictor of the mental health treatment used.[40] Thus, the primary aim of the present study is to assess the effect of pharmacotherapy used to treat depression on the HRQOL and mental health of patients, using a nationally representative sample of the US population. Based on the theory that the pharmacotherapy used to treat depression should relieve symptoms and hence improve the overall quality of life and mental health of individuals, we hypothesize that the there should be differences in the HRQOL and mental health scores over a period of time depending on the type of pharmacotherapy used.

One of the major aspects of the study was to establish criteria to determine improvement in HRQOL and mental health scores measured over two different time points (objective 1). It has been reported that as many as 40% of patients suffering from depression fail to respond to conventional monotherapy, and patients diagnosed and relieved of depression may be significantly likely to show relapse of symptoms.[21-23] Also, most studies on depression and mental health or depression and HRQOL, done using a retrospective database, follow a cross-sectional study design. It is therefore essential to evaluate the outcome measures over a period of time to see whether the HRQOL and mental health is maintained to be the same, improves or declines due to the treatment used. This has been explained in the methods section of the study.

Our sample was characterized by 72% women which corroborates with the findings of other studies that show that women are more likely to experience depression than males. The majority of our study population was Non-Hispanic whites (61%). This is in line with previous studies which report that whites are more likely to experience depression than other races. [8,46]An average of 47% of patients fell within the age category of 18-45 years. This may be because the average age of onset of depression is at the age of 32. [8,46] When comparing differences between patients on monotherapy and add-on /switch therapy, patients who had lower income, who were divorced or separated, who were unemployed and those who reported that their health stopped their social activity most of the time were significantly higher in the add-on/switch group. This could be because patients on a combination of antidepressants, or those who switch medications are more likely to have uncontrolled depressive symptoms than their counterparts on antidepressants only[94]. The above mentioned factors are associated with more severe depression symptoms.[119]

This study is unique as it is one of the few studies that evaluated the effect of various classes of medications used to treat depression in patients on monotherapy alone and in patients who are on monotherapy and add on/ switch therapy on HRQOL and mental health. Moreover, this study has a longitudinal design in contrast to most other studies that are cross sectional in nature. Assessing the above mentioned outcomes in patients only on monotherapy was chosen as a standalone objective as most patients with depression begin therapy with a single antidepressant and resort to augmenting or combining medications if they show partial or no remission.[59]

SSRIs are the most widely used antidepressants. [59]The results of the present study also show that a vast majority of the patients who were only on monotherapy were found to take SSRIs. (N=421).Very few patients were found to be taking TCAs (N=40) and this could be attributed to the more severe side effects that are exhibited by TCAs in comparison to other classes of antidepressants.[8] Furthermore, when comparing patients on monotherapy with those undergoing add on/ switch therapy, most of the patients were found to belong to the monotherapy group (N=866 versus N=116) .Another similar study looking into comparative effectiveness of antidepressant users versus concomitant users of antidepressants and AAPs showed similar numbers.[120].Descriptive statistics from the present study show that majority of the patients on monotherapy alone, taking either of the four classes of antidepressants studied, were found to show no change in HRQOL, PR-MHS and K6 scores. In addition to this, the current study showed similar results for patients on monotherapy versus those on add-on/switch therapy on all the three outcome variables. This may be because outcomes of patients who were on antidepressants since the beginning of the panel in MEPS were evaluated at two different time points. A plausible explanation for this could be that the medication treatment (either single antidepressant or combining antidepressants and AAPs) could be working for most of these

patients which could lead to better control of their symptoms and hence no change in their mental health and quality of life.

Moreover, a higher percentage of patients on monotherapy alone showed decline in PCS-12 scores as compared to the percentage of patients showing improved scores. This was seen in patients taking either of the four classes of antidepressants. Similar results were observed in patients who are on monotherapy versus those who are on add on./switch therapy. A probable explanation for this could be that the medical treatments used to treat mental disorders strongly predicts the mental health status of an individual and may improve the mental health more than the physical health. [41]Another explanation for this could be the likelihood of patients who show decline in PCS-12 scores to have higher number of co-morbidites which could affect their physical health, which assesses the burden of physical illness on patient's life.[121] However after controlling for a wide range of covariates, no significant association was found between the class of antidepressants and the tendency of patients to show improvement, decline or no change in their PCS-12 scores. This result was actually expected given the non-significant difference in the number of comorbidites among patients only on monotherapy. Also, the association between the likelihood of patients to show change in PCS-12 scores was insignificant based on them being on monotherapy or add-on/switch therapy. These findings were consistent with another study which evaluated the effect of antidepressant users and those who were concomitant users of antidepressants and AAPs. AAPs utilization was not associated with higher PCS-12 scores in their study.[120]

The percentage of people showing improvement in the mental health component summary scores of SF-12 as compared to decline were greater for both the monotherapy and the add on/switch

therapy group. This was contrary to the descriptive statistics results of PCS-12 scores mentioned above. After controlling for other covariates, the likelihood of users of monotherapy over add-on/switch therapy to have improved MCS-12 scores over a year's time was not significant. This is in line with the results from descriptive statistics, as both the groups had a higher percentage of patients who remain in the "unchanged category", followed by the "improve category."Since MCS-12 can be considered a valid tool to detect and monitor the presence and prevalence of depressive disorders, it seems that patients on both monotherapy and add-on/switch therapy have their depressive symptoms under control.[122] Combining antidepressants is a recognized step for those failing to respond to a single antidepressant treatment and may increase remission and quality of life of patients. Further, it can be implied that a correct clinical decision was made by their health care provider. Also, the present study could not distinguish between patients who switch from one antidepressant to another or those who combine medications. Those who switch medications may not be suffering the side effects of the previous medication which is eliminated from the body. This could also be the reason for no significant difference in the MCS scores of patients in both the groups. On the other hand, while comparing the effect of various classes of antidepressants on MCS-12 scores among patients only on monotherapy, significant differences were observed. Descriptive statistics showed that a greater percentage of patients on SSRIs showed improved scores as compared to decline in MCS-12 scores. This was in contrast to patients on SNRIs. Similarly, after controlling for confounding factors, it was found that patients on SNRIs and TCAs were significantly less likely to show improved scores as opposed to decline in scores when compared to patients on SSRIs. The possible reason for patients on TCAs in comparison to SSRIs to show less improvement could be their more serious side effects (which include weight gain, sedation, neurological side effects, low blood pressure on standing

and increased heart rate.) [8] Further, TCAs are prescribed for more severe depression, especially hospitalized in patients. [79,80] On the other hand, a large amount of data finds no significant evidence of the superiority of SSRIs over SNRIs and vice versa. .[63,71,72]Another study comparing the effect of venlafaxine and SSRIs on HRQOL showed no statistically significant difference. Venlafaxine has been found to be moderately superior to SSRIs in alleviating depressive symptoms; however the same does not apply for duloxetine. An investigation into adverse drug effects revealed that venlafaxine is superior to duloxetine, as fewer patients discontinued therapy due to side effects. In this context, however, both of these drugs are inferior to SSRI. [123] Even though the present study shows that SSRIs are more likely to show improvement on MCS-12 scores as opposed to SNRIs, no logical explanation can be given for this finding. The insignificant difference in MCS-12 scores between SSRIs and other antidepressants could be due to similar efficacy and side effect profiles of the two classes .[8]

The above mentioned findings of the effect of antidepressant classes on MCS-12 were not replicated when seen with respect to improvement in PR-MHS and psychological distress scores. A greater percentage of patients on SSRIs, TCAs and SNRIs were found to show improvement on PR-MHS scale as compared to decline. The percentage of patients on other antidepressants, showing improvement and decline in PR-MHS were almost the same. However these differences were found to be insignificant after controlling for covariates. Similarly, no significant difference was observed on PR-MHS between patients on monotherapy and add-on/switch therapy. Researchers have found that self reported health, both physical and mental, also reflects physical functioning, vitality, health behaviors, effective coping with disease and even spiritual orientation. [124]Respondents may integrate a variety of considerations to derive an overall health

assessment.[124] PR-MHS may hence analogously result from combining multiple considerations which may also include physical health, whereas MCS-12 may represent only a subset of factors which may be more specific to depression and mental illness. This may be a possible explanation to the results on PR-MHS being similar to PCS-12 as compared to MCS-12.

Psychological distress measured using K6 appears to be a useful screener for depression as examined by CIDI in population-based studies. [42]It was hence chosen as a separate outcome measure. In the present study, results on K6 were found to be in line with the findings of PCS-12 and PR-MHS. Neither of the groups; patients on monotherapy or add-on /switch therapy patients was significantly more likely than the other to show improvement in K6 scores as opposed to decline. Likewise, no significant difference was observed in K6 scores in patients on monotherapy based on the class of antidepressants. Questions on K6 can be more depression specific as compared to MCS-12 and PR-MHS. These findings could further confirm that most patients, irrespective of their therapy may have their depressive symptoms under control, which may suggest a good clinical decision by the patients' health care providers.

Since HRQOL and mental health are multidimensional concepts, many relevant covariates were considered. In addition to the above mentioned findings our study also found significant predictors of improvement in HRQOL, PR-MHS and K6 scores. The present study found significant association between age and change in PCS scores. Patients above 65 years were found to significantly show more improvement or remain the same as opposed to decline when compared to younger adults. The STAR*D report evaluating HRQOL in depression also found age to be a significant predictor of HRQOL. [108] One possible explanation to this could be that the

younger adults would be having more stress than older adults. Females on monotherapy were significantly more likely to show improvement on PCS-12 scores. Females have a greater likelihood of suffering from depression and other studies have shown that they have worse QOL as compared to males, hence they may have a greater tendency to show improved scores after undergoing treatment with antidepressants.[125] Further, insurance type, income and number of co-morbidities were found to have significant association with improvement in PCS- scores. This is in line with another study, which showed positive correlation between employment status and income on PCS-12 scores. Their study also showed a significant association between co-morbidities and HRQOL.[120] Significant association was found in the present study between race and ethnicity and HRQOL. Other similar studies evaluating factors affecting HRQOL in depressed patients show similar results.[108,120] Another important finding of this study is that social activity was found to be a have a significant association with all three outcomes assessing mental health. Patients who reported that their health sometimes or never stopped their social activity were less likely to show improved scores as compared to those who reported that their health always stopped their social activity. Individuals with greater depressive symptoms report more frequent negative social interactions. [126] Patients reporting that their disease state often stops them from having social interactions could be having more severe depression and could be having worse scores in round two of the panel. Further, the pharmacotherapy used to control depression may be working which could result in them reporting better scores in round 4 of MEPS.

5.1 Strengths, Implications of study findings and Future Research

Unlike most of the retrospective database studies conducted on the topic of HRQOL and mental health in depression which follow a cross sectional design, this study had a longitudinal design. Scores of patients suffering from depression who were prescribed some form of pharmacotherapy to treat depression were assessed over two time points, which were roughly a year apart. This can be considered as one of the strengths of the study, because the effect of the medications is assessed over a prolonged time to see if the scores on HRQOL and mental health improve, decline or remain the same. This may be essential for chronic debilitating conditions such as depression, which have high rates of relapse. Secondly, our study evaluated the impact of antidepressant classes and scores of patients on monotherapy versus add-on/switch therapy on three outcome measures.Thirdly, as per the authors knowledge, unlike many other studies conducted in this area, this study establishes criteria to define improvement, decline and no change in HRQOL, PR-MHS and K6 scores. Lastly, since MEPS is representative of the U.S. population our study is generalizable.

Even though the present study shows no significant difference in improvement in any of the outcome measures among patients on monotherapy and add-on/switch therapy, it can be implied that both the single antidepressant therapy as well as combining antidepressants may provide remission from depression which in turn may maintain the HRQOL and mental health of individuals. None of the groups were found to show significant decline in any of the outcome measures, which may indicate appropriate clinical judgment on the part of the healthcare providers. Since the ultimate outcome measure for patients with depression should be the overall well being and HRQOL, similar results on these measures among both the groups suggest that both the therapies may be working. Further, findings from this study may provide some cue to

clinicians in prescribing SSRIs over other classes of antidepressants, as they were significantly more likely to improve MCS-12 scores in comparison to SNRIs and TCAs. However future research needs to be done in this area to establish a casual relationship between classes of antidepressants and improved HRQOL and mental health. We suggest that future studies can examine the role of antidepressants on HRQOL and mental health after taking the baseline scores into consideration. They may also consider medication adherence, severity of illness and subjective tolerability. This study can serve as a reference for researchers in this area, who can further strengthen the study design and thereby provide some guidelines to clinicians in choosing one type of antidepressant over another. Also, since the effectiveness of medications used to treat depression may vary within each drug class, future research can focus on comparative effectiveness of the most widely prescribed antidepressants.

5.2 Study Limitations

No causal relationship can be inferred based on the sole findings of this study due to the limitation of the MEPS being a panel design. Hence baseline scores of patients on HRQOL, PR-MHS and K6 could not be considered in the study. Further, due to the structure of the MEPS database we could not adjusted for the severity of depression, illness duration or age of onset and medication adherence. Each of these covariates can influence the HRQOL and mental health outcomes in patients with depression. Also, in the add-on/switch therapy group we could not distinguish between patients concomitantly using antidepressants or AAPs and those who switch therapies.

Additionally, patients' self reported medical conditions are mapped into only 3 digit ICD-9 codes in MEPS, which makes it impossible to distinguish between non-psychotic disorders. To

overcome this limitation, only the patients who were prescribed medications that are used to treat depression were included in the study.

Other limitations of using a retrospective database include missing information, hence, a possibility of introducing bias. Social desirability bias and response bias are also possible limitations as the information in the database is self-reported by the respondents and cannot always be reliable. However, previous researchers have deemed this information to be of a reasonable quality.

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Appendix

Appendix A

SF-12 (Version 2)

1. In general, would you say your health is :

□1 Excellent □2 Very good □3 Good □4 Fair □5 Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	YES, limited a lot	YES, limited a little	No not limited at all
2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	□1	□2	□3
3. Climbing several flights of stairs.	□1	□2	□3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. Accomplished less than you would like.	□1	□2
5. Were limited in the kind of work or other activities.	□1	□2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. Accomplished less than you would like.	□1	□2
7. Did work or activities less carefully than usual.	□1	□2

8. During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?

□1 Not at all □2 A little bit □3 Moderately □4 Quite a bit □5 Extremely

These questions are about how you have been feeling during the past 4 weeks.

For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks-

All of the time	Most of the time	A good bit of time	Some of the time	A little of the time	None of the time

9. Have you felt calm & peaceful? □1 □2 □3 □4 □5 □6

10. Did you have a lot of energy? □1 □2 □3 □4 □5 □6

11. Have you felt down-hearted and blue? □1 □2 □3 □4 □5 □6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

□1 All of the time □2 Most of the time □3 Some of the time □4 A little of the time □5 None of the time.

Appendix B

Non-Specific Psychological Distress (Kessler) Index

1. During the last 30 days, about how often did you feel nervous? All of then time/Most of the time/Some of the time/A little of the time/None of the time

2. During the last 30 days, about how often did you feel hopeless? All of then time/Most of the time/Some of the time/A little of the time/None of the time

3. During the last 30 days, about how often did you feel restless or fidgety? All of then time/Most of the time/Some of the time/A little of the time/None of the time

4. During the last 30 days, about how often did you feel so sad that nothing could cheer you up? All of then time/Most of the time/Some of the time/A little of the time/None of the time

5. During the last 30 days, about how often did you feel that everything was an effort? All of then time/Most of the time/Some of the time/A little of the time/None of the time

6. During the last 30 days, about how often did you feel worthless? All of then time/Most of the time/Some of the time/A little of the time/None of the time