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Association Between Antidepressant Adherence and Major Depressive Disorder Complications

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This is to certify that the doctoral dissertation by

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has been found to be complete and satisfactory in all respects,
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Walden University
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Abstract

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Dissertation Submitted in Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Despite evidence that antidepressants are more effective at treating major depressive disorder (MDD) symptoms, there is growing evidence that MDD management is still hampered by nonadherence to antidepressant treatment regimens. Researchers have suggested that MDD, if untreated, might lead to MDD-related complications, but other researchers have argued that adherence to antidepressants can lead to these same MDD-related complications. This quantitative cross-sectional study used primary data collected from 298 volunteers to examine the association between MDD-related complications and antidepressant adherence to clarify these diverging opinions. The study's objective was to provide evidence to accept or reject the premise that antidepressant adherence is associated with a statistically significant increase in MDD-related complications. This study used the biopsychosocial model as the theoretical framework. A binary logistic regression analysis and Fisher's extract test indicated that antidepressant adherence did not statistically predict the risk of developing insomnia, poor appetite, or suicidal thoughts in patients with MDD. The findings of this study will contribute to positive social change by providing public health professionals with information they need to establish a more effective awareness campaigns regarding drivers of MDD-related complications.

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Dedication

I am dedicating this manuscript to all my children, and to the two precious Esthers in my life, my wife, Dr. Esther Lisinge, and my late mother, Esther Dale. Without their understanding, encouragement, and support, I will not be the man I am today.

Acknowledgments

I will forever be grateful to the Lord for providing the health, wisdom, love, and peace that made this journey possible. To all Walden University faculty, I say thanks for transferring your knowledge. The Bible declares “Every prudent man dealeth with knowledge: but a fool layeth open his folly” (Proverbs 13:16, King James Version).

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Chapter 1: Introduction to the Study

Health care providers have indicated that inadequate treatment of a major depressive disorder (MDD) and the poor management of MDD-related complications remains a significant global public health concern (Meng et al., 2020; Lam et al., 2015; World Health Organization [WHO], 2017). Although there is evidence that antidepressants are effective in treating MDD symptoms compared to placebos or other controls, there is also evidence that most MDD patients do not stick to their antidepressant regimen (Kini & Ho, 2018; Semahegn et al., 2020; Zipursky, 2014). Untreated MDD might lead to complications such as gaining excess weight or becoming obese, diabetes, CHD or metabolic syndrome, insomnia, poor appetite, physical illness and pain, misusing drugs or alcohol, panic attacks, social phobia or anxiety, having suicidal thoughts, and attempting suicide or committing suicide (Gutiérrez-Rojas et al., 2020; Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; McIntyre et al., 2018; Topuzoğlu et al., 2015; Tyrrell et al., 2019; Yu et al., 2015). However, several researchers have indicated that the same MDD-related complications might result from the side effects of antidepressants (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020). These diverging opinions remain an issue for further examination within the scientific community.

Though there are numerous studies on preventing MDD-related complications, few researchers have considered addressing the conflicting opinions regarding MDD-related complications. Recent MDD-related complications studies have focused on the reduction of these MDD-related complications without addressing the magnitude of these

contested opinions regarding the MDD-related complications (Jimmy & Jose, 2011; Kini & Ho; 2018; Kleinsinger, 2018; Prakash et al., 2019; Qaseem et al., 2016; Velligan et al., 2017). This study used primary data to investigate antidepressant adherence as a possible source of MDD-related complications. The research will contribute to the scientific community's existing knowledge regarding the association between antidepressant adherence and MDD-related complications outcomes for patients diagnosed with MDD.

In this chapter, I summarize the literature used to formulate the study's background, problem statement, and purpose. I discuss the study's research questions and define key terms used in the study. I also describe the assumptions, scope, and delimitations of the research, the significance, and the limitations of this study.

Background

Research indicates MDD is among the most experienced mental health disorders worldwide (Meng et al., 2020; WHO, 2017). Just in Texas, with a population of over 29 million inhabitants, there was an increase in the percentage of its population dealing with MDD from 12.5% in 2016 to 17.7% in 2020 (Centers for Medicare and Medicaid Services [CMS], 2021). A problem identified in current literature regarding those diagnosed with MDD is the rates of antidepressant medication adherence. Antidepressant non-adherence is estimated to be between 40%–50%, being one of the most significant impediments in this illness management and the cause of poor health outcomes (Semahegn et al., 2020; Zipursky, 2014).

Researchers have presented epidemiological information about the population most affected by MDD (Jin et al., 2016; McDonald et al., 2003; Pasina et al., 2014;

Villarroel & Terlizzi, 2020; Yap et al., 2016). Regarding the distribution of MDD symptoms by age, data from the National Health Interview Survey (NHIS) indicated that almost 18.5% of adults 18 years old and older in the United States experienced some level of symptoms of depression (Villarroel & Terlizzi, 2020). However, those between the ages of 18 and 29 were equally likely to experience moderate depressive symptoms as people between the ages of 45 and 64 (Villarroel & Terlizzi, 2020). Concerning the ethnicity more likely to show manifestations of mild, moderate, or severe symptoms of depression, there is a higher probability of Hispanic and non-Hispanic Black and White adults exhibiting these different level symptoms than non-Hispanic Asian adults (Villarroel & Terlizzi, 2020). Concerning gender, women are more likely to show manifestations of depression at all stages of severity than males (Villarroel & Terlizzi, 2020). The high prevalence of MDD-related complications calls for an improved strategy to enhance MDD treatment outcomes.

Researchers have suggested a growing trend regarding the financial burden of MDD on the U.S. economy. The cost of the burden of depressive disorders to the US economy is approximately $83 billion annually, with related $24 billion annual projected workforce productivity losses (Gartlehner et al., 2011). From 2010 to 2018, MDD imposed an increased financial toll on U.S. adults, rising from $236 billion to $326 billion (Greenberg et al., 2021).

Current literature suggests that adhering to a treatment regimen is a fundamental element of any strategy for improving MDD treatment outcomes. With adequate adherence to their treatment regimen, patients might be able to reduce MDD-related

complications (Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; Thase et al., 2015; Velligan et al., 2017). Antipsychotic medication significantly reduces the severity of illness symptoms and improves outcomes for patients diagnosed with major psychiatric disorders (Thase et al., 2015; Velligan et al., 2017). However, despite the advancement and innovation in pharmacotherapy, treatment outcomes remain poor among patients diagnosed with MDD (Oluboka et al., 2018), and adherence to these medications remains a global problem for individuals dealing with MDD (Bitter et al., 2015; Dufort & Zipursky, 2019; Semahegn et al., 2020).

Current initiatives to prevent MDD-related complication target persons diagnosed with MDD, their clinicians, or health systems. MDD treatment improvement strategies include patient education, medication regimen management, clinical pharmacist consultation, cognitive-behavioral interventions, automated medication monitoring system serving as reminders (e.g., text messages, telephone calls, MEMS cap device, and other electronic devices), incentives to promote adherence, and improvement in the health system (Jimmy & Jose, 2011; Kini & Ho, 2018; Kleinsinger, 2018; Prakash et al., 2019; Qaseem et al., 2016; Velligan et al., 2017). An essential factor to consider when developing an improvement strategy is the significant factors that drive MDD-related complications.

Medication adherence remains a global problem for individuals dealing with mental disorders (Bitter et al., 2015; Cutler et al., 2018; Dufort & Zipursky, 2019; Iuga & McGuire, 2014; Lam et al., 2015; Semahegn et al., 2020; Velligan et al., 2017; Zhou et al., 2019; Zipursky, 2014). A negative attitude toward medication and substance abuse

are common causes for non-adherence to medications (Lam & Fresco, 2015; Oluboka et al., 2018; Velligan et al., 2017; Zhou et al., 2019; Zipursky, 2014). Strategies that control medication adherence are crucial in improving treatment outcomes (Oluboka et al., 2018; Semahegn et al., 2020; Zipursky, 2014). There is a need for a treatment outcomes improvement strategy incorporating mechanisms for reducing medication non-adherence rate (Lam et al., 2015).

One significant aspect of improving medication adherence is understanding its magnitude (Lam & Fresco, 2015). It is important to use more robust methodological frameworks when comparing measurement methods and be aware that non-electronic measures could overestimate medication adherence (El Alili et al., 2016). This study is necessary to the research community as it deals with the conflicting opinions on which factor is significantly responsible for the increase in MDD-related complications.

Problem Statement

If left untreated, MDD may lead to a series of adverse health complications, including increased coronary heart disease (CHD) risk, obesity, poor appetite, insomnia, pain or physical illness, alcohol or drug misuse, anxiety, panic disorder, social phobia, suicidal thoughts, or suicide (Gutiérrez-Rojas et al., 2020; Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; Topuzoğlu et al., 2015; Tyrrell et al., 2019; Yu et al., 2015). Researchers also suggest that untreated MDD may increase the risk of relapse, hospitalization, and reduction in the patient's quality of life (Cutler et al., 2018; Dufort & Zipursky, 2019; Velligan et al., 2017; Zhou et al., 2019). Other complications resulting from untreated MDD include premature death from medical conditions, family conflicts,

work or school problems, relationship difficulties, insomnia, poor appetite, self-mutilation, and social isolation (Beacon Health System, 2020; Nutt et al., 2008; O'Brien et al., 2011).

Pharmacotherapeutics innovation related to MDD has resulted in antidepressants, which help reduce MDD-related complications and other mental illness symptoms (Prakash et al., 2019; Qaseem et al., 2016; Velligan et al., 2017). However, despite the numerous primary studies conducted on how to reduce MDD-related complications by improving medication adherence (Kahwati et al., 2016), other researchers argue that using some antidepressants can lead to the same complications (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020). Selective serotonin reuptake inhibitors, an antidepressant, is quoted by researchers as a medication that interfere with sleep architecture and may make it more difficult for depressed people to fall asleep (Ferguson, 2001).

An essential strategy in managing MDD-related complications will be to examine the factors contributing to MDD-related complications. Although non-adherence to antidepressants is an issue for patients diagnosed with MDD, it is unclear to what extent antidepressant adherence is essential for the optimal reduction of MDD-related complications and improves proper patient medication management strategies. Based on several contradicting scientific pieces of evidence, it is unclear to what extent poor antidepressant management (e.g., medication adherence) is associated with MDD-related complications. Thus, this study was conducted to identify the role of antidepressant medication adherence as a contributing factor to MDD-related complications.

Purpose of Study

Some researchers argue that depression, if untreated, might lead to complications such as Insomnia, poor appetite, and suicidal thoughts (Gutiérrez-Rojas et al., 2020; Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; Topuzoğlu et al., 2015; Tyrrell et al., 2019; Yu et al., 2015). In contrast, other researchers support the fact that adherence to antidepressants can lead to these same complications (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020). This quantitative study addresses the conflicting opinions behind MDD-related complications among adult patients diagnosed with MDD by investigating the association between MDD-related complications (the dependent variables: insomnia, poor appetite, and suicidal thoughts) and antidepressant adherence (the independent variable). This study measured the relationship between antidepressant adherence and MDD-related complications using a binary logistic regression statistical analysis model. The research will help fill the gap in knowledge regarding MDD-related complications and antidepressant medication management (adherence).

Research Questions and Hypotheses

Research Question 1: What is the association between patient adherence to antidepressants as measured with Morisky 8-item Medication Adherence scale (MMAS-8) and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

$H_0$1: There is no statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

H_a1: There is a statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

Research Question 2: What is the association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

$H_0 2$: There is no statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

$H_a 2$: There is a statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

Research Question 3: What is the association between patient adherence to antidepressants as measured with MMAS-8 and suicidal ideation risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

$H_0 3$: There is no statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and suicidal ideation risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

$H_a 3$: There is a statistically significant association between patient adherence to antidepressants as measured with MMAS-8 and suicidal ideation risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age.

Theoretical Framework

Theories that emphasize individual health behaviors are essential in understanding how to improve human health (Glanz et al., 2015). This study used the biopsychosocial (BPS) model as the theoretical framework to understand the association between the studied variables better. George Engel originally conceptualized the BPS model in 1977. Engel (1977) stated that in order to understand better an individual's health and illness process, not only biological and psychological factors (such as emotions, behaviors, and thoughts) but also social aspects must be considered (such as culture, socio-environmental, and socio-economical). I provided a more detailed explanation of these significant theoretical propositions in chapter two of this study. The BPS model offers a framework to study diseases, healthcare, and illness behavior, using theoretical propositions that suggest how health outcome variables are influenced by diverse levels of the organization, from molecular and individual to societal levels (Wade et al., 2017; Engel, 1977). The literature review indicates researchers' use of the BPS model as a blueprint for research and a framework for studying treatment outcome strategies (Anderson et al., 2022; Wade & Halligan, 2017).

The BPS analytical model provides the framework for this study, permitting a multivariable/covariates analysis approach to investigate the association between medication adherence and MDD-related complications. Using this model for this study is beneficial because it is holistic, cognizant of levels in nature, and the model has a diverse perspective. The BPS model considers the possible biological (e.g., age and gender), psychological (e.g., MDD-related complications and medication adherence), and social-

environmental (e.g., race) influences affecting the individual's overall health and health behaviors (Engel, 1977). This study's dependent variable (MDD-related complications) and the independent variable (medication adherence) deal with a biopsychosocial event.

Nature of Study

This study is a cross-sectional quantitative study that used primary data to assess how antidepressant adherence (independent variable) might influence MDD-related complications (dependent variable - Insomnia, poor appetite, and suicidal thoughts). The study involved an online survey using the Survey Monkey interface for data collection. Participants included adults over 18, living in the State of Texas, diagnosed with MDD. To obtain participants, I used the Survey-Monkey Targeted Audience (i.e., list of existing Survey-Monkey respondents) to send the survey to respondents from their State of Texas panel who match my criteria. The study uses statistical inference binary logistic regression analysis (with odds ratio value between 0 and ∞) to establish if the is an association between the variables while controlling for race, gender, and age.

Definitions

The definitions provided in this section explain the terms utilized in this study to facilitate comprehension of why I used these terms.

Body mass index (BMI): BMI is a metric for body fat that compares a person's weight in kilograms to their height in square meters (Merriam, 2020).

Coronary heart disease (CHD): According to the National Heart, Lung, and Blood Institute (2020), CHD is a condition, especially one caused by atherosclerosis that reduces blood flow through the coronary arteries to the heart and typically results in chest

pain or heart damage.

Diabetes: According to the Centers for Disease Control and Prevention (CDC, 2022), diabetes is a chronic (long-lasting) health condition in which the body either produces insufficient insulin or misuses it. With diabetes, too much blood sugar remains in the bloodstream due to insufficient insulin or when cells cease reacting to insulin.

Gender: According to the WHO (2022), gender refers to the socially constructed qualities of men, women, girls, and boys. Gender covers interpersonal connections and the standards, mannerisms, and roles of being a woman, man, girl, or boy (WHO, 2022). Gender is a social concept that differs from culture to culture and can evolve (WHO, 2022).

Group therapy: Group therapy is a form of psychotherapy that involves the regular gathering of individuals habitually with similar health concerns under the leadership of trained health professionals (Takahashi et al., 2019).

Insomnia: Insomnia is dissatisfaction with sleep quality or quantity (Patel et al., 2018). Per the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association [APA], 2013), insomnia is characterized by difficulties initiating sleep, difficulties maintaining sleep, early-morning awakening, and repeated awakenings or difficulties falling asleep after awakenings. According to APA (2013), patients experience insomnia even with adequate opportunity to sleep for at least three nights per week and at least 3 months. The presence of mental disorders or medical conditions does not explain insomnia's existence (APA, 2013). Insomnia is not directly associated with another sleep disorder (APA, 2013).

Major depressive disorder (MDD): Cooper (2018) defined MDD as an illness commonly manifested by unrelenting low mood, loss of happiness and interest, neurovegetative disturbance, and reduced energy. These MDD signs and symptoms often trigger various social and occupational dysfunction (Cooper, 2018). Patients are diagnosed with MDD when the patient presents with at least five depressive symptoms such as poor concentration, low mood and energy, changes in libido and weight, anhedonia, insomnia, excessive guilt, psychomotor glitches, and increased suicidal ideation (McCance & Huether, 2018). The classification of MDD is along a spectrum of mild to severe (Cooper, 2018). The author indicated that severe episodes might include psychotic symptoms such as paranoia, hallucinations, or functional incapacitation.

Marital status: Marital status encompasses various cultural practices, and anthropologists propose competing definitions (Haviland et al., 2016). An inclusive definition of marital status is if or not a legally or culturally acknowledged union exists between individuals called spouses.

Medication adherence: Medication adherence is the extent to which individuals adhere to their medication regimen as prescribed by their physicians (Hugtenburg et al., 2013; U.S. Food and Drug Administration, n.d.). According to Morrison et al. (2015), the recognized threshold for medication adherence is medication taking ≥ 80% as prescribed by the physician.

Poor appetite: According to Pilgrim et al. (2015), poor appetite reduces the desire to fulfill a bodily need and has three components: hunger, satiation, and satiety. Pilgrim et al. hypothesized that hunger is a sensation that promotes food intake; satiation is a

feeling of fullness during meals, which causes a person to stop eating; and satiety is a feeling of fullness that exists between meals.

Race: The U.S. Census Bureau (2020) describes race as an individual's self-identification with social groups. These social groups include Native Hawaiian and Other Pacific Islanders, African or Black American, White, American Indian and Alaska Native, Asian, or some other race (U.S. Census Bureau, 2020).

Social support: Social support is people (e.g., family, friends, and peers) who can provide perceived/actual practical and emotional assistance or care. Researchers have indicated that a social support system is necessary to maintain an individual's psychological and physical health (Budimir et al., 2021; Grey et al., 2020).

Suicidal thoughts: These are feelings, thoughts, contemplations, or preoccupations with taking one's own life (Harris et al., 2014). According to the National Mental Health Commission (2017), suicidal thoughts are influenced by the interaction of biological, genetic, psychological, social, environmental, and situational factors, which include psychological pain; negative thinking (e.g., helplessness, shame, hopelessness, guilt, and entrapment); and the clarity, magnitude, and persistence of suicidal ideas.

Assumptions

For this study, it was assumed that the online survey dataset collected for this research contains accurate and valid responses on antidepressants adherence, insomnia, poor appetite, and suicidal thoughts. I assumed that the original data collection was as free from bias as possible. Further, I assumed that factors such as diet, socioeconomic status, marital status, group therapy, race, gender, genetics, age, physical inactivity,

medication side effects do not influence the level of MDD-related complications. Finally, it was assumed that the variables were measured without error (reliably) and are independent observations; the variance of errors is the same across all levels of the independent variables (homoscedasticity; Osborne & Waters, 2002).

Scope and Delimitations of Study

This quantitative study addresses the diverging opinions behind MDD-related complications among adult patients diagnosed with MDD. For this study, I examined the association between antidepressant adherence and MDD-related complications. The independent variable is antidepressant medication adherence. The dependent variable is MDD-related complications (insomnia, poor appetite, and suicidal ideation), with age, gender, and race as control variables. Measures to ensure the generalizability of the results of this study included selecting the appropriate research design that assures the use of the proper data collection techniques and validated instruments of measure, as well as computation of the right sample size for the study and the application of the appropriate statistical procedures. The study indicates if the association established in this study has a statistical significance, which establishes the independent variable as a primary factor responsible for MDD-related complications, providing valuable information that addresses the contradiction behind MDD-related complications. This study's delimitations included MDD-related complications such as hippocampal volume loss, anxiety disorder, panic disorder, social phobia, self-mutilation, family conflicts, relationship difficulties, and work or school problems.

Limitations of Study

This study relied on self-reported online survey data, which might expose the study to biases that might reduce its validity and reliability (e.g., exposure to response bias due to the respondent's desire to protect their privacy and the high possibility of social desirability that comes with the research of an unhealthy healthcare behavior; Palaniappan & Kum, 2019). The study's participants are online self-selected, which might result in biased sampling (Booker et al., 2021). The deficit in financial resources and lack of time did restrict the scope of this study. The study is limited to the individual's adherence to antidepressants, measured with the Morisky 8-item Medication Adherence scale (MMAS-8). The measurement of adherence to other forms of psychotherapy (e.g., social support, group therapy, counseling or interpersonal therapy, dialectical behavior therapy (DBT), cognitive behavioral therapy, exposure therapy, eye movement desensitization and reprocessing therapy (EMDR), psychodynamic psychotherapy, metallization-based therapy) that could affect the relationship between medication adherence and MDD-related complications were not examined due to deficit in financial resources and lack of time. A longitudinal study that examines all these variables would provide a more valid result regarding the effect of adherence and duration on MDD-related complications.

Significance of Study

Public health research can promote social change by addressing treatment and prevention approaches that deal with health care outcomes. A significance of this study is its potential additional information that might be used to improve the strategy used to

reduce MDD-related complications and hence the patient's/caregiver's quality of life, reduce treatment cost to the patient and society, patient's improved social integration, and increased economic productivity. The study might also lead to positive social change by providing public health professionals, social workers, advocacy groups, and other stakeholders with additional information needed for resource management and creating public awareness campaigns regarding MDD-related complications.

Summary

This quantitative study addresses the diverging school of thought regarding MDD-related complications. The study's objective was to provide evidence to accept or reject the premise that antidepressant adherence is associated with a significant increase in MDD-related complications. In this quantitative study, I used primary self-reported online survey data to examine the association between an outcome variable (MDD-related complications: insomnia, poor appetite, and suicidal thoughts) and antidepressant adherence as the independent variable.

In Chapter 1, I summarized the literature used to formulate the background, problem statement, and purpose of this study. I also discussed the study's research questions and defined key terms used in the study. I also described the assumptions, scope, delimitations of the research, and the significance and limitations of this study. In Chapter 2 of this study, I will discuss the strategies I used in reviewing related literature and the framework for this study. I will also summarize, analyze, interpret, and critically evaluate related literature on antidepressant adherence and MDD-related complications.

Chapter 2: Literature Review

MDD and MDD-related complications affect patients' daily lives. A review of the literature indicates that despite evidence of the efficacy of antidepressants in dealing with MDD compared to placebos or other controls, researchers have underscored the significant, unresolved issues of MDD-related complications (Sim et al., 2016). If untreated, MDD might lead to gaining excess weight or becoming obese, increased diabetes risk, CHD or metabolic syndrome risk, physical illness and pain, misusing drugs or alcohol, panic attacks, social phobia or anxiety, having suicidal thoughts, attempting suicide or committing suicide, mutilating oneself through cutting or other means, suffering from premature death from other medical disorders or conditions (Gutiérrez-Rojas et al., 2020; Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; McIntyre et al., 2018; Topuzoğlu et al., 2015; Tyrrell et al., 2019; Yu et al., 2015). Researchers have suggested that in people ages 18 to 44, MDD is the leading cause of disability and premature death (WHO, 2017), and MDD is the second leading cause of disability overall (Mokdad et al., 2018).

There is growing evidence that, on average, patients with MDD do not adhere to antidepressants treatment, a presumed factor that accelerates MDD-related complications among patients diagnosed with MDD (Kini & Ho, 2018; Semahegn et al., 2020; Zipursky, 2014). Today, patients' low medication adherence rate remains a global problem for the prevention of MDD-related complications (Bitter et al., 2015; Dufort & Zipursky, 2019; Semahegn et al., 2020). A review of current literature indicates that MDD-related complications remain a significant public health issue that necessitates

additional, comprehensive consideration. Further, some researchers have indicated that MDD-related complications were side effects of some of the antidepressants used to treat MDD (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020; Read & Williams, 2018; Wang et al., 2018; Wichniak et al., 2017). These conflicting opinions in the literature represent a significant variation as to which variable is responsible for the observed trend regarding MDD-related complications. This study aims to investigate if there is an association between patients' adherence to antidepressants and MDD-related complications risk among adult U.S. individuals diagnosed with MDD. The findings of this study contribute to existing scientific knowledge regarding MDD-related complications and inform policymakers, preventive healthcare development strategists, and other members of society dealing with MDD-related complications.

This chapter discuss how the literature was reviewed and the framework for this study. It provides the extant literature on antidepressant adherence and MDD-related complications providing a perspective to position this study within the scientific community.

Literature Search Strategy

I performed an extensive literature review using the following digital databases: PsycINFO, Google scholar, the Walden of University library (to consult the following databases - MEDLINE with full text, Cochrane database of systematic reviews, Cochrane central register of controlled trials, Embase, and Thoreau multi-database search). Other non-electronic sources used for this literature search included conventionally published versions of professional journals, books on pathophysiology, etiology, and the

epidemiology of the basis of disease (e.g., McCance & Huether, 2018), and other public health publications (e.g., WHO and the Anxiety and Depression Association of America). Over 75% of journal articles, books, and other peer-reviewed electronic materials used were within the last 5 to 6 years. This literature search used the following keywords in various combinations: *insomnia, loss of appetite, poor appetite, major depressive disorder, major depressive disorder outcomes, major depressive disorder complications, medication non-adherence, medication noncompliance, medication management, antidepressants, antidepressant side effects, antipsychotics,* and *attitude toward medication.* This literature search was done to find works within the scientific community to describe the current state of knowledge related to the possible association between MDD-related complications and antidepressant adherence. This literature review will provide a better understanding of the scientific community's contribution to MDD-related complications.

Theoretical Framework

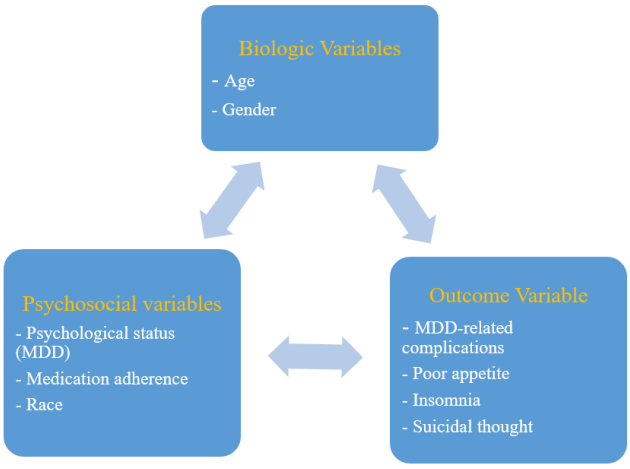
Research involving theory is a principal component of intervention development (Patton et al., 2017). This study used the BPS model to understand the association between the studied variables. George Engel originally conceptualized the BPS model in 1977, stating that it was critical to include biological, social, and psychological elements to comprehend better a patient's medical situation. A BPS perspective is an integrated approach to psychology that incorporates three different perspectives and types of analysis: biological, psychological, and social-cultural (Engel, 1977; Miaskowski et al., 2020). The biopsychosocial model encourages researchers to investigate relevant

biological, psychological, and social-cultural aspects that contribute to the development or maintenance of illnesses and their complications to explain phenomena such as MDD and its complications.

The BPS model is appropriate for this study as it considers the biological (e.g., age and gender), psychological (e.g., MDD/MDD-related problems and medication adherence), and social-environmental (e.g., race) factors that influence an individual's general health and health behaviors. Medication adherence deals with an individual's behavior which is a biopsychosocial event. Figure 1 indicates a graphical representation of the BPS model used in this study, including variables from each domain. The influence of genetics on the host population is not considered in the study's model as it is beyond the scope of this study.

Figure 1

Variables Interrelationship



Other researchers have also used the BPS model to examine topics related to

depression. Najia et al. (2021) conducted a cross-sectional study using the BPS model to examine the prevalence of antenatal depression and its significant determinants. The authors indicated that antenatal depression among pregnant women was common in Qatar and recommended using the BPS model to standardize the screening process. Vallerand et al. (2019) examined the risk of rheumatoid arthritis (RA) associated with depression. These authors suggested that a BPS framework's understanding of the bidirectional link between RA and depression may help clinicians maintain the proper level of skepticism regarding the co-occurrence of these illnesses. Anderson et al. (2022) used the BPS model to examine variables associated with MDD and hypothyroidism.

The rationale for choosing this theory is that the BPS model is well-designed, requiring few questions to assess critical constructs used to examine health outcomes. The BPS model also permits the use of a multivariable/covariates analysis approach to investigate the association between medication adherence and MDD-related complications. The model explains how the different variables in consideration are related (i.e., the BPS model help identifies essential variables that might influence MDD-related complications and highlights how these key variables differ (biological, psychological, and social environmental). The research questions of this study required the analysis of biological, psychological, and social environmental variables.

Literature Review of Key Variables

This literature review provided the background of essential elements (variables) used to develop the research topic, proving grounds for specific research problems and questions based on identified gaps. The literature review of critical variables also guided

and justified the choice of the research methodology that provided answers to the research problem and questions. This literature review synthesizes published research findings.

MDD

In the literature, the first chronicled comprehension of MDD points toward MDD resulting from a profound assault or reaction from a spiritual attack from angry gods rather than a physical one (Longrigg, 2013). However, the APA (2013) noted that MDD is a clinical disorder involving neurovegetative functions, mood, insight, and behavior. MDD is commonly described as obstinate low mindset, neurovegetative disturbance, loss of interest and pleasure, and decreased energy, causing fluctuating degrees of social and occupational-related brokenness (APA, 2013; Bains & Abdijadid, 2021).

Classifications of MDD within Depressive Disorders

According to the Diagnostic and statistical manual of mental disorders, depression includes MDD, premenstrual dysphoric disorder, persistent depressive disorder, and other depressive disorders (APA, 2013). Other depressive disorders might originate from medication side effects, substance abuse, therapeutic conditions, or other specified or unspecified causes. These types of depression are distinguished based on the length and number of symptoms. Other distinguishing factors are sad mood and anhedonia, the degree of functional impairment, and the severity of symptoms. In some cases, the mood is not sad but anxious, irritable, or flat. At least five symptoms characterize MDD and range from mild to severe. Severe MDD episodes may include psychotic symptoms such as paranoia, hallucinations, or functional incapacitation. Differential diagnoses such as

cyclothymia or bipolar disorder might also be observed in patients with MDD (APA, 2013). Researchers predict that depression will be the leading cause of disability in people of all ages by the end of 2030 (Bains & Abdijadid, 2021; Remick, 2002).

MDD Risk Factors

According to WHO (2017), globally an estimated 300 million suffer from depression. Among 36,309 U.S. adults, the 12 months and lifetime prevalence of MDD was 10.4% and 20.6%, respectively, with most being moderate (six to seven symptoms) or severe (eight to nine symptoms) and associated with MDD-related complications (Hasin et al., 2018).

Age. Age is a significant risk factor for MDD causes (Schaakxs et al., 2018). Eventually, about 20% of adults will require treatment for a mood disorder (Remick, 2002). Researchers have suggested that the prevalence of MDD in medical outpatients older than 65 years ranges from 7% to 36%, depending on the setting (Remick, 2002). The first onset of MDD occurs most frequently in patients aged 12-24 years or older than 65 (Remick, 2002). Other literature linking age to MDD risk suggests that due to an increasing trend in alcohol consumption and other drug abuse, there is an observed trend of increasing MDD and MDD-related complications incidences in the younger population (Pedersen et al., 2014).

Postpartum Status. Postpartum status refers to various depressive symptoms common in mothers (APA, 2013). Researchers indicated that the risk of developing MDD is almost double in women than in men (Fornaro et al., 2020; Pedersen et al., 2014). About 19% of postpartum women have an MDD episode during the first three months

after delivery (Gavin et al., 2005). Barlow et al. (2012) argued that women with previous psychiatric disturbance, poor social support, and unplanned pregnancy are at higher risk of postpartum depression (Barlow et al., 2012).

Adverse Effects from Medication and MDD. Depression is a documented adverse effect of patients using some prescription medication. For instance, corticosteroid therapy is associated with several cases of depression (Ciriaco et al., 2013). Some antiepileptic medications have also been associated with MDD, such as barbiturates, topiramate, and vigabatrin (Mula & Sander, 2007). Researchers have also argued that medications such as propranolol hydrochloride, oral contraceptives, and interferon were associated with an increased risk of developing MDD (Lye et al., 2020). There is also an established relationship between idiosyncratic depressive reactions and beta-1 receptor antagonists (beta-blockers; Rogers & Pies, 2008). Further, researchers at the University of Illinois at Chicago conducted a study to characterize the utilization of physician-endorsed prescriptions with depression as an expected unfavorable impact as well as the associations between prescription medication and concurrent depression (Qato et al., 2018). The results suggested that the prevalence of medications with depression as an adverse effect was 37.2% of the overall studied population, meaning using multiple medications was associated with an increased risk of coexisting medical conditions, including depression (Qato et al., 2018).

Coexisting Medical Conditions and MDD. Patients with various chronic medical conditions have a significantly higher risk of developing MDD and MDD-related complications than those without these comorbidities. Evidence in the literature

establishes that there is a higher risk of developing MDD and its complications among patients with coexisting medical conditions such as HIV (Nanni et al., 2015), cancer (Caruso et al., 2017; Pitman et al., 2018), polycystic ovary syndrome (Enjezab et al., 2017), stroke (Robinson & Jorge, 2016), coronary artery disease (Carney & Freedland, 2017), and obesity (Pereira-Miranda et al., 2017). Researchers have argued that patients with chronic illness conditions characterized by inflammation and pain are also at an increased risk of developing MDD and MDD-related complications (Lee et al., 2018; Patten et al., 2018). Other researchers established evidence of a significant association between diabetes and MDD (Khalediet al., 2019; Moulton et al., 2015). However, the review of the literature suggests that there is an argument to be made that the relationship between coexisting medical conditions and depression is bidirectional (Cooney et al., 2017; Katon, 2011). The adverse health risk behaviors and psychobiological changes associated with depression increase chronic medical disorders, and biological changes and complications associated with chronic medical diseases may precipitate depressive episodes (Katon, 2011). These observed patterns of association between coexisting medical conditions and MDD episodes indicate that there is a need to understand MDD disease burden and MDD-related complications as well as provide pieces of evidence that could be used to anticipate medical conditions and for the formulation of etiological hypotheses relative to MDD disease burden and MDD-related complications.

MDD-Related Complications

Despite the evidence found in the literature regarding the efficacy of antidepressants in reducing MDD-related complications compared to placebos or other

controls, there is growing evidence that, on average, patients with MDD do not adhere to their antidepressants treatment, probably resulting in the observed increase in MDD-related complications (Kini & Ho, 2018; Semahegn et al., 2020; Zipursky, 2014). Untreated MDD might lead to complications such as gaining excess weight or becoming obese, diabetes, CHD or metabolic syndrome, physical illness and pain, misusing drugs or alcohol, panic attacks, social phobia or anxiety, having suicidal thoughts, attempting suicide or committing suicide, mutilating oneself through cutting or other means, suffering from premature death from other medical disorders or conditions have been attributed with untreated MDD (McIntyre et al., 2018). However, some researchers have indicated that the observed MDD-related complications might have resulted from the side effects of antidepressants (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020). These diverging opinions regarding MDD complication remains an issue for further examination.

Insomnia and MDD. To better understand MDD-related complications, there is a need to evaluate the association between the patient's adherence to antidepressant medication and insomnia risk among individuals diagnosed with MDD after controlling for race, gender, and age. Insomnia is the second most prevalent mental disorder and a primary risk factor for depression (Blanken et al., 2019). The medical literature and popular press often define insomnia by the presence of the patient's report of sleep difficulty. However, the Diagnostic and Statistical Manual of Mental Disorders 5th edition (APA, 2013) indicates that insomnia disorder is the struggle to initiate or sustain sleep or get up early in the morning, resulting in dissatisfaction with quantity or quality of life

sleep (APA, 2013). The definitions of insomnia vary, with acute insomnia described as insomnia lasting less than 4 weeks and might occur as a response to an identifiable stressor (American Academy of Sleep Medicine [AASM], 2014; Sateia et al., 2017). Research indicates that insomnia might lead to social, educational, occupational, and behavioral impairments and trigger substantial distress in the patient (AASM, 2014).

It is noted in the literature that insomnia is thought to be a disorder of hyperarousal (Roth, 2007). A cognitive model suggests that sleep can be disrupted by rumination and worries about life traumas (Harvey, 2002). This rumination and worry might create difficulties with sleep onset and resumption after awakening (Harvey, 2002). The authors argued that changes in the sleep environment, increased light exposure, noise, excessively high or low ambient temperatures, or poor mattresses might lead to acute insomnia (Harvey, 2002). Additionally, life events or stresses affect sleep (Harvey, 2002).

Classification of Insomnia. The literature review indicates that insomnia disorders could be classified as either primary or secondary insomnias (Thorpy, 2012). Primary insomnias have intrinsic and extrinsic variables involved in their etiology, not seen as occurring secondary to another medical condition (Thorpy, 2012). The literature review suggests that secondary insomnia is when the insomnia symptoms result from substance abuse, another sleep disorder, or other mental health problems (Thorpy, 2012). Insomnia classification should include the chief complaint of difficulty initiating sleep, retaining sleep, too early waking from sleep, and inadequate quality sleep (Thorpy, 2012). When classifying insomnia, researchers need to include other variables such as

sleep impediment that arises notwithstanding how adequate the sleep opportunity may be and circumstances for sleep, and that more than one impairment of daily living is due to sleep difficulty (Thorpy, 2012).

The review of the literature suggests that patients with insomnia can be divided into five clinically relevant subtypes by using high-dimensional data-driven subtyping (i.e., highly distressed; moderately distressed but reward sensitive (i.e., with intact responses to pleasurable emotions), moderately distressed and reward insensitive; slightly distressed with high reactivity (to their environment and life events; and slightly distressed with low reactivity; Blanken et al., 2019). These researchers suggest that such classification could reduce the heterogeneity of insomnia disorder and facilitate the elucidation of underlying causes, development of personalized treatments, and identification of patients with the highest exposure to MDD.

Insomnia as a Risk Factor. Researchers noted that chronic insomnia could be comorbid with an underlying medical condition (e.g., COPD, cancer, congestive heart failure, Parkinson's disease), mental disorder (e.g., MDD, schizophrenia, bipolar disorder, anxiety disorders), drug or alcohol use (or withdrawal), or environmental factors (Gates et al., 2016; Perney & Lehert, 2018; Reeve et al., 2015).

When insomnia is comorbid with MDD (i.e., one of its most common comorbidities), insomnia frequently precedes the onset of MDD disturbing symptoms. and is among the most likely symptoms to persist once the affective symptoms of an MDD episode have been treated (Nierenberg et al.,1996). Among patients treated for insomnia, 13.56% and 24.55% in the US and Western Europe (i.e., five EU countries;

France, Germany, Italy, Spain, and the UK), respectively, were non-adherent to their medications due to medication side effects (DiBonaventura et al., 2015). Extrapolating from the above findings, one can argue that untreated MDD or non-adherence to MDD treatment might result in lasting insomnia episodes.

However, conflicting research suggests that certain antidepressants might contribute to insomnia complaints, although some antidepressants have lower insomnia effects than others (Doufas et al., 2017; Krystal et al., 2007). Acetylcholinesterase inhibitors, SSRIs, and dopamine agonists were medications associated with sleep disturbance (Doufas, 2017). Other researchers have argued that antidepressants such as fluoxetine induce several side effects, such as nausea, insomnia, and sexual dysfunction (Mutsatsa, 2016).

Further clarification is needed from the above controversy in the literature regarding MDD and insomnia. This controversy validates the need for this study to evaluate the level of association between the patient's antidepressant medication adherence status and the insomnia risk among individuals diagnosed with MDD after controlling for race, gender, and age.

Poor appetite and MDD. To better understand MDD-related complications, there is a need to evaluate the level of association between the patient's antidepressant medication adherence and poor appetite risk among individuals diagnosed with MDD after controlling for race, gender, and age.

Classification of Poor Appetite. Hypoactivation of the insular areas that maintain the censoring of the body's physiological condition associated with MDD is correlated

with appetite loss (Simmons et al., 2016). Poor appetite reduces the desire to fulfill a bodily need and can be divided into three components: hunger, satiation, and satiety (Pilgrim et al., 2015). These authors argued that hunger is the phenomenon that stimulates food ingestion. They indicated that satiation is the phenomenon that promotes fullness during food ingestion leading to meal termination. These authors noted that satiety is the fullness between eating occasions. According to these authors, the risk of nutritional deficiencies and weight loss is associated with worse health outcomes for patients and an increased risk of dying.

Poor Appetite as a Risk Factor. The most common depressive symptoms are poor appetite, insomnia, and low energy (Wasil et al., 2020). Poor appetite increases an individual's risk of nutritional deficiencies and weight loss, which is tough to reverse (Pilgrim et al., 2015). Changes occur within the human systems and around an individual are responsible for decreased appetite (Amarya et al., 2015; Malafarina et al., 2013). These changes may include "the body's physiology, psychological functioning, and social circumstances" (Amarya et al., 2015, p.78). Some illnesses, such as MDD, are known to impair appetite and are common in older people, with reported rates of 9% in community-dwelling older people, 27% in those who live in care homes in the UK, and 24% in older inpatients (Engel et al., 2011; Goldberg et al., 2012; McDougall et al., 2007). Amarya et al. (2015) noted that appetite impairment might result from some physiological changes that come with aging, such as reduced energy requirement, diseases that cause modification in smell, vision, and taste, hormonal changes, changes in the digestive system, and pain. Appetite and weight changes are expected variable

diagnostic markers in MDD (Simmons et al., 2016). If poor appetite is a diagnostic marker in MDD (Simmons et al.), one can argue that the patient will improve their appetite by adhering to effective MDD treatment.

However, contrary findings indicates that some antidepressant medications might be responsible for the MDD patient's poor appetite. A study by Schiffman (1997) pointed to some 250 commonly used medications with a reduced appetite as a possible side effect. MDD complication of poor appetite is linked to medication use and not the outcome of medication non-adherence (Schiffman (1997).

This contradiction in the literature requires further investigation of this topic. To better understand MDD-related complications, this study evaluated the association between the patient's adherence to antidepressant medication and poor appetite risk among individuals diagnosed with MDD after controlling for race, gender, and age.

Suicidal Thoughts and MDD. Suicide rates in the US have increased significantly since 1999 (US National Center for Health Statistics, 2018)Suicide is one of the most pressing public health concerns facing modern society, with more than 40,000 people dying by suicide each year in the United States (Center for Disease Control [CDC], 2016; Naghavi, 2019). This MDD complication includes an individual's thoughts, feelings, ruminations, or preoccupations with death, in general, and suicide in particular (Hedegaard et al., 2018). Emerging chronological trends suggest that suicide rates increase within the United States and globally (Hedegaard et al., 2018; Naghavi, 2019). . In a study of 1051 participants interviewed, 364 reported lifetime symptoms of MDD, 48% reported lifetime suicidal thoughts, and 16% reported a lifetime suicide attempt

(Handley et al., 2018). According to this study, while the severity of MDD was fundamentally connected to suicidality for both sexes, suicide attempts were fundamentally more normal among females with a younger age of the disease onset and a higher number of mental comorbidities (Handley et al., 2018).

Classification of Suicidal Thoughts. Suicide thoughts may occur during severe mental illnesses such as MDD, Bipolar Disorder, or schizophrenia, as well as other conditions. Researchers have noted that the risk of suicidal thoughts is influenced by many factors, including the magnitude, clarity, clinical psychological factors, pain; the presence of anxiety, personality and substance use disorders, severe neuropsychiatric disorders and head injury; inherent genetic factors, aggression, and impulsivity, hopelessness, helplessness, guilt, entrapment, burdensomeness, shame, history of childhood abuse, adverse life events and psychosocial stressors (Glenn et al., 2018).

Suicidal Thoughts as a Risk Factor. **The diagnostic and statistical manual of mental disorders** noted that suicide is conceptualized primarily as a specific symptom of MDD and borderline personality disorder or a possible negative consequence of other psychiatric diagnoses (APA, 2013). The literature suggests that suicide attempts decreased after the onset of treatment for depression compared with the month before initiating therapy (Khanet et al., 2018; Termorshuizen et al., 2016). Morgan and associates (2018) confirmed that adherence to antidepressant treatment for MDD is associated with a substantial decrease in suicide thoughts risk. Increase in the prescription of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) used in treating MDD is associated with a decline in the annual suicide rate (Chen et al., 2021; Forsman

et al., 2019; Ludwig & Marcotte, 2005; Nakagawa et al., 2007).

The literature review presents lingering controversy; about the proportional impact of, and potential for, suicide-promoting effects of some antidepressants in children, adolescents, and young adults under the age of 25 years (Hammad et al., 2006; Sharma et al., 2016). This argument is confirmed by a consensus statement released by the World Psychiatric Association Section on Pharmacopsychiatry in 2008 that indicated that antidepressants containing SSRIs carry a minimal risk of provoking suicidal thoughts and suicide attempts in individuals 25 years old or younger (Bschor et al., 2016). Sharma et al. (2016) argued that in children and adolescents on antidepressants, the risk of suicidality and aggression doubled. When present, this risk appears to relate to the initial weeks of treatment, suggesting a need for close monitoring for the worsening of depressive symptoms and the emergence or worsening of suicidal thoughts during the initial phase of MDD treatment (Kessler et al., 2018; Strawbridge et al., 2019). A small number of young patients may develop new suicidal thoughts or self-harm with SSRI treatment, overall, there is an agreement that antidepressant treatment for MDD substantially decreases suicide thoughts rates (Pompili et al., 2010).

Researchers have suggested that MDD is strongly related to suicidal thoughts and attempts (Grunebaum et al., 2018; Handley et al., 2018). However, these researchers also argued that MDD shows deficiencies as a suicide thought predictor, and there is inadequate knowledge concerning characteristics that intensify suicide thought risk among individuals with MDD (Grunebaum et al., 2018; Handley et al., 2018). However, suicidal thoughts and mental disorders do not always or exclusively predict suicidal

behavior (Klonsky & May, 2014).

Suicide prevention efforts have proven difficult to develop, possibly because no one risk factor predicts suicide with high accuracy (Fehling & Selby, 2020). Combat suicide thoughts will need public health efforts to require an in-depth analysis of this MDD complication. To better understand the diverging opinions regarding this MDD complication (i.e., suicidal thoughts), this study evaluated the association between the patient's adherence or non-adherence to antidepressants medication and associated suicide thoughts risk among individuals diagnosed with MDD-related complications, after controlling for race, gender, and age.

MDD Treatment and Complications Prevention Options

MDD-related complications treatment and prevention mechanisms relate to specific, population-based, and individual-based interventions aiming to minimize the burden of MDD-related complications and associated risk factors. MDD treatment and prevention goals are to eradicate the symptoms of MDD, improve daily functioning and quality of life, improve workplace functioning, reduce suicidality, minimize adverse treatment effects, and prevent relapse (Hofmann et al., 2017; Lee et al., 2018). MDD treatment modalities include antidepressants, other pharmacotherapies, psychotherapies, supportive interventions, and electroconvulsive therapy. For patients with MDD undergoing outpatient treatment, significant benefits are associated with the collaborative chronic care model that incorporates patient training, organizational support, community resources, and other multidisciplinary interventions (Richards et al., 2013). Coordinated care appears to be effective for patients with depression alone and those with depression

and comorbid chronic physical conditions (Panagioti et al., 2016). Issues yet to be resolved in the effective deployment of collaborative care models include the education of providers, reimbursement, and communication (Overbeck et al., 2016). The internet and mobile-based interventions have also been shown to reduce MDD symptoms (Josephine et al., 2017; Păsărelu et al., 2017). However, the literature suggests that despite the effectiveness of these antidepressant medications, the high rate of non-adherence to medication produces an ever increased devastating consequence to both the patients and society.

Adherence to Antidepressants

A vital risk variable associated with relapse of MDD and MDD-related complications is adherence to antidepressant medications. Inadequate treatment of MDD and the poor management of MDD-related complications remains a significant global public health concern (Meng et al., 2020; WHO, 2017). Despite the evidence of the effectiveness of antidepressants in reducing MDD symptoms and their complications, non-adherence to these medications remains a major global healthcare issue (WHO, 2017). Researchers' consensus is that adherence to antidepressants reduces the severity of MDD and improves patient treatment results only when these medications are taken as prescribed. Non-adherence to MDD treatments increases the risk of MDD-related complications, disease relapse, reduces the patient's quality of life, and increases hospitalization chances (Cutler et al., 2018).

The literature review indicates that selective serotonin reuptake inhibitor (SSRI), prescribed by health care providers for several mental disorders and MDD is associated

with reduced MDD prognosis, and improves CHD prognosis (Rutjes et al., 2011). Findings from a cohort study by Biffi et al. (2018), which included 29,845 individuals aged ≥ 65 years, confirmed the finding by Rutjes et al. (2011) that better adherence to antidepressants is associated with a reduction in MDD and CHD all-cause mortality.

Reasons for Non-Adherence

Gender, education, employment, and the total number of medications used significantly influence adherence to antidepressants (Amir et al., 2020). In a prospective study by Shrestha Manandhar et al. (2017) exploring the adherence pattern to antidepressants in patients with depression, most patients in the research thought that taking their drug regularly may make them feel better. However, only a few patients adhere to treatment (Shrestha Manandhar et al., 2017). The relationship between factors and adherence changes with the duration of therapy (Amir et al. (2020). A lack of accurate information causes an early interruption of treatment (Martin-Vazquez, 2016). This author indicated that other sociodemographic factors are common to inadequate adherence, such as low income, low socio-educational status, the severity of depression, and demanding access to physicians or medication.

The reasons for patient medication non-adherence fall under two categories: intentional (resulting from personal choice) and unintentional (resulting from objective barriers to taking medication; Velligan et al., 2017). Intentional non-adherence refers to a conscious patient's decision to stop taking or take less medication than prescribed (Velligan et al.). According to these authors, the identified reasons in this category include poor insight, a negative attitude toward medication, distressing medication side

effects, poor therapeutic alliance, and stigma (Velligan et al.). These authors included the following reasons for non-adherence under the unintentional non-adherence category: access to mental health care, depression, cognitive impairments, substance abuse, family/social support, and social functioning (Velligan et al.). The authors noted that substance abuse was included in this category because a patient's non-adherence to medication is unintentional during using the substance (Velligan et al.).

Consequences of Non-Adherence

Medication non-adherence places a significant cost burden on healthcare systems, increases the risk of MDD-related complications, relapses the disease, reduces the patient's quality of life, and increases the chances of hospitalization (Cutler et al., 2018). Research conducted by Kini and Ho (2018) indicated that in the United States, an estimated 125,000 deaths, 10% of hospitalizations, and $100 billion in healthcare services annually are associated with patients' non-adherence to medication. The annual adjusted disease-specific financial cost of non-adherence per person ranged from $949 to $44 190 (Culter et al.). According to these authors, costs attributed to 'all causes' non-adherence ranged from $5271 to $52 341 (Culter et al.). Ho and associates (2016) conducted a systematic review of the literature to determine the clinical and economic outcomes of non-adherence. The authors reviewed eleven articles, with eight reporting on clinical outcomes, two reporting on financial outcomes, and one reporting on both. These authors argued that non-adherence to antidepressants was associated with an increased risk of MDD relapse and recurrence, increased hospitalization rates and emergency department visits, worsening symptoms, and decreased response and remission rates. The authors

noted that non-adherence to antidepressants was associated with worsening clinical outcomes and increasing healthcare utilization.

To better analyze the above controversy regarding MDD-related complications, there is the need to evaluate further the level of association between the patient's adherence or non-adherence to antidepressant medication and the risk of associated complications among individuals diagnosed with MDD after controlling for race, gender, and age.

Previous Studies Using the Same Methodology

This study is a quantitative, cross-sectional analysis that used primary data to assess how antidepressant adherence impacts MDD-related complications (insomnia, poor appetite, and suicidal thoughts). Statistical inference analysis (i.e., binary logistic regression analysis model and Fisher's extract test) is used to establish the association between the dependent variable (MDD-related complications) and the independent variables (antidepressant adherence).

Online Primary Data Collection

Adu et al. (2021) used primary data for their study. The authors conducted a cross-sectional research during the COVID-19 pandemic in Ghana using online survey data collection methods, similar to what this study used (Adu et al., 2021). Their research involved 1068 participants, with the initial online data collection process beginning with a survey link distributed primarily through WhatsApp-based platforms. The authors evaluated the prevalence of MDD symptoms as they relate to social, clinical, demographic, and other COVID-19-related correlates. The authors should have specified

what conceptual model they used. The authors assessed the association between MDD symptoms as a dependent variable and employment, loss of jobs during the pandemic, rate of exposure to COVID-related news, gender, relationship, housing status, and having a family member or friend who was sick from COVID-19 as independent variables. Both descriptive and inferential statistics were analyzed. The author used Cross-tabular univariate analyses with Chi-square or Fisher's exact tests to explore the relationship between the categorical variables in the study and moderate/high depression symptoms. The authors examined Odds ratios from binary logistic regression analysis to determine the association between each of the variables in the model and the likelihood of individuals reporting moderate/high depression symptoms, controlling for the other variables in the model. Some weaknesses of the study by Adu et al. (2021) included using internet-based data collection methods and English language-only survey questions. The data collection method might have prevented individuals who wished to participate but had no internet access or were not educated enough to read and write in English from participating in the study. Also, the distribution of survey links on WhatsApp groups means a large section of Ghanaians who were not members of these social media groups or affiliated with members of the group were excluded from the survey. Therefore, the results cannot be generalized. All the analyzed data were based on self-report data hence the possibility of social desirability and recall biases. Finally, the cross-sectional nature of the survey prevented the authors from establishing a direct causal relationship between the variables included in the regression model and MDD risk. The study by Adu et al. (2021) did not consider MDD-related complications, the gap addressed by this study.

During the COVID-19 lockdown, Perveen et al. (2020) also used the same online survey method to collect primary data for their cross-section research involving n = 716 participants. The authors examined the adult population's psychological health issues, including depression, anxiety, and stress. The authors should have specified what conceptual model they used. The variables of depression, anxiety, and stress, were studied during the period of movement control order in Malaysia. The authors collected data using the depression, anxiety, and stress scale (DASS-6). Data were statistically analyzed using IBM SPSS software 25, providing descriptive statistics for the prevalence of the significance level of variables. A significant weakness of the study was that the authors provided results from only descriptive statistics, which was limited to a summary of the dataset's characteristics. The authors should use inferential statistics to test hypotheses and assess whether the study's analyzed data were generalizable. All the analyzed variables were based on self-report data hence the possibility of social desirability and recall biases. The study's results might have been different had the study been conducted during a period of lesser restricted daily life activities, social distance, and continuous uncertainties. This study uses inferential statistics to test hypotheses and assess whether the collected dataset is generalizable, an analytical step that Perveen et al., 2020 omitted.

Paiva and associates (2021) also used primary data for their study. The authors used an online survey method to collect primary data from *n* = 5479 eligible participants for their cross-section research that assesses sleep and awakening quality during the COVID-19 pandemic. The authors should have specified what conceptual model they

used. Variables used included conventional demographics, health status (confinement mood, attitudes, and behaviors; Calamity Experience Check List (CECL); sleep; physical activity (PA), multimedia use, nutrition, toxic habits, and addictions). Other demographic variables, in addition to the conventional demographic variable examined, included the number of people living together during the pandemic. The authors noted that health status also included “yes/no questions to the following topics: being healthy (subjective) or suffering from sleep, psychiatric, neurologic, cardiovascular, respiratory, allergies, gastrointestinal, rheumatologic, endocrinologic/metabolic, autoimmune, orthopedic, cancer, renal, dermatologic, hematologic, gynecologic, urologic, ear/nose/throat (ENT), or ophthalmologic disorders, chronic pain, fatigue, and dizziness” (p.3-4). Both descriptive and inferential statistics were analyzed. The authors evaluated the effect of the independent variables on the dependent variable using a paired t-test. They compared sleep quality and awakening quality before and during COVID-19, using paired t-tests, chi-square tests, and ANOVA with post hoc Bonferroni tests. The authors use a logistic regression model to establish the relationship between "sleep/awakening quality and age, sex, Calamity Experience Check List (CECL), the number of morbidities, sleep latency and sleep awakenings on weekdays during COVID-19, and physical activity intensity as covariates" (Paiva et al., 2021, p.4). The authors used SPSS®v25 to perform all statistical tests, with a significance set at 0.05. The design (self-reported cross-sectional nature) of this study is a weakness. This study was not a national prevalence study and was based online, exposing the study to selection bias.

Tengilimoğlu et al. (2021) also utilized an online primary data collection method

for their study. The authors' research was conducted with n = 2076 eligible participants in Turkey, using a cross-sectional online survey method similar to this proposed study's data collection design. The authors did not specify what conceptual model they used. The authors analyzed the collected data using the SPSS-23 statistical software. The authors reported descriptive statistics and inferential statistics results from the t-test and ANOVA test used to observe whether healthcare employees' depression, anxiety, and stress levels varied based on other variables. The authors used the TUKEY LSD test to find out from which groups the difference came, if there were any. This study is limited to determining depression, anxiety, and stress levels of health employees during the COVID-19 outbreak. The study's results might have been different had the study been conducted during a period of lesser restricted daily life activities, social distance, and continuous uncertainties. For accurate findings, the authors should consider another study to determine the social, psychological, and physical needs of health employees after COVID-19.

The quantitative research approach is generally recommended when the study's primary purpose is to evaluate or provide explanations (Leavy, 2017). This research used primary data from a survey questionnaire hosted by Survey Monkey to assess the association between the study's variables. The suggested research method (quantitative analysis) is appropriate for this study as it involves measuring variables and testing relationships between variables to reveal patterns, correlations, or associations (Leavy, 2017).

This study did not involve the deliberate manipulation of the research predictor

variables. This research used a quantitative study design, which is appropriate because it provides a better method to record and analyze information concerning the study's participants without any interference with generating the information (Leavy, 2017; Ott & Longnecker, 2015). Since this researcher will not manipulate the independent variables, the study did not use the quantitative experimental research design.

Cross-Sectional Study

Observational cross-sectional design is the most predominant design used in social sciences (Nachmias & Nachmias, 2008). In 2019, Zhou et al. conducted a cross-sectional study to investigate the clinical characteristics of medication non-adherence in patients with MDD (Zhou et al., 2019). The 3,214 eligible participants for this study, ages 16-87 years, were recruited from 22 cities in 15 provinces in China (Zhou et al., 2019). The researchers conducted this nationwide survey using a doctor-rating questionnaire with 64 symptoms (Zhou et al., 2019). A limitation of this study was the exposure to response bias. The self-reported questionnaire used for the analysis was not validated. Due to their illness, some patients may not answer the questions thoughtfully, which may cause biases in the data.

Prakash and associates (2019) documented the association of various psychosocial variables affecting adherence to antidepressant treatment among patients diagnosed with depressive disorder in a psychiatric tertiary care hospital. This cross-sectional analysis involved 150 patients diagnosed with depressive disorder. The authors noted that the participants "were subjected to medico-psychosocial-structured per forma, Beck's Depression Inventory, The Belief About Medicines Questionnaire, and the

Morisky Medication Adherence Scale" (Prakash et al., 2019, p.135). The study identified various clinical and psychosocial correlates of medication adherence. This study, however, had some limitations that reduced its reliability and generalization. First, the sample size of 150 was small, and there was no indication that the authors performed a power analysis to determine that the 150 sample size was suitable to detect the effect. Secondly, the cross-sectional analysis design calls for caution when attributing a causal inference vis-a-vis the predictors for medication adherence. Lastly, the study was exposed to information bias as the self-reported questionnaire relied solely on the information provided by the patient regarding their treatment history and compliance.

Statistical Analysis

The study used binary logistic regression analysis and Fisher's extract test to examine the association between medication adherence and MDD-related complications. Zhou et al. (2019) carried out research to study the clinical characteristics associated with non-adherence. These authors used a single-factor logistic regression to screen variables and multifactor logistic regressive analysis to identify risk or protective factors for non-adherence (Zhou et al., 2019). Researchers used logistic regression to determine the association between the likelihood of cognitive impairment and being physically inactive compared to physical activity status at each age (Middleton & associates, 2010). Keyloun and associates (2017) assessed adherence and persistence to specific antidepressants, therapeutic classes, and antidepressant therapy at multiple time points among US individuals from commercial, Medicare supplemental, and Medicaid insurance plans. The authors used multivariable logistic regression to estimate the adjusted odds ratios (ORs)

of adherence to initial antidepressant medication by comparing antidepressant therapeutic classes.

Summary

The fundamental fact behind this study is that preventing and reducing disease complications is a significant pillar in every population's healthcare program. Chapter 2 of this study covered the literature review, identifying research trends and conflicts in research findings regarding medication adherence and MDD-related complications. The literature review indicates that MDD-related complications remain a healthcare issue that has raised the attention of healthcare professionals, medical institutions, and policymakers (WHO, 2017). Untreated MDD might lead to complications such as gaining excess weight or becoming obese, diabetes, CHD or metabolic syndrome, physical illness and pain, misusing drugs or alcohol, panic attacks, social phobia, or anxiety, having suicidal thoughts, attempting suicide, or committing suicide, mutilating oneself through cutting or other means, suffering from premature death from other medical disorders or conditions (McIntyre et al., 2018). Researchers' consensus is that adherence to antidepressants reduces the severity of MDD and improves patient treatment results only when these medications are taken as prescribed. However, researchers argued that despite the evidence regarding the efficacy of anti-depressive treatment in reducing MDD-related complications compared to placebos or other controls, there is growing evidence that, on average, patients with MDD do not adhere to their anti-depressive treatment, resulting in the observed increase in MDD-related complications (Kini & Ho, 2018; Semahegn et al., 2020; Zipursky, 2014). Low adherence to treatment rates is one of

the most significant impediments in preventing MDD illness complications and an important public health issue (Lam et al., 2015). Cutler and associates (2018) suggested that non-adherence to MDD treatments increases the risk of MDD-related complications, relapse of the disease, reduces the patient's quality of life, and increases hospitalization chances. However, some researchers have indicated that the observed MDD-related complications result from the side effects of antidepressants used to treat MDD (Coupland et al., 2011; Ferguson, 2001; Marasine et al., 2020). The literature review indicated that conflicting opinions vis-à-vis MDD-related complications remain an issue for further examination within the scientific community.

Global research to identify the association between MDD and the causes of MDD-related complications remains inadequate. This literature review exposed a gap in research regarding MDD-related complications and antidepressants. Antidepressants are among the most frequently prescribed drugs globally, but their association with MDD-related complications has not been thoroughly evaluated (Kim et al., 2013). A literature review indicates a strong encouragement for further evaluations of specific improved individual and combination therapeutic strategies that identify MDD disease complications and clinical predictors of unfavorable treatment outcomes in patients diagnosed with MDD (Sim et al., 2016). Correlation between increased non-adherence and higher disease prevalence should be examined and used to inform policymakers to help circumvent avoidable costs to the healthcare system (Culter et al., 2018).

An adequate intervention strategy to deal with MDD-related complications can only be possible if variables significantly associated with MDD-related complications are

fully understood. The study examined the relationship between antidepressant adherence and MDD-related complications in people with MDD after adjusting for race, gender, and age.

In this chapter, I discussed how the literature was reviewed and the framework for this study. I examined the extant literature on antidepressant adherence and MDD-related complications providing a perspective to position this study within the scientific community. Chapter 3 of this study provides the population and sample selected, sources of the primary dataset used, the threat to the study's validity and reliability, ethical considerations, limitations, and delimitations. I discussed the data collection procedures, the research questions, the matching hypotheses, and the operationalization of the study's variables. I also discussed the analytical methods used to answer the research questions and hypothesis.

Chapter 3: Research Method

This quantitative study addresses the disagreement behind the driver of MDD-related complications among adult patients diagnosed with MDD in Texas. This study addressed the relationship between adherence to antidepressants (the independent variable) and MDD-related complications (the dependent variable). Researchers have indicated that additional information from the statistical analysis involving these variables will clarify the association between antidepressant medication adherence and MDD-related complications (Howitt & Cramer, 2017). This study used a binary logistic regression model and Fisher's extract test to examine the association between antidepressant adherence and MDD-related complications while controlling for race, gender, and age. Chapter 3 provides an overview, and the appropriateness of the research methodology and design used. I describe the population and sample selected, the threats to the study's validity and reliability, and ethical considerations. I also discuss the data collection procedures, the research questions, and the operationalization of the study's variables.

Research Design

There are two primary methodological designs in non-experimental research: cross-sectional and longitudinal (Ruel et al., 2016). This study did not use the longitudinal design due to financial and time constrain. I used a cross-sectional approach to examine the extent antidepressant medication adherence is associated with MDD-related complications. This helped answer the research questions:

- Research Question 1: What is the association between patient adherence to

antidepressants as measured with MMAS-8 and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

- Research Question 2: What is the association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?
- Research Question 3: What is the association between patient adherence to antidepressants as measured with MMAS-8 and suicidal ideation risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

Cross-sectional designs are typical of most non-experimental social research designs (Howitt & Cramer, 2017; Nachmias, 2015). The cross-sectional design is appropriate as this design is effective in evaluating the association between the independent and dependent variables (Howitt & Cramer, 2017). The design is also appropriate in that the extent to which the association between the dependent and independent variables is influenced by controlling other variables (such as race, gender, and age) could also be assessed (Howitt & Cramer, 2017). The shortfall of the cross-sectional design is that it cannot be used to test causality. However, these researchers often support their augment for potential causal interpretations from the relationships they obtained from cross-sectional studies.

Research Methodology

This section addresses the method I used to answer the research questions and

why I selected this method instead of the alternative methodologies. This study is an explanatory social study that did not involve deliberately manipulating the research predictor variables. The quantitative study design was appropriate for this study because it provided a better method to record and analyze information concerning the study's participants without any interference with generating the information (Leavy, 2017; Ott & Longnecker, 2015). Since I did not manipulate the independent variables, the study did not use the quantitative experimental research design. In this quantitative research study I evaluated the association between antidepressant adherence and MDD-related complications. The research used primary data from a survey questionnaire hosted by Survey Monkey to determine the association between the study's variables.

Population and Sample Selection

This section discusses the sample setting, the target population, and the study's sample. I carried out this cross-sectional survey in Texas. According to the U.S. Census Bureau, in 2020, Texas had a population of over 29 million inhabitants. Texas is the second-largest U.S. state by population (after California) and by area (after Alaska) (U.S. Census Bureau, 2020).

Following permission from the Walden University Institutional Review Board (IRB, approval no. 11-23-22-0918806), the recruitment of participants began. I used Survey-Monkey's target audience to find volunteers for the study. I sent the survey to individuals who fit the study's requirements. At the start of the survey, I attached an informed consent form with information related to the study that included a concise problem statement, the study's purpose, and other critical study-related details (including

ethical research obligations linked to the study). After reading the consent document, respondents were then allowed to take the survey. The consent form noted that individuals could discontinue their participation at any time and were free to complete the questionnaires at any place and time of their choice.

Population

For this study, I generated primary data from individual-level, de-identified individuals using an online survey hosted by Survey Monkey. The study's general population was adult residents of Texas currently diagnosed with MDD, aged 18 years and over, and from diverse ethnic backgrounds. This study involved recruiting participants from individuals receiving ongoing MDD treatment under the supervision of a physician. Participants were excluded if they were younger than 18, had organic brain disorders, had alcohol or drug addiction, were undergoing therapy with forensic psychiatric services, are unable to communicate in English, have learning disabilities or other severe mental handicaps, and cannot provide binding consent to participate. The study examined the risk of MDD-related complications (i.e., insomnia, poor appetite, and suicidal thoughts) and antidepressant adherence status following self-reported answers to a survey questionnaire, a section of which included the MMAS-8.

Sample Size

The most obvious way to prevent Type-2 errors is to ensure that the sample size is large enough to detect real effects (Howitt & Cramer, 2017). Researchers have also suggested that a priori statistic power analysis is required to estimate the study's sample size before conducting the study based on the anticipated effect size and selected design

(Das et al., 2016). It is advisable to use the event per variable of 50 and the formula $n = 100 + 50i$, where i is the number of independent variables in the final model, to determine the sample size for observational studies with large populations that use logistic regression in the analysis (Bujang et al., 2018; Pavlou et al., 2016).

In the study proposal, the dependent variables were insomnia, poor appetite, suicidal thoughts, and independent variables were adherence to antidepressants, marital status, group therapy, race, gender, CHD, diabetes, BMI, duration of treatment, social support (living alone), and age. The total sample size according to G*power analysis with 14 variables was (N) = 1,188.

The initial amount of control variables for the study needed to be lowered, according to recent literature. The high number of control variables proposed initially, according to recent research, significantly increased the likelihood of missing data, decreased the number of valid responses, introduced bias through opaque mechanisms, increased the possibility of model overfitting, and significantly diluted the mathematics, all of which significantly increased the likelihood of non-significant results (Ranganathan et al., 2017). Additionally, some of these variables had a strong correlations with one another, making it impossible to employ them in the study's selected statistical model as this will cause the results to be less precise (i.e., using them will violate the logistic regression model assumptions). As a result, I decided to choose the covariates that did not have a strong relationship to adherence to antidepressants. Hence the study's final dependent variables were insomnia, poor appetite, suicidal thoughts, and independent variables were adherence to antidepressants, race, gender, and age.

An estimate of $n = 100 + (50 * 4) = 300$ was the suggested sample size for this investigation. However, I also conducted a statistical power analysis (*z*-tests – logistic regression, a priori: Compute required sample size, using *G**Power 3.1 software) as a rough guide for determining the required sample size to help reduce the risk of making a Type-2 error or obtaining a false negative (Howitt & Cramer, 2017). The statistical *G**Power analysis performed for this study generated the following output parameters: Total sample size (N) = 139 with a Critical $z = 1.9599640$, Actual Power = 0.9513446, α err prob. = 0.05, Power (1-β err prob.) = 0.95. The modeled error estimate for this study's was ± 5.77% with the sample size of 300 respondents.

Instruments Used

I used a self-serve survey platform (Survey Monkey) to collect primary data using an online survey. This survey involved individuals completing a consent form and a survey questionnaire. After going through the consent form, the participant had to respond to the screening question that enquires if the participant has had one or more physician visits related to MDD, any recent changes in the type of antidepressant medication used or in antidepressants medication dose to identify suitable respondents for this study (i.e., the participants must have an MDD physician diagnosed and follow-up). Participants responded to the approved survey questionnaire statements by checking the box with the answer that best describes each statement's variables. The first section of the questionnaire obtained information regarding the control variables (participants' demographic data such as age, race, and gender). The second section indicated the existence or not of a physician-diagnosed medical condition (i.e., yes/no for insomnia,

poor appetite, or suicidal ideation), providing data regarding the dependent variable (MDD-related complications). The last section of this self-reported questionnaire comprises questions on current antidepressants and the validated MMAS-8 questions, providing information regarding prescribed antidepressant medication used and the independent variable (individual's current antidepressant medications adherence status).

MMAS-8

Dr. Morisky copyrighted the MMAS-8 in 2006 and used this instrument of measure in a 2008 study to establish the predictive validity of MMAS-8 in patients with hypertension (Morisky et al., 2008). MMAS-8 has a good reliability with an internal consistency Cronbach's alpha of .83, a sensitivity of 93%, and a specificity of 57% (Morisky et al., 2008). Other researchers examined the validity and reliability of MMAS-8 to evaluate an individual's medication adherence status in clinical research and medical practice (Janežič et al., 2017; Moon et al., 2018). The authors concluded that MMAS-8 as an instrument of measurement had adequate internal reliability and validity in a few diseases, such as type 2 diabetes and asthma (Janežič et al., 2017; Moon et al., 2018). Using the Persian version of the MMAS-8, researchers came to the same conclusion that MMAS-8 is a substantially valid and reliable questionnaire to investigate the medication adherence status of Persian-speaking patients with diabetes (Laghousi et al., 2021). This study will use the MMAS-8 instrument to screen for antidepressant medication adherence in patients diagnosed with MDD. Based on the above researcher's validation of the MMAS-8, using this instrument of measure reduces any measurement validity of this study. To score the MMAS-8, the sum (total) of negative scores for each patient is

subtracted from their sum (total) of positive scores. A total MMAS-8 positive score indicates medication adherence, while a total MMAS-8 negative score indicates nonadherence to medication. The construct validity of the study is reduced as the MMAS-8 used in the study aligns with the theoretical framework.

Self-Reported Online Survey Questionnaire

The self-reported answers to the online questionnaire was adequate and relevant for this study.

Data Collection and Management

Table 1

Variables Codes

Variables	Level of measurement	Code
Insomnia	Nominal	Yes = 1, No = 0
Poor Appetite	Nominal	Yes = 1, No = 0
Suicidal Ideation	Nominal	Yes = 1, No = 0
Race	Nominal	White = 1 Hispanic or Latino = 2 All Other = 3
Gender	Nominal	Male = 1. Female = 2
Age	Categorical	18-24 = 1 25-34 = 2 35-44 = 3 45-54 = 4 55-64 = 5 65+ = 6
Antidepressant Adherence	Categorical	Low = 1 Moderate = 2 High = 3

Researchers suggested that, due to its extensive participant self-report data collection ability, enormous user base, and national representation, Survey Monkey is frequently utilized in epidemiological, pharmacological, and health services research

(SurveyMonkey, 2022). Every day, more than two million individuals use Survey Monkey's platform to complete surveys (SurveyMonkey, 2022). I used a selection of these individuals living in Texas to participate in this optional survey. Upon completing the survey, I filtered out all individuals who still needed to complete the survey (nonresponses). Recruitment and data collection commenced immediately after IRB approval for the study. I stopped the data collection after I had the number of responses equal to the calculated required sample size of approximately 300 individual responses.

Regarding data management, I will keep the dataset used for the study no longer than is necessary for this study and as required by IRB (i.e., five years). I will ensure that the data is safe from unauthorized access, accidental loss, or destruction by keeping the data storage unit in a lock-secured fireproof cabinet. I will ensure that all digital datasets used for this study are stored as encrypted files that can be accessed with a password.

Data Analysis Procedures

I used the IBM Statistical Package for the Social Sciences (SPSS) - Statistics Data V27 software for the data analysis. SPSS generated descriptive statistics (Percentage, Mean, and Standard Deviation) that arranged the dataset scientifically. I used tables and graphical representations to understand better baseline characteristics of the demographic variables used for this study. I used inferential statistics to examine the research questions/hypotheses. This study used two primary hypothesis statements [null and alternative] (Fallon, 2016). Researchers have indicated that the conventional method of inferential statistics is null hypothesis significance testing (NHST), which allows for inferences to be made about the population from which the sample was selected (Vogt et

al., 2014). This study used the NHST to accept or reject the prediction at a 0.05 alpha level ($p < .05$.) of significance. This study also used a binary logistic regression model and Fisher's extract test for inferential. I used the binary logistic regression model for this study because it is a predictive analysis that is used to analyze data and explain the connection between one dependent binary variable and one or more predictor variable(s) (either categorical or continuous) (Ranganathan et al., 2017).

Threats to Validity

I ensured the data validity by providing Survey Monkey (the survey host company) with the questionnaire used for the survey and other measures such as the accuracy of the data required, the data collection period, the purpose for which the data is collected, the data content, the research topic, research questions, and the appropriate statistical analysis I used to answer the research questions. I was able to gather data and make accurate generalizations about the population from the sample data thanks to the instruments of measurement I used. The validity and reliability of the study's conclusions could be affected, though, due to reduced trust in responders' self-reported answers and the lack of time used for the study.

To use the binary logistic regression statistical model for this study, I assessed the dataset to ensure it meets the basic assumptions for binary logistic regression which might affect the statistical conclusion validity. These assumptions included:

- No correlation between the independent variables – I checked this assumption using Spearman's correlation coefficient.
- Lack of strongly influential outliers – I checked this assumption using a box

plot.

- No severe multicollinearity – I checked this assumption using the variance inflation factor (VIF)

Ethical Considerations

This section explains how the study met formulated ethical guidelines regarding using primary data and protecting the dataset. The discussion in this section also addressed anonymization and consent in using primary data collection for this study. Before collecting any data for this study, I obtained the Walden University Institutional Review Board (IRB) approvals (approval number: 11-23-22-0918806). For this study, I consented with IRB that the dataset will be anonymous, and using this data will result in minimal or no damage or distress to the participants. The dataset for this study was appropriately coded by survey monkey, so I could not access any participants' codes. I did not collect identifying information (e.g., participants' names, street addresses, telephone numbers, and social security numbers). Participation in the survey was anonymous, and the outcomes of the study's analysis did not require or allow for re-identifying participants.

Due to the sensitive nature of the collected data, I used a set of tools designed to meet the requirements of the HIPAA during the data collection process. Survey Monkey provided participants with a commitment to protecting the privacy of the data collected (SurveyMonkey, 2022). Survey Monkey provided a commitment that ensured the data collected using their platform was secure and compliant with the Health Insurance Portability and Accountability Act (HIPAA) requirements of 1996 (SurveyMonkey,

2022; Hayes & Vance, 2020). Using the consent form, I described the survey, its voluntary nature, risks and benefits to participants, privacy/confidentiality, and participants' rights. Participants proceeded with the survey to indicate their acceptance to participate before accessing the online survey questionnaire. The informed consent form indicated that the survey was a voluntary participation study. The voluntary nature of the survey meant that if individuals opted not to continue participating in the study at any time throughout this survey, they might do so. Participants were free to complete the survey questionnaires at any place and time.

Summary

To answer the research questions based on the observed MDD-related complications conflict found in the literature, I used a quantitative cross-sectional study strategy to analyze primary survey data obtained from the Survey Monkey online survey. I used the cross-sectional design to evaluate the statistically significant association between the independent and dependent variables. I did construct and utilized a cohort of individuals diagnosed with MDD. The study focused on Texas-based adults (eighteen years old and over) who present with symptoms of MDD, and this study identified MDD-related complications (i.e., insomnia, poor appetite, and suicidal ideation) and their adherence to antidepressant status using MMAS - 8. An event per variable and A priori statistic G*Power analysis were performed to estimate the study's requirements. I used the higher of these two sample sizes (N = 300) for the study. I made the inference using a binary logistic regression model and Fisher’s extract test.

In this chapter, I provided the foundation for the conclusions and

recommendations. I described the research population and sample setting. I explained the methodology used for this study, why this design was the most appropriate for this study, as well as provided the envisaged study's scope, delimitations, and limitations. I presented some anticipated validation and reliability issues basis for grounds for limitation for accepting and generalizing the conclusions and recommendations presented later in this study. In chapter 4, I discussed the results of descriptive and inferential statistics.

Chapter 4: Results

Based on diverging evidence, it is unclear to what extent poor antidepressant management (e.g., medication adherence) is associated with MDD-related complications. Researchers have suggested that MDD, if untreated, might lead to complications such as insomnia, poor appetite, and suicidal thoughts. In contrast, other researchers argued that adherence to antidepressants could lead to these same complications. This quantitative cross-sectional study aimed to use primary data collected from 298 adults diagnosed with MDD to investigate the association between MDD-related complications and antidepressant adherence to clarify the conflicting opinions found in the literature. Three debatable questions and hypotheses provided the path for this quantitative study.

Chapter 4 includes a summary of the data-collecting approach and a description of the method used to analyze the data. I present a descriptive summary of the study's sample characteristics and the participants' demographics. I also present information related to data completion and accuracy, indicating changes from the data collection plan described in the preceding chapters of this dissertation. I provided information on how I tested the collected data to ensure that it met the requirements for the statistical test used for analyzing the data (binary logistic regression). Finally, I provide the results of the statistical tests (descriptive and inferential) as they relate to the research questions and hypotheses.

Data Collection

I used SurveyMonkey for data collection. A random selection of individuals (from the SurveyMonkey targeted audience) residents in Texas participated in this optional

survey. I conducted this online survey from December 10, 2022, to December 12, 2022. Over 300 volunteers completed the survey, with a 100% response rate. The number of control variables for the study was reduced to three. The main reason for this reduction was that the high number of variables diluted the mathematics, significantly increasing the likelihood of non-significant results and missing data, lowering valid responses (Ranganathan et al., 2017).

Results

Organizing Collected Data for Analysis

This study used a modeled error estimate determined via a bootstrap confidence interval (SurveyMonkey, 2022). This approach is best practice for non-probability surveys, according to the American Association for Public Opinion Research (AAPOR), as it approximates the variance of a survey estimator by the variability of that estimator determined from a series of subsamples taken from the survey data set (SurveyMonkey, 2022). The modeled error estimate for this study's online survey was ± 5.77%.

After data collection, I used advanced statistical inferences to adjust the dataset to depict an accurate representation of the sample population. To reflect the demographic makeup of the United States, I weighted the online survey's data for age, race, and gender using the American Community Survey from the Census Bureau. One hundred and thirty-eight volunteers who responded "none of the above" to the survey's first logical question (Q1 = the screening question) were immediately redirected to the disqualification page and not considered as this study's participants. The final dataset obtained from SurveyMonkey included 300 volunteers. I eliminated two volunteers

because of their age (under 18), and only 298 volunteers who fit the study's parameters were included in the final dataset. I coded all disease-related variables with a 0 for the absence of the disease and a 1 for the presence of the disease. I coded the male gender as 1 and the female gender as 2. I coded the different races as indicated in the 2020 US Census (White, Hispanic or Latino, and All other races) as 1-3, respectively. Lastly, I coded the age ranges (18-24, 25-34, 35-44, 45-54, 55-64, and 65+) as 1-6, respectively.

Questions 8–15 of the survey questionnaire were based on the MMAS-8 instrument of measure, which indicated the patient's medication adherence status. According to Morisky et al. (2008), a "yes-saying" bias was avoided while creating the MMAS-8 questions. To avoid the propensity to react the same way to a sequence of questions regardless of their content, Question 12's wording was reversed (Morisky et al., 2008). Questions 8 through 14, had two possible answers—"yes" or "no"—whereas question 15 features a 6-point Likert scale. Except for Question 12, where each "yes" response receives a score of 1, and each "no" response receives a score of 0, each "no" response receives a score of 1. To determine the summated score for Question 15, the code (0-4) was normalized by dividing the outcome by four. The final MMAS-8 scores ranged from 0-8, with 8 representing high adherence, 7 or 6 representing moderate adherence, and anything less than 6 indicating low adherence.

Descriptive Statistics

A notable aspect of the results of this study was the very few respondents who reported high adherence to their antidepressants regimen 29 (0.09%) out of the 298 respondents, whereas a minority of the respondents also reported the presence of the

investigated MDD-related complications; insomnia 140 (46.9%), poor appetite 42 (14.1%), and suicidal thoughts 4 (0.03%). The gender distribution of the respondents shows that most were male (see Table 2). Considering the age of the respondents, the highest number of respondents were aged 45–54. Regarding the race of the respondents, from 298 respondents, 150 (50.3%) were White, 71 (23.8%) Hispanic or Latino, and 77 (25.8) all other races (see Table 2).

Table 2

Descriptive Statistics Showing Gender Distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Gender					
Valid	Male	156	52.3	52.3	52.3
	Female	142	47.7	47.7	100.0
	Total	298	100.0	100.0	
Age					
Valid	18-24	37	12.4	12.4	12.4
	25-34	60	20.1	20.1	32.6
	35-44	50	16.8	16.8	49.3
	45-54	86	28.9	28.9	78.2
	55-64	42	14.1	14.1	92.3
	65+	23	7.7	7.7	100.0
	Total	298	100.0	100.0	
Race					
Valid	White	150	50.3	50.3	50.3
	Hispanic or Latino	71	23.8	23.8	74.2
	All Other	77	25.8	25.8	100.0
	Total	298	100.0	100.0	

Testing Statistical Assumptions for Binary Logistic Regression Model

To ensure that the dataset was a good fit for binary logistic regression analysis, I checked that the dependent variable (MDD-related complications) was binary (coded as 0 or 1). I made sure that I had a large sample size, independent observations, there was no multicollinearity between the independent variables, and there were no outliers that would significantly influence the model.

Binary Dependent Variables

I measured the dependent variable (MDD-related complications—insomnia, poor appetite, and suicidal thoughts) on a dichotomous scale in each research question (i.e., the presence or absence of the disease). Hence, the binary nature of the dependent variable was not a setback in using this selected model (binary logistic regression model).

Larger Sample Size

It is advised to use the event per variable of 50 and the formula $n = 100 + 50i$, where i is the number of independent variables in the final model, for observational studies with large populations that use logistic regression in the analysis (Bujang et al., 2018; Pavlou et al., 2016). Therefore, an estimate of $n = 100 + (50 * 4) = 300$ would be the appropriate suggested sample size for this investigation.

No Significant Correlation between the Independent Variables

To test this assumption of no significant correlation between the independent variables, I used Spearman's rho correlation test. Spearman's rho correlation was calculated to evaluate the relationship between antidepressant adherence and race, age,

and race, gender and race, gender and age, gender and antidepressant adherence, and age and antidepressant adherence. There was a weak correlation between antidepressant adherence and race, as well as age and race (see Table 3). There was a very weak correlation between gender and race, and there was a very weak or no correlation between gender and age. There was also a weak to no correlation between gender and antidepressant adherence. Further, there was a very weak correlation between antidepressant adherence and age. Hence, the assumption of no significant correlation between the independent variables was not a setback in using the binary logistic regression model.

Table 3

Spearman's Rho Nonparametric Correlation Matrix

		1	2	3	4	5	6	7	8	9	10	11	12	13
1	Med_adh=Low	1.00												
2	Med_adh= Moderate	-.84												
3	Med_adh=High	-.27	-.3											
4	Age=18-24	.120*	-.07	-.08										
5	Age=25-34	.05	-.03	-.04	-.19									
6	Age=35-44	.04	-.02	-.04	-.17	-.23								
7	Age=45-54	.05	-.03	-.04	-.24	-.32	-.29							
8	Age=55-64	-.16	.116*	.08	-.15	-.2	-.18	-.26						
9	Age=65+	-.15	.05	.18	-.11	-.145*	-.130*	-.18	-.117*					
10	Race=White	-.21	.07	.24	-.09	-.15	-.11	.07	.17	.16				
11	Race=Hispanic or Latino	.01	.05	-.1	-.02	.06	-.03	-.01	.03	-.05	-.33			
12	Race=All other	.21	-.11	-.18	.11	.120*	.129*	-.07	-.19	-.133*	-.82	-.27		
13	Gender	.00	.11	-.20	-.01	.06	-.11	.07	-.04	.00	-.05	-.06	.09	

Note. * Correlation is significant at the 0.05 level (2-tailed)
Number of paired observations (N) = 298

Test for Multicollinearity

I used the variance inflation factor (VIF) to test for multicollinearity. The preliminary analysis indicates that the tolerance was ≥ .9, and the *VIF* is ≥ 1.0. The collinearity analysis revealed that the assumption of collinearity was satisfied if the tolerance scores were higher than 0.2 and the VIF scores were significantly lower than 10 (Senaviratna & Cooray, 2019; see Table 4). Hence multicollinearity was not a setback in this selected model (regression model).

Table 4

Collinearity Statistics

		Collinearity Statistics	
Model		Tolerance	*VIF*
1	Med_adherence	.903	1.108
	Race	.891	1.122
	Gender	.981	1.019
	Age	.899	1.113

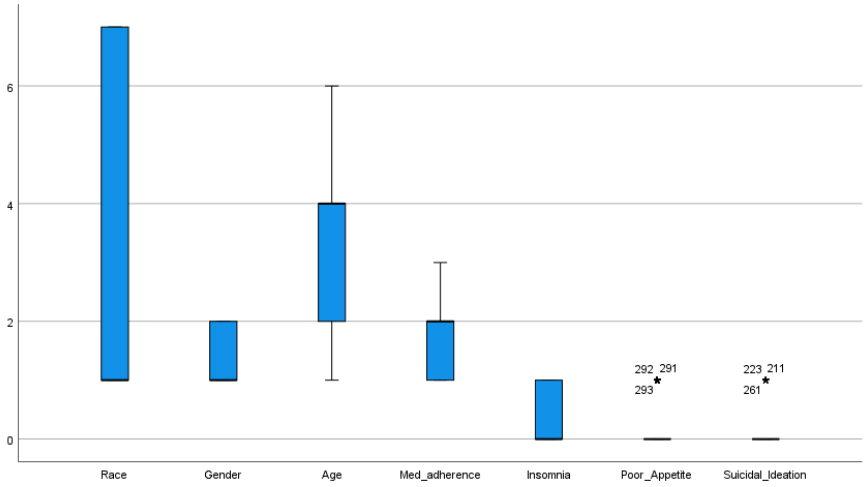
Note: a. Dependent Variable: Insomnia, Poor Appetite, and Suicidal thoughts

Test for Outliers

I used a box plot (Box-Whisker Diagram) to test for outliers. I considered an outlier as a data coordinate positioned outside the box plot's whiskers. As shown in Figure 2, our dataset included six outliers. Six individuals indicated either suicidal thoughts or poor appetite out of the 298 volunteers (see Figure 2).

Figure 2

Box Plot Showing Outliers



The results of the basic univariate analyses justified the inclusion of the following controlling variables in the binary logistic regression model: race, gender, and age. The independent variable was antidepressant adherence, and the dependent variable was MDD-related complications (Insomnia, poor appetite, and suicidal thoughts).

Inferential Statistical Analysis

The inferential statistics analysis for this study's research questions comprised a binomial dependent variable (MDD-related complications - Insomnia, poor appetite, and suicidal thoughts) and an independent variable (antidepressant adherence). I established the premises regarding the hypothesis testing and the target demographic employed for this testing using the primary data from the online survey. The conventional method of

inferential statistics is NHST, which allows for inferences about the sample's population (Adler & Clark, 2011; Vogt et al., 2014). Hence I used the NHST to accept or reject the study's null predictions at a 0.05 alpha level (p is < .05.) of significance. To answer the three research questions of this study, and in line with the requirements for NHST, I made six predictions about the expected relationships among the study's variables. I performed a binary logistic regression analysis to test the null hypothesis for each question.

Research Question 1

What is the association between patient adherence to antidepressants as measured with MMAS-8 and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

I tested the predictor variables a priori to verify there was no violation of the assumptions for binary logistic regression. An Omnibus test of model coefficients for insomnia indicated that chi-square was statistically non-significant [X^2 (10, N = 298) = 10.771, p = .376]. This result led me to conclude that adding the independent variables did not add statistically meaningful information to the baseline model (p >.05).

I also estimated the chi-square value using a Hosmer and Lemeshow Test to evaluate the goodness-of-fit of the binary logistic regression model. The Hosmer and Lemeshow test's goodness-of-fit results for the complete model with all predictors were statistically non-significant, X^2 (8, N = 298) = 6.202, P = .625. Since the P value is > .050, this statistically non-significant Hosmer and Lemeshow test indicates that the model was a good fit (Nattino et al., 2020). The model could distinguish between those

respondents who reported an insomnia problem and those who did not report an insomnia problem and adequately describes the dataset.

The model, as a whole, produced a -2 Log likelihood = 401.257, Cox and Snell *R* square = .035, and Nagelkerke *R* square = .047. According to the model, antidepressant adherence explains between 3.5% and 4.7% of the variance in the likelihood of reporting insomnia while controlling for age, gender, and race.

After completing the model selection step, I constructed the final binary logistic regression model to confirm the statistical significance of each selected variable included in the model using the Wald statistical analysis. The model contained one independent variable (antidepressant adherence) and three control variables (gender, race, and age). I performed the binary logistic regression test to assess the impact of antidepressant adherence, age, race, and gender on the likelihood that respondents would report an insomnia diagnosis.

The model predicts that an event occurs "Yes or no" (i.e., the likelihood of reporting insomnia) if p (report insomnia) ≥ 0.50 (i.e., a cut value of .500). This model correctly classified 60.1% of insomnia cases. The model indicated that 74 respondents out of 298 were more likely to report suffering from insomnia due to antidepressant adherence controlling for age, gender, and race. The SPSS resulting model block-1, shown in Table 11 (variables in the equation), suggested that all categories of the predictor variable (i.e., low, moderate, and high antidepressant adherence) were found not to contribute to the model in the binary logistic regression analysis after controlling for age, gender, and race (at the significant level of $p < .05$). The unstandardized Beta weight

for the constant; β = (-.685), *SE* = 0.533, *Wald* = 1.711, *df* = 1, *p* = .504, *Exp* (β) = .536 (see table 11). As shown in Table 5, using low antidepressant adherence as a reference category, the unstandardized Beta weight for moderate antidepressant adherence was; β = (-.345), *SE* = .253, *Wald* = 1.853, *df* = 1, *p* = .173, *Exp* (β) = .1.412, 95% *CI* (.859, 2.320). The unstandardized Beta weight for high antidepressant adherence was; β = (-.742), *SE* = .508, *Wald* = 2.128, *df* = 1, *p* = .145, *Exp* (β) = .476, 95% *CI* (.176, 1.290). The *p*-value is greater than the significance level ($p > 0.05$), and the confidence interval (CI) crosses one, indicating that the association between the variables was statistically non-significant. This suggests strong evidence for the null hypothesis, as there is more than a 5% probability that the null is correct. Therefore, I accept the null hypothesis and reject the alternative hypothesis.

Table 5

Variables in the Equation for Insomnia

								95% C.I.for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Med_adherence			5.714	2	.057			
	Med_adherence(1)	.345	.253	1.853	1	.173	1.412	.859	2.320
	Med_adherence(2)	-.742	.508	2.128	1	.145	.476	.176	1.290
	Race			.711	2	.701			
	Race(1)	-.135	.419	.103	1	.748	.874	.384	1.988
	Race(2)	-.226	.269	.706	1	.401	.798	.471	1.351
	Age			1.453	5	.918			
	Age(1)	.397	.427	.862	1	.353	1.487	.643	3.437
	Age(2)	.136	.443	.094	1	.759	1.146	.481	2.729
	Age(3)	.026	.404	.004	1	.949	1.026	.464	2.267
	Age(4)	.104	.475	.048	1	.827	1.110	.437	2.818
	Age(5)	.010	.566	.000	1	.986	1.010	.333	3.063
	Gender	.294	.244	1.450	1	.228	1.342	.832	2.164
	Constant	-.685	.523	1.711	1	.191	.504		

Note. a. Variable(s) entered on step 1: Med_adherence, Race, Age, and Gender.

Research Question 2

What is the association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after

controlling for race, gender, and age?

I performed a binary logistic regression test to assess the impact of antidepressant adherence, age, race, and gender on respondents' likelihood of reporting a poor appetite problem. The model contained one independent variable (antidepressant adherence) and three control variables (gender, race, and age). I tested the predictor variables a priori to verify there was no violation of the assumptions for binary logistic regression. An Omnibus test of model coefficients for poor appetite indicated that the chi-square is statistically non-significant [X^2 (10, N = 298) = 9.26, P = .447]. From this, I inferred that the independent variables' additions to the model are statistically non-significant.

I estimated the chi-square value using a Hosmer and Lemeshow Test to evaluate the goodness-of-fit of the binary logistic regression model. The Hosmer and Lemeshow test's goodness-of-fit results for the complete model with all predictors were statistically non-significant, X^2 (8, N = 298) = 9.254, P = .321. Since the value of P is > .050, the statistically non-significant Hosmer and Lemeshow test indicates that the model is a good fit and can distinguish between those respondents who reported a poor appetite problem and those who did not report a poor appetite problem and adequately describes the dataset (Nattino et al., 2020).

The model as a whole, with a -2 Log likelihood = 232.446, explained between 3.3 % (Cox and Snell R square) and 5.9% (Nagelkerke R squared) of the variance in poor appetite status and correctly classified 85.9 % of poor appetite cases. After completing the model selection step, I constructed the final binary logistic regression model to confirm the contribution/statistical significance of each selected variable included in the

model using the Wald statistical analysis. The model contained one independent variable (antidepressant adherence) and three control variables (gender, race, and age). I performed the binary logistic regression test to assess the impact of antidepressant adherence, age, race, and gender on the likelihood that respondents would report a poor appetite problem.

The model predicts that an event occurs "Yes or no" (i.e., the likelihood of reporting insomnia) if p (report insomnia) ≥ 0.50 (i.e., a cut value of .500). This model correctly classified 85.9% of poor appetite cases. The model indicated that 42 respondents out of 298 were more likely to report suffering from poor appetite due to antidepressant adherence controlling for age, gender, and race. All categories of the predictor variable (i.e., low, moderate, and high antidepressant adherence) were found not to contribute to the model in the binary logistic regression analysis after controlling for age, gender, and race (at the significant level of $p < .05$; see Table 6). The unstandardized Beta weight for the constant was; $\beta = (-1.326)$, $SE = .699$, $Wald = 3.597$, $df = 1$, $p = .058$, Exp $(\beta) = .266$ (see Table 6). As shown in Table 6, using low antidepressant adherence as a reference category, the unstandardized Beta weight for moderate antidepressant adherence was; $\beta = (-.200)$, $SE = .357$, $Wald = .314$, $df = 1$, $p = .575$, $Exp\ (\beta) = .819$, 95% CI (.406, 1.649). The unstandardized Beta weight for high antidepressant adherence was; $\beta = (-1.517)$, $SE = 1.081$, $Wald = 1.969$, $df = 1$, $p = .161$, $Exp\ (\beta) = .219$, 95% CI (.026, 1.825). The p-value is greater than the significance level ($p > 0.05$), and the confidence interval (CI) crosses one, indicating that the association between the variables was statistically non-significant. This suggests strong evidence for the null hypothesis, as

there is more than a 5% probability that the null is correct. Therefore, I accept the null hypothesis and reject the alternative hypothesis.

Table 6

Variables in the Equation for Poor Appetite

								95% CI for EXP(B)	
		B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Med_adherence			2.057	2	.358			
	Med_adherence(1)	-.200	.357	.314	1	.575	.819	.406	1.649
	Med_adherence(2)	-1.517	1.081	1.969	1	.161	.219	.026	1.825
	Race			.900	2	.638			
	Race(1)	.030	.610	.002	1	.961	1.030	.312	3.403
	Race(2)	.345	.379	.828	1	.363	1.412	.671	2.971
	Age			4.573	5	.470			
	Age(1)	-.033	.520	.004	1	.949	.967	.349	2.677
	Age(2)	-1.118	.661	2.859	1	.091	.327	.090	1.195
	Age(3)	-.624	.530	1.390	1	.238	.536	.190	1.512
	Age(4)	-.422	.648	.424	1	.515	.656	.184	2.334
	Age(5)	-.198	.770	.066	1	.797	.820	.181	3.708
	Gender	-.043	.344	.016	1	.901	.958	.488	1.880
	Constant	-1.326	.699	3.597	1	.058	.266		

Note. a. Variable(s) entered on step 1: Med_adherence, Age, Race, Gender.

Research Question 3

What is the association between patient adherence to antidepressants as measured with MMAS-8 and suicidal ideation risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?

I performed a Fisher's Extract Test to assess the impact of antidepressant adherence on respondents' likelihood would of reporting a suicidal ideation problem. I tested the predictor variable a priori to verify that there was no violation of Fisher's extract test assumptions. A total of 290 participants out of 298 participants reported no suicidal ideation compared to eight who reported suicidal ideation (see Table 7). Of those participants who reported suicidal ideation, the majority, $n = 7$ (87.5%), were participants

with low antidepressant adherence (see Table 7).

Table 7

Suicidal Ideation and Medication Adherence Cross-Tabulation

		Med_adherence			
Count		Low	Moderate	High	Total
Suicidal_Ideation	No	123	141	26	290
	Yes	7	1	0	8
Total		130	142	26	298

After completing the model selection step, I performed the Fisher's Extract test to assess the impact of antidepressant adherence on the likelihood that respondents would report a suicidal ideation problem. There was no statistically significant association between suicidal ideation and antidepressant adherence as assessed by Fisher's exact test, X^2 (N = 298) = 5.306, p = .091 (see Table 8). The p-value is greater than the significance level ($p > 0.05$), indicating that the association between the variables was statistically non-significant. This suggests strong evidence for the null hypothesis, as there is more than a 5% probability that the null is correct at this significant level ($p > 0.05$). Therefore, I accept the null hypothesis and reject the alternative hypothesis.

Table 8

Chi-Square Tests for Association between Suicidal Ideation and Medication Adherence

				Monte Carlo Sig. (2-sided)			Monte Carlo Sig. (1-sided)		
					99% Confidence Interval			99% Confidence Interval	
	Value	df	Asymptotic Sig (2-sided)	Sig	Lower Bound	Upper Bound	Sig	Lower Bound	Upper Bound
Pearson Chi-Square	6.477[a]	2	.039	.074[b]	.035	.113			
Likelihood Ratio	7.242	2	.027	.047[b]	.015	.079			
Fisher-Freeman-Halton Exact Test	5.306			.091[b]	.048	.133			
Linear-by-Linear Association	5.643[c]	1	.018	.034[b]	.007	.060	.027[b]	.003	.051
N of Valid Cases	298								

Note. a. 3 cells (50.0%) have an expected count of less than 5. The minimum expected count is .70.
b. Based on 298 sampled tables with starting seed 1314643744.
c. The standardized statistic is -2.376.

Summary

For this study, I used the SurveyMonkey online platform for data collection. A random selection of 300 volunteers, irrespective of gender or race (from the SurveyMonkey Targeted Audience) in Texas, completed the optional online survey. Only 298 volunteers who fit the study's parameters were included in the final dataset for statistical analysis. Most respondents were male, 156 (52.3%), followed by 142 (47.7%) females. The highest number, 86 (28.9%) of respondents were aged 45-54. Of 298 respondents, the majority, 150 (50.3%), were white. In order to reflect the demographic makeup of the United States, I weighted the online survey's data for age, race, and gender using the American Community Survey from the Census Bureau. Researchers have

indicated that the conventional method of inferential statistics is NHST, which allows for inferences about the sample's population (Adler & Clark, 2011; Vogt et al., 2014).

I established the premises regarding the hypothesis test and the target demographic employed for this test using the primary data from the online survey. After confirming that the dataset used for this investigation was correct and comprehensive, I evaluated the dataset to ensure that it matched the criteria for data used with the selected statistical analysis model (binary logistic regression model and Fisher's extract test) by testing the required model assumptions. The inferential statistics analysis for this study's research questions comprised a binomial dependent variable for research question one, two, and three and an independent variable (antidepressant adherence) while controlling for age, gender, and race. The binary logistic regression hypothesis test and the Fisher's Extract test findings suggested that there was a statistically non-significant association between patient adherence to antidepressants as measured with MMAS-8 and MDD-related complications (insomnia, poor appetite, and suicidal thoughts) risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age (at the significant level of $p < .050$).

I thoroughly explain the study's results in Chapter 5 while staying within the study's limits and scopes. Additionally, I examine the study's consequences and provide a conclusion and recommendations. In Chapter 5, I also discuss this study's limitations, indicating how the study affects societal changes.

Chapter 5: Discussion, Conclusions, and Recommendations

By examining the relationship between MDD-related complications (the dependent variable: insomnia, poor appetite, and suicidal thoughts) and antidepressant medication adherence (the independent variable), this cross-sectional quantitative study addresses the divergent views regarding MDD-related complications among adult patients who have been diagnosed with the condition in Texas. I assessed the association between antidepressant adherence and MDD-related complications using a binary logistic regression statistical analysis approach and Fisher's extract test. After adjusting for all other variables in the regression model, the study's odds ratio for each of the three MDD-related complications shows that for every additional unit of antidepressant adherence, the respondents with moderate to high antidepressant adherence were less likely to report having insomnia, or poor appetite, or suicidal thoughts than those who reported low antidepressant adherence. However, these effects relationship mentioned above were statistically non-significant. In this chapter, I analyze and discuss the results and the implications for action and offer recommendations for further research using the synthesis and analysis from the data and statistical analysis offered in Chapter 4.

Interpretation of the Results

According to current literature, two dominant diverging views exist on what drives the complications associated with MDD. The first attributes the complications to non-adherence to antidepressants, and the second attributes the complications to the adverse effects of antidepressants. There are several MDD-related complications found in the literature. However, for this study, I examined the association of three of these MDD-

related complications (insomnia, poor appetite, and suicidal thoughts) due to time and financial constraints. To test the study's null hypotheses, I used the binary logistic regression model, a statistical method used to measure the association between categorical variables while controlling for covariates.

MDD-Related Complication (Insomnia)

Research Question 1 was "What is the association between patient adherence to antidepressants as measured with MMAS-8 and insomnia risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?" The binary logistic regression results suggest that there was a statistically non-significant association ($p > .05$) between patients' adherence to antidepressants as measured with MMAS-8 and insomnia among adults in Texas diagnosed with MDD after controlling for race, gender, and age. The *p*-value is greater than the significance level ($p < 0.05$), and the confidence interval (CI) crosses the value q, indicating that the association between the variables was statistically non-significant. Therefore, this study's findings indicate that adherence to antidepressants did not predict the presence of insomnia (at a statistically significant value of $p < .05$ for all levels of antidepressant adherence).

To further interpret the findings of this study, I also examined the odds ratio of the binary logistic regression model (equation of variables). The resulting odds ratio showed a negative statistically nonsignificant relationship between antidepressant adherence and insomnia. The reference category for the model is low antidepressant adherence. The results indicate that respondents who reported high adherence to antidepressants record an estimated odds ratio of [*Exp* (β) = .476, 95% *CI* (.176, 1.290)]. The odds ratio of *Exp*

(β) = .476, 95% *CI* (.176, 1.290) for high antidepressant adherence indicated that for every additional unit of antidepressant adherence, the respondents are .476 times less likely to report having an insomnia problem compared to those who reported low antidepressant adherence, after controlling for all other factors in the regression model. The study's findings suggest a statistically non-significant relationship between insomnia and antidepressant adherence, which supports previous research that found no correlation between the intensity of insomnia symptoms and treatment adherence in the depression group as well as between the quality of sleeplessness and treatment compliance (Bosch et al., 2016). However, others concluded that non-adherence to antidepressant treatment significantly worsened insomnia symptoms (DiBonaventura et al., 2015; Gharzeddine, 2020; Riegel et al., 2011; Rogers et al., 2021). Some scholars have attributed the contrasting association between insomnia and antidepressants to the type of antidepressant used for therapy (Doufas et al., 2017, p. 82). Although certain antidepressants have less impact on insomnia than others, diverging research suggests that some antidepressants may add to insomnia complaints (Doufas et al., 2017; Krystal et al., 2007; Marasine et al., 2020). Acetylcholinesterase inhibitors, SSRIs, and dopamine agonists have been associated with insomnia, according to a meta-analysis of randomized controlled trials (Riemann et al., 2020). At least in short-term treatment, some medications used in MDD therapy with activating effects, such as fluoxetine (Prozac), citalopram (Celexa), and venlafaxine, might cause insomnia (Wichniak et al., 2017).

My study's statistically non-significant association findings indicate that insomnia as an MDD-related complication is related to other factors rather than the result of non-

adherence to antidepressant as a standalone factor. Scholars have suggested that insomnia may coexist with underlying medical conditions, including COPD, cancer, congestive heart failure, Parkinson's disease, mental illnesses like MDD, schizophrenia, bipolar disorder, and anxiety disorders, as well as environmental influences like drug or alcohol use (or withdrawal; Gates et al., 2016; Perney & Lehert, 2018; Reeve et al., 2015). These medical conditions and factors that coexist with insomnia might have a statistically significant effect as modifiers that I did not consider in my analysis. The multiple modifiers and confounders that different authors applied in their investigation of insomnia could account for the contrasting results of this study's analysis. To draw any meaningful conclusions about antidepressant adherence as a key insomnia driver, it is necessary to take into account other social, psychological, and biological modifiers and cofounding variables that are interconnected and have a positive impact on insomnia and antidepressant adherence, as suggested by the BPS model.

MDD-Related Complication (Poor Appetite)

This study evaluated the statistical significance of the association between adherence to antidepressants and poor appetite. Research Question 2: "What is the association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite risk among adults in Texas diagnosed with MDD after controlling for race, gender, and age?" The binary logistic regression results suggest that there is a statistically non-significant association between patient adherence to antidepressants as measured with MMAS-8 and poor appetite among adults in Texas diagnosed with MDD after controlling for race, gender, and age ($p > .05$ at all levels of antidepressant adherence).

The *p*-value is greater than the significance level ($p < 0.05$), and the confidence interval (*CI*) crosses the value 1, indicating that the association between the variables was statistically non-significant. Therefore, this study's findings indicate that investigators cannot use adherence to antidepressants to statistically predict the presence of poor appetite (at a statistically significant value of $p < .05$ for all levels of antidepressant adherence).

I also examined the odds ratio provided by the study's result of the hypothesis testing from the regression equation of variables. The odds ratio from the binary logistic regression model showed some statistically non-significant negative relationship between antidepressant adherence and poor appetite. The reference category for the study's model use in this analysis is low antidepressant adherence. The binary logistic regression model's results indicate that respondents who reported high adherence to antidepressants record an estimated odds ratio of [*Exp* (β) = .219, 95% *CI* (.026, 1.825)], which suggested that for high antidepressant adherence level, for every additional unit of antidepressant adherence, the respondents is .219 times less likely to report having a poor appetite problem compared to those who reported low antidepressant adherence, after controlling for all other factors in the regression model. This study's odds ratio findings support the results of other studies showing that respondents with high adherence to their medications were less likely to report having a poor appetite problem compared to those who reported low antidepressant adherence after controlling for all other factors in the regression model (Hoogendoorn, 2019). However, in contrast, some scholars argued that many alterations in human systems and environments may be to blame for a person's poor

appetite (Amarya et al., 2015; Malafarina et al., 2013). Hypoactivation of the insular regions that preserve the censoring of the body's physiological status associated with MDD is correlated with poor appetite (Simmons et al., 2016). These confounding variables were not considered in my study and may explain the contrasting results.

Other modifiers and confounders utilized by various writers in their analyses may be responsible for the findings' divergence from those of my study (e.g., the type of antidepressants, duration of antidepressant usage, and the dose of antidepressant used). The direction and statistical significance of this study's effect may vary if other modifiers and confounders are considered. Therefore, to draw any meaningful conclusions about antidepressant adherence as a key poor appetite driver, it is essential not to use adherence as a standalone variable for predicting the presence of poor appetite but to consider other social, psychological, and biological modifiers and cofounding variables that are interconnected and have a positive impact on poor appetite as suggested by the BPS model.

MDD-Related Complication (Suicidal Thoughts)

Researchers noted that up to 90% of those who commit suicide have a mental diagnosis, most typically MDD or substance abuse (McGirr et al., 2008). Researchers also noted that suicidal thoughts are linked to several physiological, genetic, psychologic, social, and environmental variables. However, it is unclear if these factors are causal. Combating suicidal thoughts will necessitate public health measures and an in-depth examination of suicidal thoughts drivers. Researchers concluded that untreated MDD might lead to complications such as suicidal thoughts, suicide attempts, or suicide (APA,

2013; Gutiérrez-Rojas et al., 2020; McIntyre et al., 2018; Woldu et al., 2011). If these researchers' assertion is authentic, that suicidal thoughts can be a diagnostic sign of untreated MDD-related complications, it stands to reason that the patient's suicidal thoughts problem would improve if they received appropriate MDD therapy. To better understand the diverging opinions regarding suicidal thoughts, this study evaluates the association between the patient's adherence to antidepressants and suicide thoughts risk among individuals diagnosed with MDD after controlling for race, gender, and age (research question three).

The BPS model requires that the results be interpreted taking into account potential psychological factors (such as the different complications associated with MDD and antidepressant adherence) that could affect an individual's general health and health habits. I used these BPS cornerstones of the interrelationship between factors to partition and interpreted this study's findings. Suicidal thoughts and antidepressant adherence were considered as a biopsychosocial event, which forms the basis of the BPS model.

To answer this study's research question three, I used the Fisher’s Extract test. The test indicated that there was no statistically significant association between suicidal ideation and antidepressant adherence as assessed by Fisher's Exact test, X^2 (N = 298) = 5.306, p = .091 (see table 18). This suggests strong evidence for the null hypothesis, as there is more than a 5% probability that the null is correct at this significant level ($p >$ 0.05). I, therefore, accept the null hypothesis of research question three (see Table 18).

Researchers have had trouble coming to a conclusion about the association between antidepressant use and suicidal thoughts since it's hard to get a firm view on the

subject. Initiatives to prevent suicide have proven challenging to establish, partly because no single risk factor reliably predicts suicidal thoughts or suicide (Fehling & Selby, 2020). This postulation confirms the result of this study (i.e., investigators cannot use adherence to antidepressants to statistically predict the presence of suicidal thoughts). Other scholars suggested that certain antidepressant medications may not be blamed for the MDD patient's suicidal thoughts. This study's findings were in contrast to those of other studies, which showed a strong association and came to the conclusion that poor antidepressant adherence behavior significantly worsens insomnia. This could be a result of the various additional confounders that these writers utilize, which were not used in this study.

Antidepressant usage doubles the risk of suicidality and aggression in children and adolescents (Sharma et al., 2016). Other scholars, such as Morgan et al. (2018), noted that adherence to antidepressant treatment for MDD could cause a substantial decrease in suicide thoughts risk. In the month preceding death, 1,576 (13%) of 12,124 suicidal patients were non-adherent with their medication therapy (NCISH, 2017). The literature suggests that suicide attempts decreased after the onset of treatment for depression compared with the month before initiating therapy (Khan et al., 2018; Termorshuizen et al., 2016). When determining the association between antidepressant adherence and suicidal thoughts in these trials, the authors considered the length of the therapy as a significant confounding variable.

Other researchers argued that an increase in the prescription of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) used in treating MDD is

associated with a decline in the annual suicide rate (Chen et al., 2021; Forsman et al., 2019). Antidepressants containing SSRIs carry a potential risk of causing suicidal thoughts and suicide attempts in those aged twenty-five and younger (Bschor et al., 2016). When determining the association between antidepressant adherence and suicidal thoughts, Bschor et al. considered the type of antidepressant medication as a significant confounding variable. The direction and statistical significance of this study's effect may have differed if other confounders are taken into account. To this regard, and as per the biopsychosocial model, and as noted by the findings of this study, the role of other modifiers and confounding variables interconnected with antidepressant adherence and suicidal thoughts could not be ignored when drawing any conclusion regarding antidepressant adherence and suicidal thoughts.

Gender, Race, Age, and MDD-Related Complications

I also analyzed biological factors, such as the relationship between age and gender, and social-environmental factors, such as the influence of race, that may have an impact on MDD-related complications and a person's overall health and health behaviors. The logistic regression model (variables in the equation) suggests that gender, age, and race do not contribute to the logistic regression model (at the significance level of $p < .05$). The three variables showed a statistically non-significant relationship with MDD-related complications. I, therefore, infer that investigators could not use these three variables to statistically predict the occurrence of MDD-related complications (insomnia, poor appetite, and suicidal thoughts). However, for this study, it should be noted that gender, age, and race were used as control variables and were not the focus of this study.

Limitations of the Study

The fact that I used a sizable representative sample (n = 298) of individuals in Texas for this study was one of the study's strengths; however, the generalizability, validity, and reliability of the study may have certain drawbacks. The research question three hypothesis was not testable with binominal logistic regression due to the limited number of participants (n = 8) who reported having suicidal ideation.

I collected the dataset for this study using an online-accessible SurveyMonkey platform. Despite the increased access to the internet, this form of data collection still has built-in access biases. A face-to-face interview will provide a more representative dataset and eliminate access biases.

I used a cross-sectional design, limiting all the volunteers to report the study's variables at the same point in time. Hence, I could not analyze the individuals' medication adherence behavior over a specific time frame. The fact that this study's design did not permit the examination of the individuals' medication adherence behavior over time did reduce the study's reliability. Because I collected the data for MDD-related complications and antidepressant adherence simultaneously, it is difficult to determine any temporal link between MDD-related complications and antidepressant adherence.

The study's participants were online and self-selected. This method of data harvesting may result in biased sampling (Booker et al., 2021). The self-reported data collection method is also a limitation, as self-reported data might expose the study to response bias that might reduce the study's validity and reliability. Researchers noted that exposure to response bias results from the respondent's desire to protect their privacy, and

the high possibility of social desirability that comes with the research on unhealthy healthcare behavior reduces the study's reliability (Palaniappan & Kum, 2019).

Finally, the deficit in financial resources and lack of time did restrict the scope of this study and the study's instrument of measurement. I did consider the individual's adherence to antidepressants as measured with only the Morisky 8-item Medication Adherence scale (MMAS-8). Also, the study did not include the influence and quality of social support systems (e.g., marital status and if the individual lived alone or not) and attending group therapy related to MDD. The study did not consider the measurement of adherence to other forms of psychotherapy and their relationship with MDD-related complications. Also, the variability of some of the study's variables might have influenced their statistical significance.

Recommendations

Future studies can use the limitations of this study as a starting point. First, I do recommend further research in MDD-related complications that consider sources of social support (e.g., informational support), as well as counseling or interpersonal therapy, dialectical behavior therapy (DBT), cognitive behavioral therapy, exposure therapy, eye movement desensitization and reprocessing therapy (EMDR), psychodynamic psychotherapy, and metallization-based therapy. Any study on MDD-related complications that examines these factors will add validity and reliability because it will include more insights into how these controlling variables may impact the association between medication adherence and MDD-related complications.

Future studies should also consider following participants over time to determine

any temporal link between MDD-related complications and antidepressant adherence. I used a cross-sectional research methodology in this study. However, a longitudinal study design that considers both the impact of antidepressant adherence and antidepressant side effects over time is recommended for a more accurate conclusion about the divergent opinions on MDD-related complications.

Implications for Action

The results of this study offer added scientific evidence that, when applied across the health care system, can improve the quality of life for those struggling with complications associated with MDD. The characteristics of MDD-related complications, how they are managed, the health care system, and service delivery can all have an enormous impact on MDD-related complications, even though some of these drivers are patient-related. Because health stakeholders frequently disregard specific drivers (such as divergent viewpoints regarding antidepressant side effects and adherence issues), treatment outcomes have taken a toll.

Research on public health issues is a powerful arm for advancing social change. Medical personnel must comprehensively understand the drivers of MDD-related complications, which demands a multidimensional view, to properly manage treatment outcomes and scarce resources available to patients with MDD-related complications. A critical implication of this study is its preventive inner tone that can improve the strategy used to reduce MDD-related complications. This study demonstrates the divergent opinions held by scientists on MDD-related complications, highlighting the urgent need to implement programs that incorporate both antidepressant side effects and adherence as

crucial elements of managing MDD-related complications.

After adjusting for all other variables in the regression model, the study's odds ratio for each of the three MDD-related complications shows that for every additional unit of antidepressant adherence, the respondents with moderate to high antidepressant adherence were less likely to report having insomnia, or poor appetite, or suicidal thoughts than those who reported low antidepressant adherence. However, these effects negative relationship mentioned above were statistically non-significant as per this study. At the individual level, if this research's slight negative relationship (as shown by the odds ratio) results are relied upon by individuals suffering from MDD-related complications, they might see improvement in their MDD treatment outcome. Increased patient understanding of the implications of managing better their antidepressant therapy creates awareness, causing the patient to be more likely to take their medication as prescribed, which can enhance their mental health and reduce any potential problems resulting from MDD-related complications.

This study will significantly benefit stakeholders, such as public health professionals, social workers, and advocacy groups, as it provides them with the data regarding the relationship between MDD-related complications and antidepressant adherence they need to create educational materials, manage health care resources, and launch public awareness campaigns about MDD-related complications. This could bring about positive social change, increase knowledge, spread a positive attitude, and encourage a shift in behavior regarding MDD-related complications. The results of this study can also be used to emphasize the need for further studies regarding the value of

patients' social support networks to their families and caregivers.

As previously mentioned, Greenberg et al. (2021) suggested that from 2010 to 2018, MDD imposed an increased financial toll on US adults, rising from $US236 billion to $US326 billion. The authors noted that the percentage of workplace expenditures ascribed to MDD grew from 48% to 61%. Policymakers could use this study's conclusion to create more efficient public health efforts and legislation that support encouraging antidepressant management and disease awareness to lessen the observed MDD financial burden to society. If the study's conclusions are put into practice, both public and private businesses might experience an improvement in organizational performance. Due to their heightened awareness of MDD-related problems, these institutions can benefit from improved MDD education/treatment outcomes that will immediately increase productivity and fewer days lost to absenteeism due to economic participant sickness.

Methodologically, I ensured that the research design was robust and included a wide range of factors that might influence MDD-related complications, thereby providing a better understanding of MDD-related complications drivers and opening the field for future research. The study provides grounds for future research on this topic, especially when considering the selection of the length of research, the study’s variables, covariates, modifiers, and other confounders.

Theoretically, this research complemented current knowledge on MDD-related complications. This study paves the way for further investigation into additional potential mediating factors that may affect MDD-related complications.

Empirically this research provides information to assess the effectiveness of

interventions designed to reduce MDD-related complications by providing additional information regarding critical drivers of MDD-related complications. This research highlights two key drivers cited in the literature (i.e., antidepressant adherence/side effects). According to the study's findings, such evaluation (the effectiveness of interventions designed to reduce MDD-related complications) requires assessing the efficiency of patient education programs, medication reminders, and other psychosocial treatments linked to the indicated drivers of MDD-associated problems (i.e., antidepressant adherence and their side effects). In order to gauge the success of such programs or awareness campaigns, participants' knowledge and understanding of MDD-related complications drivers and how to decrease or eliminate them (i.e., antidepressant adherence/side effects) could be assessed at the beginning and end of the programs/campaigns to determine their effectiveness.

Conclusion

Public health research is a powerful arm for promoting positive social change by addressing treatment and prevention approaches that deal with societal health care issues. Mental health poses a serious public health problem worldwide. Adults with mental illnesses in 2019-2020 accounted for 20.78% of the population, around 50 million Americans, to be exact (Mental Health America, 2020). Twenty-one million adults in the United States experienced at least one MDD episode in 2020 (National Institute of Mental Health, 2022). This figure corresponded to 8.4% of all American adults.

If social and economic success is a primary goal for positive social transformation, the impact of a healthy population must be recognized and requires

proper consideration. By figuring out the leading causes of mental health problems (i.e., MDD-related complications), we can lower the likelihood that they will occur. Researchers provide strategies to improve daily activities for people with difficulties associated with MDD. This study focuses on one of these topics: how to prevent MDD-related complications by identifying the key factors that drive these complications. Several studies confirmed the prevalence of MDD-related complications and showed that this public health concern is growing (Gutiérrez-Rojas et al., 2020; Lichtman et al., 2009; Maleki & Oscar-Berman, 2020; Topuzoğlu et al., 2015; Tyrrell et al., 2019; Yu et al., 2015).

This study adds to the scientific community's understanding of the drivers of MDD-related complications by looking at a potential driver (antidepressant adherence). The connection between MDD-related complications and medication adherence has been the subject of a significant study. The literature indicated mixed outcomes regarding the association between MDD-related complications and adherence to treatment regimens. The current literature presents two diverging viewpoints that require further clarification.

According to some researchers, the growth in MDD-related complications can be attributed to poor medication management (i.e., the patient is not adhering to their treatment regimens). In contrast, others blame the increase on the adverse effects of medications used to treat MDD. This study's objective was to provide evidence to accept or reject the premise that antidepressant adherence is associated with a significant increase in MDD-related complications. To achieve this objectives, it was necessary to provide the scientific evidence needed to obtain a buy-in into a shared objective of

reducing MDD-related complications by providing a compelling argument enabling people to make informed decisions based on these research findings. The findings of this research lend credence to the school of thought that claims there is a statistically non-significant association between antidepressant adherence and MDD-related complications, as suggested in the recent literature review.

Understanding the factors contributing to MDD-related complications is a crucial first step in searching for more effective ways of dealing with this mental health issue. This study lays the groundwork for a better knowledge of some of the issues associated with MDD-related complications, awareness of which can improve patients' chances of social integration and boost their economic productivity. In an effort to create the ties that will be the driving force behind a positive shift in how MDD-related complications are perceived and treated, it is my hope that the findings of this research will link and cultivate public health researchers and the public in a common understanding of the need for change. Therefore, considering that public health research (epidemiology) is built on the primary tenet of providing relevant scientific evidence based on information collected within the community, in this study, to achieve this tenet, I gathered information, made connections, and presented a compelling picture of complications related to MDD, providing the diverging views in the scientific community on two causes of these complications associated to MDD, and the reasons why the intervention of public health professionals was needed to fill in the gap recorded in the improvement of MDD treatment outcome.

The study’s findings provide additional information for public health researchers

and the general public regarding the relationship between critical drivers of MDD-related complications. The findings of this study, combined with other scientific evidence on antidepressant adherence, may inform individual antidepressant adherence behaviors. This study's scientific evidence may be used to create awareness, increase knowledge and improve understanding of MDD complications which are essential for bringing about the kind of desirable societal change that we want to see in the public health sector.

References

Adu, M. K., Wallace, L. J., Lartey, K. F., Arthur, J., Oteng, K. F., Dwomoh, S., Owusu-Antwi, R., Larsen-Reindorf, R., & Agyapong, V. I. (2021). Prevalence and correlates of likely major depressive disorder among the adult population in Ghana during the covid-19 pandemic. *International Journal of Environmental Research and Public Health*, *18*(13), 7106. https://doi.org/10.3390/ijerph18137106

American Academy of Sleep Medicine. (2014). *International classification of sleep disorders* (3rd ed.).

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. https://doi.org/10.1176/appi.books.9780890425596

Amarya, S., Singh, K., & Sabharwal, M. (2015). Changes during aging and their association with malnutrition. *Journal of Clinical Gerontology and Geriatrics*, *6*(3), 78–84. https://doi.org/10.1016/j.jcgg.2015.05.003

Amir, M., Rickles, N., Feroz, Z., & Beg, A. E. (2020). Determination of factors affecting medication adherence in depressed patients receiving antidepressants in Pakistan. *RADS Journal of Pharmacy and Pharmaceutical Sciences*, *8*(1), 1–6. https://doi.org/10.37962/jpps.v8i1.396

Anxiety and Depression Association of America. (n.d.). Facts and statistics. https://adaa.org/about-adaa/press-room/facts-statistics#:~:text=MDD%20affects%20more%20than%2016.1,in%20women%20than%20in%20men

Bains, N., & Abdijadid, S. (2021). Major depressive disorder. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK559078/

Barlow, J., Smailagic, N., Huband, N., Roloff, V., & Bennett, C. (2012). Group-based parent training programs for improving parental psychosocial health. *Campbell Systematic Reviews, 8*(1), 1–197. https://doi.org/10.1002/14651858.CD002020.pub3

Beacon Health System (2020). Depression (major depressive disorder). https://www.beaconhealthsystem.org/library/diseases-and-conditions/teen-depression/

Benjamin, R. M. (2012). Medication adherence: Helping patients take their medicines as directed. *Public Health Reports*, *127*(1), 2–3. https://doi.org/10.1177/003335491212700102

Biffi, A., Scotti, L., Rea, F., Lucenteforte, E., Chinellato, A., Vetrano, D. L., Vitale, C., Agabiti, N., Sultana, J., Roberto, G., Mugelli, A., & Corrao, G. (2018). Adherence to antidepressants and mortality in elderly patients with cardiovascular disease. *Clinical Drug Investigation*, *38*(7), 593–602. https://doi.org/10.1007/s40261-018-0642-4

Bitter, I., Fehér, L., Tényi, T., & Czobor, P. (2015). Treatment adherence and insight in schizophrenia. *Psychiatria Hungarica: A Magyar Pszichiatriai Tarsasag Tudomanyos Folyoirata*, *30*(1), 18–26. https://pubmed.ncbi.nlm.nih.gov/25867885/

Blanken, T. F., Benjamins, J. S., Borsboom, D., Vermunt, J. K., Paquola, C., Ramautar,

J., Dekker, K., Stoffers, D., Wassing, R., Wei, Y., & Van Someren, E. J. (2019). Insomnia disorder subtypes derived from life history and traits of affect and personality. *The Lancet Psychiatry*, *6*(2), 151–163. https://doi.org/10.1016/S2215-0366(18)30464-4

Booker, Q. S., Austin, J. D., & Balasubramanian, B. A. (2021). Survey strategies to increase participant response rates in primary care research studies. Family Practice, *38*(5), 699–702. https://doi.org/10.1093/fampra/cmab070

Bosch, M. P. C., Waberg, J., van den Noort, M. W. M. L., Staudte, H., Lim, S., & Egger, J. I. M. (2016). Symptom severity, quality of sleep, and treatment adherence among patients suffering from schizophrenia and depression. https://www.oaepublish.com/neurosciences/articles/2347-8659.2015.54/

Bremner, J. D., Campanella, C., Khan, Z., Fani, N., Kasher, N., Evans, S., Reiff, C., Mishra, S., Ladd, S., Nye, J. A., Raggi, P., & Vaccarino, V. (2019). Brain mechanisms of stress and depression in coronary artery disease. *Journal of Psychiatric Research*, *109*, 76–88. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6317866/

Bschor, T., Kern, H., Henssler, J., & Baethge, C. (2016). Switching the antidepressant after nonresponse in adults with major depression: A systematic literature search and meta-analysis. *The Journal of Clinical Psychiatry*, *77*(1). https://doi.org/10.4088/JCP.16r10749

Budimir, S., Probst, T., & Pieh, C. (2021). Coping strategies and mental health during COVID-19 lockdown. *Journal of Mental Health*, *30*(2), 156–163.

https://doi.org/10.1080/09638237.2021.1875412

Carney, R. M., & Freedland, K. E. (2017). Depression and coronary heart disease. *Nature Reviews Cardiology*, *14*(3), 145–155.

Caruso, R., Nanni, M. G., Riba, M., Sabato, S., Mitchell, A. J., Croce, E., & Grassi, L. (2017). Depressive spectrum disorders in cancer: Prevalence, risk factors and screening for depression: a critical review. *Acta Oncologica*, *56*(2), 146-155. https://doi.org/10.1080/0284186X.2016.1266090

Cay, E. L., Vetter, N., Philip, A. E., & Dugard, P. (1972). Psychological status during recovery from an acute heart attack. *Journal of Psychosomatic Research*, *16*(6), 425-435. https://doi.org/10.1016/0022-3999(72)90068-2

Centers for Medicare & Medicaid Services (2021). Chronic conditions. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/CC_Main

Center for Disease Control and Prevention (2016). 10 Leading Caused by Death by Age Group, United States – 2014, Web-based Injury Statistics Query and Reporting System of the National Center for Injury Prevention and Control. (2016). http://www.cdc.gov/injury/wisqars/pdf/leading_causes_of_death_by_age_group_2014-a.pdf

Centers for Disease Control and Prevention (2022). What is diabetes? https://www.cdc.gov/diabetes/basics/diabetes.html

Champion, V. L., & Skinner, C. S. (2008). The health belief model. *Health behavior and health education: Theory, Research, and Practice*, *4*, 45-65.

https://d1wqtxts1xzle7.cloudfront.net/49289960/Health_Behavior___Health_Education_book_4th_Ed-libre.pdf?1475413657=&response-content-disposition=inline%3B+filename%3DHealth_Behavior_and_Health_Education_boo.pdf&Expires=1683145963&Signature=OD-vse2LTCWuOQL5eTjRKwUclUYwlTVzWJjWOKBwo5hCKxzFvSAlZ7MukqALKf7aiBPs9gE7741W6Y20n2kTQiNKHATXjqdACMt4QJHYZ0rclXCH6EEsBFRSgtdpCXo~ZiyvYHYbWSY4tR6o-ErdwaMXSiyIxUI-~fMc37yd5aCt2Y12yb9pn0E76Qn1eNgEmJlFR9oebvmQrUuFSuZ0pG0NpF7BhoY60hEFxeCRhjfujjfDP08IjaR8CU1AlLKkBYeXxT2K2yKDL7drNWXhn~3cZSSrqa5T0wtw4CPHHOzQ3ZaJwUaG3-GDAwP7ifiTy9uwGxlWH8lJjEW7CnQnSg__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA#page=83

Chen, Q.-H., Li, Y.-L., Hu, Y.-R., Liang, W.-Y., & Zhang, B. (2021). Observing time effect of SSRIs on suicide risk and suicide-related behaviour: a network meta-analysis protocol. BMJ Open, *11*(12), e054479. https://doi.org/10.1136/bmjopen-2021-054479

Ciriaco, M., Ventrice, P., Russo, G., Scicchitano, M., Mazzitello, G., Scicchitano, F., & Russo, E. (2013). Corticosteroid-related central nervous system side effects. *Journal of Pharmacology & Pharmacotherapeutics*, *4*(Suppl1), S94. https://doi.org/10.4103/0976-500x.120975

Clark, A., Durkin, M., Olsen, M., Keller, M., Ma, Y., O'Neil, C., & Butler, A. (2021). Rural-urban differences in antibiotic prescribing for uncomplicated urinary tract

infection. *Infection Control & Hospital Epidemiology*, 1-8. https://doi.org/10.1017/ice.2021.21

Colquhoun, D. M., Bunker, S. J., Clarke, D. M., Glozier, N., Hare, D. L., Hickie, I. B. & Branagan, M. G. (2013). Screening, referral, and treatment for depression in patients with coronary heart disease. *Medical Journal of Australia*, *198*(9), 483-484. https://doi.org/10.5694/mja13.10153

Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. *Human Reproduction*, *32*(5), 1075-1091. https://doi.org/10.1093/humrep/dex044

Cooper, R. (2018). Diagnostic and statistical manual of mental disorders (DSM). *Ko Knowledge Organization*, *44*(8), 668-676. https://www.nomos-elibrary.de/10.5771/0943-7444-2017-8-668.pdf

Corden, M. E., Koucky, E. M., Brenner, C., Palac, H. L., Soren, A., Begale, M, & Mohr, D. C. (2016). MedLink: A mobile intervention to improve medication adherence and processes of care for treatment of depression in general medicine. *Digital Health*, *2*. https://doi.org/10.1177/2055207616663069

Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G., & Hippisley-Cox, J. (2011). Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *British Medical Journal*, *343*. https://doi.org/10.1136/bmj.d4551

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., & Garcia-Cardenas, V.

(2018). Economic impact of medication nonadherence by disease groups: a systematic review. *British Medical Journal Open*, *8*(1), e016982. http://dx.doi.org/10.1136/bmjopen-2017-016982

Das, S., Mitra, K., & Mandal, M. (2016). Sample size calculation: Basic principles. *Indian Journal of Anaesthesia*, *60*(9), 652. https://doi.org/10.4103/0019-5049.190621

DiBonaventura, M., Richard, L., Kumar, M., Forsythe, A., Flores, N.M., Moline, M. (2015). The association between insomnia and insomnia treatment side effects on health status, work productivity, and healthcare resource use. *PLoS ONE 10*(10). https://doi.org/10.1371/journal.pone.0137117

Doufas, A. G., Panagiotou, O. A., Panousis, P., Wong, S. S., & Ioannidis, J. P. (2017). Insomnia from drug treatments: evidence from meta-analyses of randomized trials and concordance with prescribing information. *Mayo Clinic Proceedings, 92* (1), 72-87. https://doi.org/10.1016/j.mayocp.2016.09.005

Dufort, A., & Zipursky, R. B. (2019). Understanding and managing treatment adherence in schizophrenia. *Clinical Schizophrenia & Related Psychoses*. http://dx.doi.org/10.3371/CSRP.ADRZ.121218

El Alili, M., Vrijens, B., Demonceau, J., Evers, S. M., & Hiligsmann, M. (2016). A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *British Journal of Clinical Pharmacology*, *82*(1), 268-279. https://doi.org/10.1111/bcp.12942

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science*, *196*(4286), 129-136. https://doi: 10.1126/science.847460

Enjezab, B., Eftekhar, M., & Ghadiri-Anari, A. (2017). Association between severity of depression and clinico-biochemical markers of polycystic ovary syndrome. *Electronic Physician*, *9*(11), 5820. https://doi.org/10.19082/5820

Fallon, M. (2016). What did you do? In *writing up quantitative research in the social and behavioral sciences* (pp. 75-84). Sense Publishers. https://doi.org/10.1007/978-94-6300-609-5_5

Fehling, K. B., & Selby, E. A. (2020). Suicide in DSM-5: current evidence for the proposed suicide behavior disorder and other possible improvements. *Frontiers in Psychiatry*, *11*, 499980. https://doi.org/10.3389/fpsyt.2020.499980

Fekadu, N., Shibeshi, W., & Engidawork, E. (2017). Major depressive disorder: pathophysiology and clinical management. *Journal of Depression and Anxiety*, *6*(1), 255-257. https://doi.org/10.4172/2167-1044.1000255

Ferguson, J. M. (2001). SSRI antidepressant medications: adverse effects and tolerability. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(1), 22. https://www.psychiatrist.com/read-pdf/23317/

Fornaro, M., Solmi, M., Stubbs, B., Veronese, N., Monaco, F., Novello, S., & Vieta, E. (2020). Prevalence and correlates of major depressive disorder, bipolar disorder and schizophrenia among nursing home residents without dementia: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *216*(1), 6-15. https://doi.org/10.1192/bjp.2019.5

Forsman, J., Masterman, T., Ahlner, J., Isacsson, G., & Hedström, A. K. (2019). Selective serotonin re-uptake inhibitors and the risk of violent suicide: a nationwide postmortem study. *European Journal of Clinical Pharmacology, 75*(3), 393–400. https://doi.org/10.1007/s00228-018-2586-2

Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., Huang, X., ... & Nock, M. K. (2017). Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological Bulletin*, *143*(2), 187. https://psycnet.apa.org/doi/10.1037/bul0000084

Friedman, R. A. (2014). Antidepressants' black-box warning—10 years later. *New England Journal of Medicine*, *371*(18), 1666-1668. https://doi.org/10.1056/NEJMp1408480

Gartlehner, G., Hansen, R. A., Morgan, L. C., Thaler, K., Lux, L., Van Noord, M., Mager, U., Thieda, P., Gaynes, B., Wilkins, T., Strobelberger, M., Lloyd, S., Reichenpfader, U., & Lohr, K. N. (2011). Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: An updated meta-analysis. *Annals of Internal Medicine, 155*(11), 772-785. https://doi.org/10.7326/0003-4819-155-11-201112060-00009

Glanz, K., Rimer, B. K., & Viswanath, K. (2015). *Health Behavior: Theory, Research, and Practice*. John Wiley & Sons.

Greenberg, P. E., Fournier, A. A., Sisitsky, T., Simes, M., Berman, R., Koenigsberg, S. H., & Kessler, R. C. (2021). The economic burden of adults with major depressive disorder in the United States (2010 and

2018). *Pharmacoeconomics*, *39*(6), 653-665. https://doi.org/10.1007/s40273-021-01019-4

Grey, I., Arora, T., Thomas, J., Saneh, A., Tohme, P., & Abi-Habib, R. (2020). The role of perceived social support on depression and sleep during the COVID-19 pandemic. *Psychiatry Research*, *293*, 113452. https://doi.org/10.1016/j.psychres.2020.113452

Grove, S., Cipher, D. (2017). *Statistics for nursing research: a workbook for evidence-based practice.* (2nd. Ed.). Elsevier

Gutiérrez-Rojas, L., Porras-Segovia, A., Dunne, H., Andrade-González, N., & Cervilla, J. A. (2020). Prevalence and correlates of major depressive disorder: A systematic review. *Brazilian Journal of Psychiatry*, *42*(6), 657-672. https://doi.org/10.1590/1516-4446-2020-0650

Gates, P., Albertella, L., & Copeland, J. (2016). Cannabis withdrawal and sleep: A systematic review of human studies. *Substance Abuse*, *37*(1), 255-269. https://doi.org/10.1080/08897077.2015.1023484

Gavin, N. I., Gaynes, B. N., Lohr, K. N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal depression: A systematic review of prevalence and incidence. *Obstetrics & Gynecology*, *106*(5 Part 1), 1071-1083. https://doi.org/10.1097/01.AOG.0000183597.31630.db

Gharzeddine, R. (2020). *An exploratory analysis of sociodemographic, clinical, and lifestyle factors associated with insomnia symptoms and the relationship between insomnia symptoms and medication adherence among individuals with heart*

failure (Doctoral dissertation, New York University).

Glenn, C. R., Kleiman, E. M., Cha, C. B., Deming, C. A., Franklin, J. C., & Nock, M. K. (2018). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. *Depression and Anxiety*, *35*(1), 65-88. https://doi.org/10.1002/da.22686

Grunebaum, M. F., Galfalvy, H. C., Choo, T. H., Keilp, J. G., Moitra, V. K., Parris, M. S., ... & Mann, J. J. (2018). Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *American Journal of Psychiatry*, *175*(4), 327-335. https://doi.org/10.1176/appi.ajp.2017.17060647

Hacker, M. A. (2007). Adherence to antiretroviral therapy in a context of universal access, in Rio de Janeiro, Brazil. *AIDS Care*, *19*(6), 740-748. https://doi.org/10.1080/09540120600842516

Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*, *63*(3), 332-339. https://doi.org/10.1001/archpsyc.63.3.332

Hansen, L. (2019). White Paper: IBM MarketScan research databases for life sciences researchers. https://www.ibm.com/downloads/cas/0NKLE57Y

Handley, T., Rich, J., Davies, K., Lewin, T., & Kelly, B. (2018). The challenges of predicting suicidal thoughts and behaviours in a sample of rural Australians with depression. *International Journal of Environmental Research and Public Health*, *15*(5), 928. https://doi.org/10.3390/ijerph15050928

Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2014). Depression and cardiovascular disease: A clinical review. *European Heart Journal*, *35*(21), 1365-1372. https://doi.org/10.1093/eurheartj/eht462

Harris, P., Nagy, S., & Vardaxis, N. (2014). *Mosby's Dictionary of Medicine, Nursing and Health Professions-Australian & New Zealand Edition-eBook*. Elsevier Health Sciences.

Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour Research and Therapy*, *40*(8), 869-893. https://doi.org/10.1016/S0005-7967(01)00061-4

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336-346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Haviland, W. A., Prins, H. E., & McBride, B. (2016). *Cultural anthropology: The human challenge*. Cengage Learning.

Hayes, E. L., & Vance, K. A. (2020). Health insurance portability and accountability act of 1996: Health & Public Welfare. *Georgia State University Law Review*, *37*(1), 153. https://readingroom.law.gsu.edu/gsulr/vol37/iss1/14

Hedegaard, H., Curtin, S. C., & Warner, M. (2018). Suicide mortality in the United States, 1999–2017. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. *National Center for Health Statistics Data Brief*, (330). https://www.cdc.gov/nchs/products/databriefs/db330.htm

Heo, S., Moser, D. K., Lennie, T. A., Fischer, M., Kim, J., Walsh, M. N., Thurston, M.,

& Webster, J. H. (2021). Varied factors were associated with different types of self-care in heart failure. *Western Journal of Nursing Research*, *43*(4), 298-306. https://doi.org/10.1177/0193945920950334

Hetrick, E., McKenzie, E., Cox, G., Simmons, B., & Merry, N. (2017). Newer generation antidepressants for depressive disorders in children and adolescents. *BJPsych Advances*, *23*(2), 74-74. https://doi.org/10.1192/apt.23.2.74

Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of nonadherence to antidepressants in major depressive disorder: a systematic review. *Journal of Affective Disorders*, *193*, 1-10. https://doi.org/10.1016/j.jad.2015.12.029.

Hofmann, G., Curtiss, J., Carpenter, K., & Kind, S. (2017). Effect of treatments for depression on quality of life: a meta-analysis. *Cognitive Behaviour Therapy*, *46*(4), 265-286. https://doi.org/10.1080/16506073.2017.1304445

Hochbaum, G., Rosenstock, I., & Kegels, S. (1952). Health belief model. *United States Public Health Service*, *1*.

Hoogendoorn, C. J., Shapira, A., Roy, J. F., Walker, E. A., Cohen, H. W., & Gonzalez, J. S. (2019). Depressive symptom dimensions and medication non-adherence in suboptimally controlled type 2 diabetes. *Journal of Diabetes and its Complications*, *33*(3), 217-222. https://doi.org/10.1016/j.jdiacomp.2018.12.001

Howitt, D., & Cramer, D. (2017). *Research methods in psychology*. Harlow: Pearson.

IBM Watson Health (2018). IBM MarketScan Research Databases for life sciences researchers. White paper.

https://www.ibm.com/downloads/cas/0NKLE57Y#:~:text=The%20IBM%C2%AE%20MarketScan%C2%AE,risk%20assessments%20(HRAs)%2C%20hospital

Iuga, O., & McGuire, J. (2014). Adherence and health care costs. *Risk Management and Healthcare Policy*, *7*, 35-44. https://doi.org/10.2147/RMHP.S19801

Janežič, A., Locatelli, I., & Kos, M. (2017). Criterion validity of 8-item Morisky medication adherence scale in patients with asthma. *PloS One*, *12*(11), e0187835. https://doi.org/10.1371/journal.pone.0187835

Jimmy, B., & Jose, J. (2011). Patient medication adherence: measures in daily practice. *Oman Medical Journal*, *26*(3), 155. https://doi.org/10.5001/omj.2011.38

Jin, H., Kim, Y., & Rhie, J. (2016). Factors affecting medication adherence in elderly people. *Patient Preference and Adherence*, *10*, 2117. https://doi.org/10.2147/PPA.S118121

Johnston, M. P. (2017). Secondary data analysis: A method of which the time has come. *Qualitative and Quantitative Methods in Libraries*, *3*(3), 619-626. https://www.qqml-journal.net/index.php/qqml/article/view/169/170

Josephine, K., Josefine, L., Philipp, D., David, E., & Harald, B. (2017). Internet-and mobile-based depression interventions for people with diagnosed depression: a systematic review and meta-analysis. *Journal of Affective Disorders*, 223, 28-40. https://doi.org/10.1016/j.jad.2017.07.021

Kahwati, L., Viswanathan, M., Golin, C. E., Kane, H., Lewis, M., & Jacobs, S. (2016). Identifying configurations of behavior change techniques ineffective medication adherence interventions: a qualitative comparative analysis. *Systematic*

Reviews, *5*(1), 83. https://doi.org/10.1186/s13643-016-0255-z

Kang, H. (2021). Sample size determination and power analysis using the G* Power software. *Journal of Educational Evaluation for Health Professions*, *18*. https://doi.org/10.3352/jeehp.2021.18.17

Katon, W. J. (2011). Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues in Clinical Neuroscience*, *13*(1), 7. https://doi.org/10.31887/DCNS.2011.13.1/wkaton

Kessler, D., Burns, A., Tallon, D., Lewis, G., MacNeill, S., Round, J., Hollingworth, W., Chew-Graham, C., Anderson, I., Campbell, J., Dickens, C., Macleod, U., Gilbody, S., Davies, S., Peters, J., & Wiles, N. (2018). Combining mirtazapine with SSRIs or SNRIs for treatment-resistant depression: the MIR RCT. *Health Technology Assessment*, 1-136. https://doi.org/10.3310/hta22630

Khaledi, M., Haghighatdoost, F., Feizi, A., & Aminorroaya, A. (2019). The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetologica*, *56*(6), 631-650. https://doi.org/10.1007/s00592-019-01295-9

Khan, A., Mar, K. F., Gokul, S., & Brown, W. A. (2018). Decreased suicide rates in recent antidepressant clinical trials. *Psychopharmacology*, *235*(5), 1455-1462. https://doi.org/10.1007/s00213-018-4856-1

Keyloun, K. R., Hansen, R. N., Hepp, Z., Gillard, P., Thase, M. E., & Devine, E. B. (2017). Adherence and persistence across antidepressant therapeutic classes: a retrospective claims analysis among insured U.S. patients with major depressive

disorder (MDD). *CNS Drugs*, *31*(5), 421-432. https://doi.org/10.1007/s40263-017- 0419-y.

Kim, J., Oh, S. W., Myung, S. K., Park, J. Y., & Yoon, D. H. (2013). Antidepressant use and risk of coronary heart disease: A meta-analysis. *Cardiology*, *125*, 478. https://doi.org/10.1111/bcp.12383

Kini, V., & Ho, M. (2018). Interventions to improve medication adherence: A review. *Jama*, *320*(23), 2461-2473. https://doi.org/10.1001/jama.2018.19271

Kleinsinger, F. (2018). The unmet challenge of medication nonadherence. *The Permanente Journal*, *22*. https://doi.org/10.7812/TPP/18-033

Klonsky, E. D., & May, A. M. (2014). Differentiating suicide attempters from suicide ideators: A critical frontier for suicidology research. *Suicide and Life-Threatening Behavior*, *44*(1), 1-5. https://doi.org/10.1111/sltb.12068

Kreyenbuhl, J., Record, E. J., & Palmer-Bacon, J. (2016). A review of behavioral tailoring strategies for improving medication adherence in serious mental illness. *Dialogues in Clinical Neuroscience*, *18*(2), 191. https://doi.org/10.31887/DCNS.2016.18.2/jkreyenbuhl

Krystal, A. D., Thase, M. E., Tucker, V. L., & Goodale, E. P. (2007). Bupropion HCL and sleep in patients with depression. *Current Psychiatry Reviews*, *3*(2), 123-128. https://doi.org/10.2174/157340007780599096

Laghousi D, Rezaie F, Alizadeh M, Asghari Jafarabadi M. (2021). The eight-item Morisky Medication Adherence Scale: validation of its Persian version in diabetic adults. *Caspian Journal of Internal Medicine*; *12*(1):77-83.

https://doi.org/10.22088/cjim.12.1.77

Lam, W. Y., & Fresco, P. (2015). Medication adherence measures: An overview. *BioMed Research International,* 1-12. https://doi.org/10.1155/2015/217047

Leavy, P. (2017). *Research design: Quantitative, qualitative, mixed methods, arts-based, and community-based participatory research approaches.* The Guilford Press.

Lee, H. J., Choi, E. J., Nahm, F. S., Yoon, I. Y., & Lee, P. B. (2018). Prevalence of unrecognized depression in patients with chronic pain without a history of psychiatric diseases. *The Korean Journal of Pain, 31*(2), 116. https://doi.org/10.3344/kjp.2018.31.2.116

Lee, Y., Rosenblat, J. D., Lee, J., Carmona, N. E., Subramaniapillai, M., Shekotikhina, M., Rodrigo B. Mansur, R., Brietzke, E., Lee, J., Ho R., Yim, S., & McIntyre, R. S. (2018). Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. *Journal of Affective Disorders, 227*, 406-415. https://doi.org/10.1016/j.jad.2017.11.003

Lichtman, J. H., Bigger Jr, J. T., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lespérance, F., Mark, D., Sheps, D., Taylor, B., & Froelicher, E. S. (2009). Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Focus, 7*(3), 406-413.

https://doi.org/10.1176/foc.7.3.foc406

Longrigg, J. (2013). *Greek medicine: From the heroic to the Hellenistic age a sourcebook*. Routledge.

Ludwig, J., & Marcotte, D. E. (2005). Antidepressants, suicide, and drug regulation. Journal of Policy Analysis and Management: *The Journal of the Association for Public Policy Analysis and Management, 24*(2), 249-272. https://doi.org/10.1002/pam.20089

Lye, S., Tey, Y., Tor, S., Shahabudin, F., Ibrahim, N., Ling, H., Stanslas, J., Loh, S., Rosli, R., Lokman, K., Badamasi, I., Asraa Faris-Aldoghachi, A., and Razak, N. (2020). Predictors of recurrence of major depressive disorder. *PloS one*, *15*(3), e0230363. https://doi.org/10.1371/journal.pone.0230363

Mahendran, N., & Vincent, D. R. (2019). Effective classification of major depressive disorder patients using machine learning techniques. *Recent Patents on Computer Science*, *12*(1), 41-48. https://doi.org/10.2174/2213275911666181016160920

Maher, A. R., Hempel, S., Apaydin, E., Shanman, R. M., Booth, M., Miles, J. N., & Sorbero, M. E. (2016). St. John's Wort for major depressive disorder: A systematic review. *Rand Health Quarterly*, 5(4). https://doi.org/10.1186/s13643-016-0325-2

Maleki, N., & Oscar-Berman, M. (2020). Chronic Pain in Relation to Depressive Disorders and Alcohol Abuse. *Brain Sciences*, *10*(11), 826. https://doi.org/10.3390/brainsci10110826

Marasine, N. R., Sankhi, S., Lamichhane, R., Marasini, N. R., & Dangi, N. B. (2020).

Self-Reported Antidepressant Drug Side Effects, Medication Adherence, and Its Associated Factors among Patients Diagnosed with Depression at the Psychiatric Hospital of Nepal. *Depression Research and Treatment, 2020*. https://doi.org/10.1155/2020/7024275

Martin-Vazquez, M. J. (2016). Adherence to antidepressants: A review of the literature. *Neuropsychiatry*, *6*(5), 236-241. https://doi.org/10.4172/Neuropsychiatry.1000145

McDonald, W. M., Richard, I. H., & DeLong, M. R. (2003). Prevalence, etiology, and treatment of depression in Parkinson's disease. *Biological Psychiatry*, *54*(3), 363-375. https://doi.org/10.1016/S0006-3223(03)00530-4

McCance, K. L., & Huether, S. E. (2018). *Pathophysiology-E-book: the biologic basis for disease in adults and children*. Elsevier Health Sciences.

McGirr, A., Renaud, J., Séguin, M., Alda, M., & Turecki, G. (2008). Course of major depressive disorder and suicide outcome: a psychological autopsy study. *Journal of Clinical Psychiatry*, *69*(6), 966-970. https://doi: 10.4088/jcp.v69n0612

McIntyre, R. S., Lee, Y., Carmona, N. E., Subramaniapillai, M., Cha, D. S., Lee, J., Lee, J. H., Alageel, A., Rodrigues, N., Park, C., Ragguett, R., Rosenblat, J., Almatham, F., Pan, Z., Rong, C., & Mansur, R. B. (2018). Characterizing, assessing, and treating cognitive dysfunction in major depressive disorder. *Harvard Review of Psychiatry*, *26*(5), 241-249. https://doi: 10.1097/HRP.0000000000000171

Meng, R., Yu, C., Liu, N., He, M., Lv, J., Guo, Y., Bian, Z., Yang, L., Chen, Y., Zhang, X., Chen, Z., Wu, T., & Li, L. (2020). Association of depression with all-cause

and cardiovascular disease mortality among adults in China. *JAMA Network Open*, *3*(2), e1921043-e1921043. https://doi.org/10.1001/jamanetworkopen.2019.21043

Mental Health America (2020). The state of mental health in America. MHA [internet publication]. https://mhanational.org/issues/state-mental-health-america#:~:text=In%202019%2D2020%2C%2020.78%25,disorder%20in%20the%20past%20year.

Merriam, W. (2020). Merriam-Webster online dictionaries: An encyclopedia Britannica company. https://www.merriam-webster.com/

Miaskowski, C., Blyth, F., Nicosia, F., Haan, M., Keefe, F., Smith, A., & Ritchie, C. (2020). A biopsychosocial model of chronic pain for older adults. *Pain Medicine*, *21*(9), 1793-1805. https://doi.org/10.1093/pm/pnz329

Middleton, L. E., Barnes, D. E., Lui, L. Y., & Yaffe, K. (2010). Physical activity over the life course and its association with cognitive performance and impairment in old age. *Journal of the American Geriatrics Society*, *58*(7), 1322-1326. https://doi:10.1111/j.1532-5415.2010.02903.x.

Mokdad, A. H., Ballesteros, K., Echko, M., Glenn, S., Olsen, H. E., Mullany, E., & US Burden of Disease Collaborators. (2018). The state of U.S. health, 1990-2016: burden of diseases, injuries, and risk factors among U.S. states. *JAMA*, *319*(14), 1444-1472. https://doi.org/10.1001/jama.2018.015810.1001

Moon, J., Lee, Y., Hwang, S., Hong, P., and Morisky, E. (2018). Correction: Accuracy of a screening tool for medication adherence: A systematic review and meta-analysis

of the Morisky Medication Adherence Scale-8. PLoS ONE 13(4): e0196138. https://doi.org/10.1371/journal.pone.0196138

Morgan, J. A., Olagunju, A. T., Corrigan, F., & Baune, B. T. (2018). Does ceasing exercise induce depressive symptoms? A systematic review of experimental trials including immunological and neurogenic markers. *Journal of Affective Disorders, 234*, 180-192. https://doi.org/10.1016/j.jad.2018.02.058

Morres, I. D., Hatzigeorgiadis, A., Stathi, A., Comoutos, N., Arpin-Cribbie, C., Krommidas, C., & Theodorakis, Y. (2019). Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depression and Anxiety*, *36*(1), 39-53. https://doi.org/10.1002/da.22842

Morrison, A., Stauffer, M. E., & Kaufman, A. S. (2015). Defining medication adherence in individual patients. *Patient Preference and Adherence*, *9*, 893. https://doi.org/10.2147/PPA.S86249

Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive validity of a medication adherence measure in an outpatient setting. *The Journal of Clinical Hypertension*, *10*(5), 348-354. https://doi.org/10.1111/j.1751-7176.2008.07572.x

Moulton, C. D., Pickup, J. C., & Ismail, K. (2015). The link between depression and diabetes: the search for shared mechanisms. *The Lancet Diabetes & Endocrinology*, *3*(6), 461-471. https://doi.org/10.1016/S2213-8587(15)00134-5

Mula, M., & Sander, J. W. (2007). Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Safety*, *30*(7), 555-567.

https://doi.org/10.2165/00002018-200730070-00001

Murphy, B., Le Grande, M., Alvarenga, M., Worcester, M., & Jackson, A. (2020). Anxiety and depression after a cardiac event: prevalence and predictors. *Frontiers in Psychology*, *10*, 3010. https://doi.org/10.3389/fpsyg.2019.03010

Murray, C. J., & Lopez, A. D. (2013). Measuring the global burden of disease. *New England Journal of Medicine*, *369*(5), 448-457. https://doi.org/10.1056/NEJMra1201534

Mutsatsa, S. (2016). A guide to medication adherence in depression. *British Journal of Mental Health Nursing*, *5*(6), 259-261. https://doi.org/10.12968/bjmh.2016.5.6.259

Nachmias, C. F. (2015). *Research methods in the social sciences* 8th Ed. Worth Publishers, Inc. New York: Worth.

Naghavi, M. (2019). Global, regional, and national burden of suicide mortality 1990 to 2016: Systematic analysis for the Global Burden of Disease Study 2016. *British Medical Journal*, 364. https://doi.org/10.1136/bmj.l94

Naja, S., Al Kubaisi, N., Singh, R., Abdalla, H., & Bougmiza, I. (2021). Screening for antenatal depression and its determinants among pregnant women in Qatar: revisiting the biopsychosocial model. *BMC Pregnancy and Childbirth*, *21*(1), 1-12. https://doi.org/10.1186/s12884-021-03793-7

Nakagawa, A., Grunebaum, M. F., Ellis, S. P., Oquendo, M. A., Kashima, H., Gibbons, R. D., & Mann, J. J. (2007). Association of suicide and antidepressant prescription rates in Japan, 1999–2003. *The Journal of Clinical Psychiatry*, *68*(6),

908. https://doi.org/10.4088%2Fjcp.v68n0613

Nanni, M. G., Caruso, R., Mitchell, A. J., Meggiolaro, E., & Grassi, L. (2015). Depression in HIV infected patients: a review. *Current Psychiatry Reports*, *17*(1), 1-11. https://doi.org/10.1007/s11920-014-0530-4

National Center for Health Statistics (U.S. (2018). Health, United States, 2017: With Special Feature on Mortality.. https://www.ncbi.nlm.nih.gov/books/NBK551099/

National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (2017): annual report - England, Northern Ireland, Scotland and Wales. *University of Manchester*.. https://documents.manchester.ac.uk/display.aspx?DocID=37560

National Heart, Lung, and Blood Institute (2020). Coronary Heart Disease. What Is Coronary Heart Disease? NIH.. https://www.nhlbi.nih.gov/health/coronary-heart-disease

National Institute of Mental Health (2022). Major depression. NIMH https://www.nimh.nih.gov/health/statistics/major-depression

National Mental Health Commission (2017). Review into the suicide and self-harm prevention services available to current and former serving ADF members and their families. Final report: Findings and recommendations. https://www.dva.gov.au/sites/default/files/files/publications/health/Literature_Review.pdf

Nattino, G., Pennell, M. L., & Lemeshow, S. (2020). Assessing the goodness of fit of logistic regression models in large samples: A modification of the Hosmer-Lemeshow test. *Biometrics*, *76*(2), 549-560. https://doi.org/10.1111/biom.13249

Nierenberg, A. A., Pava, J. A., Clancy, K., Rosenbaum, J. F., & Fava, M. (1996). Are neurovegetative symptoms stable in relapsing or recurrent atypical depressive episodes*? Biological Psychiatry*, *40*(8), 691-696. https://doi.org/10.1016/0006-3223(96)00029-7

Nutt, D., Wilson, S., & Paterson, L. (2008). Sleep disorders as core symptoms of depression. *Dialogues in Clinical Neuroscience*, *10*(3), 329. https://doi.org/10.31887/DCNS.2008.10.3/dnutt

O'Brien, E. M., Chelminski, I., Young, D., Dalrymple, K., Hrabosky, J., & Zimmerman, M. (2011). Severe Insomnia is associated with more severe presentation and greater functional deficits in depression. *Journal of Psychiatric Research, 45*(8), 1101-1105. https://doi.org/10.1016/j.jpsychires.2011.01.010

Oh, S. W., Kim, J., Myung, S. K., Hwang, S. S., & Yoon, D. H. (2014). Antidepressant use and risk of coronary heart disease: Meta-analysis of observational studies. *British Journal of Clinical Pharmacology, 78*(4), 727-737. https://doi.org/10.1111/bcp.12383

Oluboka, O. J., Katzman, M. A., Habert, J., McIntosh, D., MacQueen, G. M., Milev, R. V. McIntyre, R., & Blier, P. (2018). Functional recovery in major depressive disorder: providing early optimal treatment for the individual patient. *International Journal of Neuropsychopharmacology, 21*(2), 128-144. https://doi.org/10.1093/ijnp/pyx081

Osborne, J. W., & Waters, E. (2002). Four assumptions of multiple regression that researchers should always test. *Practical Assessment, Research, and*

Evaluation, *8*(1), 2. https://doi.org/10.7275/r222-hv23

Overbeck, G., Davidsen, A. S., & Kousgaard, M. B. (2016). Enablers and barriers to implementing collaborative care for anxiety and depression: a systematic qualitative review. *Implementation Science*, *11*(1), 1-16. https://doi.org/10.1186/s13012-016-0519-y

Ott, R. L., & Longnecker, M. T. (2015). *An introduction to statistical methods and data analysis*. 7th Ed.Cengage Learning.

Paiva, T., Reis, C., Feliciano, A., Canas-Simião, H., Machado, M. A., Gaspar, T., ... & Matos, M. G. (2021). Sleep and awakening quality during COVID-19 confinement: complexity and relevance for health and behavior. *International Journal of Environmental Research and Public Health*, *18*(7), 3506. https://doi.org/10.3390/ijerph18073506

Palaniappan, K., & Kum, I. Y. S. (2019). Underlying Causes behind Research Study Participants' Careless and Biased Responses in the Field of Sciences. *Current Psychology*, *38*(6), 1737-1747. https://doi.org/10.1007/s12144-017-9733-2

Panagioti, M., Bower, P., Kontopantelis, E., Lovell, K., Gilbody, S., Waheed, W., Chris Dickens, C., Archer, J., Simon, G., Ell, K., Huffman, J., Richards, D., Feltz-Cornelis, C., Adler, D., Bruce, M., Buszewicz, M., Cole, M., Davidson, K., Jonge, P., Gensichen, J., Huijbregts, K., Menchetti, M., Vikram Patel, V., ... & Coventry, P. A. (2016). Association between chronic physical conditions and the effectiveness of collaborative care for depression: an individual participant data meta-analysis. *JAMA Psychiatry*, *73*(9), 978-989.

https://doi.org/10.1001/jamapsychiatry.2016.1794

Păsărelu, C. R., Andersson, G., Bergman Nordgren, L., & Dobrean, A. (2017). Internet-delivered transdiagnostic and tailored cognitive behavioral therapy for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials. *Cognitive Behaviour Therapy*, *46*(1), 1-28. https://doi.org/10.1080/16506073.2016.1231219

Pasina, L., Brucato, A. L., Falcone, C., Cucchi, E., Bresciani, A., Sottocorno, M., Taddei, C., Casati, M., Franchi, C., Djade, C., & Nobili, A. (2014). Medication nonadherence among elderly patients newly discharged and receiving polypharmacy. *Drugs & Aging*, *31*(4), 283-289. https://doi.org/10.1007/s40266-014-0163-7

Patel, D., Steinberg, J., & Patel, P. (2018). Insomnia in the elderly: a review. *Journal of Clinical Sleep Medicine*, *14*(6), 1017-1024. https://doi.org/10.5664/jcsm.7172

Patten, S., Williams, J., Lavorato, D., Wang, J., Jetté, N., Sajobi, T., Fiest, M., & Bulloch, A. (2018). Patterns of association of chronic medical conditions and major depression. *Epidemiology and Psychiatric Sciences*, *27*(1), 42-50. https://doi.org/10.1017/S204579601600072X

Pedersen, C. B., Mors, O., Bertelsen, A., Waltoft, B. L., Agerbo, E., McGrath, J. J., Mortensen, P. B., & Eaton, W. W. (2014). A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*, *71*(5), 573-581. https://doi.org/10.1001/jamapsychiatry.2014.16

Pereira-Miranda, E., Costa, P. R., Queiroz, V. A., Pereira-Santos, M., & Santana, M. L.

(2017). Overweight and obesity associated with higher depression prevalence in adults: a systematic review and meta-analysis. *Journal of the American College of Nutrition*, *36*(3), 223-233. https://doi.org/10.1080/07315724.2016.1261053

Perney, P., & Lehert, P. (2018). Insomnia in alcohol-dependent patients: prevalence, risk factors and acamprosate effect: an individual patient data meta-analysis. *Alcohol and Alcoholism*, *53*(5), 611-618. https://doi.org/10.1093/alcalc/agy013

Perveen, A., Hamzah, H. B., Othamn, A., & Ramlee, F. (2020). Prevalence of Anxiety, Stress, Depression among Malaysian Adults during COVID-19 Pandemic Movement Control Order. *Indian Journal of Community Health*, *32*(3). https://doi.org/10.47203/ijch.2020.v32i03.020.

Pilgrim, A. L., Robinson, S. M., Sayer, A. A., & Roberts, H. C. (2015). An overview of appetite decline in older people. *Nursing Older People*, *27*(5), 29–35. https://doi.org/10.7748/nop.27.5.29.e697

Pitman, A., Suleman, S., Hyde, N., & Hodgkiss, A. (2018). Depression and anxiety in patients with cancer. *British Medical Journal*, *361*. https://doi.org/10.1136/bmj.k1415

Pizzi, C., Rutjes, A. W. S., Costa, G. M., Fontana, F., Mezzetti, A., & Manzoli, L. (2011). Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *The American Journal of Cardiology*, *107*(7), 972-979. https://doi.org/10.1016/j.amjcard.2010.11.017

Pompili, M., Serafini, G., Innamorati, M., Ambrosi, E., Giordano, G., Girardi, P., Tatarelli, R., & Lester, D. (2010). Antidepressants and suicide risk: a

comprehensive overview. *Pharmaceuticals*, *3*(9), 2861-2883. https://doi.org/10.3390/ph3092861

Prakash, J., Yadav, Y., Srivastava, K., & Madhusudan, T. (2019). Psychosocial correlates of medication adherence in patients with depressive illness. *Industrial Psychiatry Journal*, *28*(1), 135–140. https://doi.org/10.4103/ipj.ipj_78_19

Prayaga, R. B., Jeong, E. W., Feger, E., Noble, H. K., Kmiec, M., & Prayaga, R. S. (2018). Improving refill adherence in medicare patients with tailored and interactive mobile text messaging: pilot study. *JMIR mHealth and uHealth*, *6*(1), e30. https://doi.org/10.2196/mhealth.8930

Qaseem, A., Barry, M. J., Kansagara, D., & Clinical Guidelines Committee of the American College of Physicians. (2016). Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *164*(5), 350-359. https://doi.org/10.7326/M15-2570

Qato, D. M., Ozenberger, K., & Olfson, M. (2018). Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *Jama*, *319*(22), 2289-2298. https://doi.org/10.1001/jama.2018.6741

Quilliam, B. J., Ozbay, A. B., Sill, B. E., & Kogut, S. J. (2013). The association between adherence to oral antidiabetic drugs and hypoglycaemia in persons with Type 2 diabetes. *Journal of Diabetic Medicine*, *30*(11), 1305-1313. https://doi.org/10.1111/dme.12217

Ranganathan, P., Pramesh, C. S., & Aggarwal, R. (2017). Common pitfalls in statistical

analysis: Logistic regression. *Perspectives in Clinical Research*, *8*(3), 148. https://doi.org/10.4103/picr.PICR_87_17

Read, J., & Williams, J. (2018). Adverse effects of antidepressants reported by a large international cohort: emotional blunting, suicidality, and withdrawal effects. *Current Drug Safety*, *13*(3), 176-186. https://doi.org/10.2174/1574886313666180605095130

Reeve, S., Sheaves, B., & Freeman, D. (2015). The role of sleep dysfunction in the occurrence of delusions and hallucinations: a systematic review. *Clinical Psychology Review*, *42*, 96-115. https://doi.org/10.1016/j.cpr.2015.09.001

Remick, R. A. (2002). Diagnosis and management of depression in primary care: a clinical update and review. *Canadian Medical Association Journal*, *167*(11), 1253-1260. https://www.cmaj.ca/content/cmaj/167/11/1253.full.pdf

Remien, R. H., Bastos, F. I., Terto Jnr, V., Raxach, J. C., Pinto, R. M., Parker, R. G., Berkman, A., & Hacker, M. A. (2007). Adherence to antiretroviral therapy in a context of universal access, in Rio de Janeiro, Brazil. *AIDS care*, *19*(6), 740-748. https://doi.org/10.1080/09540120600842516

Richards, D. A., Hill, J. J., Gask, L., Lovell, K., Chew-Graham, C., Bower, P., Cape, J., Pilling, S., Araya, R., Kessler, D., Bland, M., Green, C., Gilbody, S., Lewis, G., Manning, C., Hughes-Morley, A., & Barkham, M. (2013). Clinical effectiveness of collaborative care for depression in U.K. primary care (CADET): Cluster randomised controlled trial. *British Medical Journal*, 347. https://doi.org/10.1136/bmj.f4913

Riegel, B., Moelter, S. T., Ratcliffe, S. J., Pressler, S. J., De Geest, S., Potashnik, S., Fleck, D., Sha, D., Sayers, S., Weintraub, W., Weaver, T., & Goldberg, L. R. (2011). Excessive daytime sleepiness is associated with poor medication adherence in adults with heart failure. *Journal of Cardiac Failure, 17*(4), 340-348. https://doi.org/10.1016/j.cardfail.2010.11.002

Riemann, D., Krone, L. B., Wulff, K., & Nissen, C. (2020). Sleep, insomnia, and depression. *Neuropsychopharmacology, 45*(1), 74-89. https://doi.org/10.1038/s41386-019-0411-y

Robinson, R. G., & Jorge, R. E. (2016). Post-stroke depression: A review. *American Journal of Psychiatry, 173*(3), 221-231. https://doi.org/10.1176/appi.ajp.2015.15030363

Rogers, B. G., Bainter, S. A., Smith-Alvarez, R., Wohlgemuth, W. K., Antoni, M. H., Rodriguez, A. E., & Safren, S. A. (2021). Insomnia, health, and health-related quality of life in an urban clinic sample of people living with HIV/AIDS. *Behavioral Sleep Medicine*, *19*(4), 516-532. https://doi.org/10.1080/15402002.2020.1803871

Rogers, D., & Pies, R. (2008). General medical with depression drugs associated. *Psychiatry (Edgmont (Pa.: Township))*, *5*(12), 28–41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729620/pdf/PE_5_12_28.pdf/?tool=EBI

Rootes-Murdy, K., Glazer, K. L., Van Wert, M. J., Mondimore, F. M., & Zandi, P. P. (2018). Mobile technology for medication adherence in people with mood

disorders: A systematic review. *Journal of Affective Disorders*, *227*, 613-617. https://doi.org/10.1016/j.jad.2017.11.022

Roth, T. (2007). Insomnia: definition, prevalence, etiology, and consequences. *Journal of Clinical Sleep Medicine*, *3*(5 suppl), S7-S10. https://doi.org/10.5664/jcsm.26929

Ruel, E., Wagner III, W. E., & Gillespie, B. J. (2016). *The practice of survey research: Theory and applications*. Sage Publications.

Russell, C. L., Ashbaugh, C., Peace, L., Cetingok, M., Hamburger, K. Q., Owens, S., Coffey, D., Webb, A., Hathaway, D., Winsett, R., Madsen, R., & Wakefield, M. R. (2013). Time-in-a-bottle (TIAB): a longitudinal, correlational study of patterns, potential predictors, and outcomes of immunosuppressive medication adherence in adult kidney transplant recipients. *Clinical transplantation*, *27*(5), E580-E590. https://doi.org/10.1111/ctr.12203

Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N., & Heald, J. L. (2017). Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *Journal of Clinical Sleep Medicine*, *13*(2), 307-349. https://doi.org/10.5664/jcsm.6470

Schaakxs, R., Comijs, H. C., Lamers, F., Kok, R. M., Beekman, A. T., & Penninx, B. W. (2018). Associations between age and the course of major depressive disorder: a 2-year longitudinal cohort study. *The Lancet Psychiatry*, *5*(7), 581-590. https://doi.org/10.1016/S2215-0366(18)30166-4

Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020).

Psychotropic medication nonadherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. *Systematic Reviews*, *9*(1), 1-18. https://doi.org/10.1186/s13643-020-1274-3

Sharma, T., Guski, L. S., Freund, N., & Gøtzsche, P. C. (2016). Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *British Medical Journal, 352*. https://doi.org/10.1136/bmj.i65

Shrestha Manandhar, J., Shrestha, R., Basnet, N., Silwal, P., Shrestha, H., Risal, A., & Kunwar, D. (2017). Study of adherence pattern of antidepressants in patients with depression. *Kathmandu University Medical Journal*, *57*(1), 3-9. http://kumj.com.np/issue/57/3-9.pdf

Simmons, W. K., Burrows, K., Avery, J. A., Kerr, K. L., Bodurka, J., Savage, C. R., & Drevets, W. C. (2016). Depression-related increases and decreases in appetite: dissociable patterns of aberrant activity in reward and interoceptive neurocircuitry. *American Journal of Psychiatry*, *173*(4), 418-428. https://doi.org/10.1176/appi.ajp.2015.15020162

Solmi, M., Miola, A., Croatto, G., Pigato, G., Favaro, A., Fornaro, M., Berk, M., Smith, L., Quevedo, J., Maes, M., Correll. C.U., & Carvalho, A. F. (2020). How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. *Brazilian Journal of Psychiatry*, *43*, 189-202. https://doi.org/10.1590/1516-4446-2020-0935

Strawbridge, R., Carter, B., Marwood, L., Bandelow, B., Tsapekos, D., Nikolova, V. L., Taylor, R., Mantingh, T., Angel, V., Patrick, F., Cleare, A., & Young, A. H. (2019). Augmentation therapies for treatment-resistant depression: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *214*(1), 42-51. https://doi.org/10.1192/bjp.2018.291

Strecher, V. J., & Rosenstock, I. M. (1997). The health belief model. *Cambridge Handbook of Psychology, Health and Medicine*, *113*, 117.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, *157*(10), 1552-1562. https://doi.org/10.1176/appi.ajp.157.10.1552

SurveyMonkey (2022). How SurveyMonkey gets its data. SurveyMonkeyhttps://www.surveymonkey.com/mp/survey-methodology/

Takahashi, T., Sugiyama, F., Kikai, T., Kawashima, I., Guan, S., Oguchi, M., Uchida, T., & Kumano, H. (2019). Changes in depression and anxiety through mindfulness group therapy in Japan: The role of mindfulness and self-compassion as possible mediators. *BioPsychoSocial Medicine*, *13*(1), 1-10. https://doi.org/10.1186/s13030-019-0145-4

Tengilimoğlu, D., Zekioğlu, A., Tosun, N., Işık, O., & Tengilimoğlu, O. (2021). Impacts of COVID-19 pandemic period on depression, anxiety and stress levels of the healthcare employees in Turkey. *Legal Medicine*, *48*, 101811. https://doi.org/10.1016/j.legalmed.2020.101811

Termorshuizen, F., Palmen, S. J., & Heerdink, E. R. (2016). Suicide behavior before and

after the start with antidepressants: a high persistent risk in the first month of treatment among the young. *International Journal of Neuropsychopharmacology*, *19*(2), pyv081. https://doi.org/10.1093/ijnp/pyv081

The National Heart, Lung, and Blood Institute (NHLBI, 2019). Coronary Heart Disease. https://www.nhlbi.nih.gov/health-topics/coronary-heart-disease

The State of Texas (2022). Exploring and visiting Texas. https://www.texas.gov/exploring-visiting-texas/

Thase, M. E., Youakim, J. M., Skuban, A., Hobart, M., Augustine, C., Zhang, P., McQuade, R., Carson, W., Nyilas, M., Eriksson, H., & Sanchez, R. (2015). Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *The Journal of Clinical Psychiatry*, *76*(9), 1224-1231. https://doi.org/10.4088/JCP.14m09688

Thorpy M. J. (2012). Classification of sleep disorders. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics*, *9*(4), 687–701. https://doi.org/10.1007/s13311-012-0145-6

Topuzoğlu, A., Binbay, T., Ulaş, H., Elbi, H., Tanık, F. A., Zağlı, N., & Alptekin, K. (2015). The epidemiology of major depressive disorder and subthreshold depression in Izmir, Turkey: Prevalence, socioeconomic differences, impairment, and help-seeking. *Journal of Affective Disorders*, *181*, 78-86. https://doi.org/10.1016/j.jad.2015.04.017

Tripathy, J. P. (2013). Secondary data analysis: Ethical issues and challenges. *Iranian*

Journal of Public Health, *42*(12), 1478. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4441947/

Tully, P. J., & Baumeister, H. (2015). Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomized controlled trials. *British Medical Journal Open*, *5*(12), e009128. http://dx.doi.org/10.1136/bmjopen-2015-009128

Tyrrell, J., Mulugeta, A., Wood, A. R., Zhou, A., Beaumont, R. N., Tuke, M. A., Jones, S., Ruth, K., Yaghootkar, H., Sharp, S., Ji, Y., Harrison, J., Freathy, R., Murray, A., Weedon, M., Lewis, C., Frayling, T., Hyppönen, E., & Thompson, W. D. (2019). Using genetics to understand the causal influence of higher BMI on depression. *International Journal of Epidemiology*, *48*(3), 834-848. https://doi.org/10.1093/ije/dyy223

United States Census Bureau (2020). Quick Facts, Texas https://www.census.gov/quickfacts/fact/table/TX/PST045221

Vaccarino, V., Badimon, L., Bremner, J. D., Cenko, E., Cubedo, J., Dorobantu, M., Duncker, D.J., Koller, A., Manfrini, O., Milicic, D., Padro, T., Pries, A.R., Quyyumi, A.A., Tousoulis, D., Trifunovic, D., Vasiljevic, Z., De Wit, C., Bugiardini, R., & ESC Scientific Document Group Reviewers Lancellotti Patrizio Carneiro António Vaz. (2020). Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *European Heart Journal*, *41*(17), 1687-1696. https://doi.org/10.1093/eurheartj/ehy913

Vallerand, I. A., Patten, S. B., & Barnabe, C. (2019). Depression and the risk of rheumatoid arthritis. *Current Opinion in Rheumatology*, *31*(3), 279. https://doi.org/10.1097%2FBOR.0000000000000597

Velligan, D. I., Sajatovic, M., Hatch, A., Kramata, P., & Docherty, J. P. (2017). Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. *Patient Preference and Adherence*, *11*, 449. https://doi.org/10.2147/PPA.S124658

Villarroel, M. A., & Terlizzi, E. P. (2020). Symptoms of Depression among Adults: the United States, 2019. *Centers for Disease Control and Prevention: Atlanta, GA, USA*. https://www.cdc.gov/nchs/data/databriefs/db379-H.pdf

Vogt, W. P., Gardner, D. C., Haeffele, L. M., & Vogt, E. R. (2014). *Selecting the right analyses for your data: Quantitative, qualitative, and mixed methods*. Guilford Publications.

Wade, D. T., & Halligan, P. W. (2017). The biopsychosocial model of illness: a model whose time has come. *Clinical Rehabilitation*, *31*(8), 995-1004. https://doi.org/10.1177/0269215517709890

Wang, S. M., Han, C., Bahk, W. M., Lee, S. J., Patkar, A. A., Masand, P. S., & Pae, C. U. (2018). Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Medical Journal*, *54*(2), 101-112. https://doi.org/10.4068/cmj.2018.54.2.101

Wasil, A. R., Venturo-Conerly, K. E., Shinde, S., Patel, V., & Jones, P. J. (2020). Applying network analysis to understand depression and substance use in Indian

adolescents. *Journal of Affective Disorders*, *265*, 278-286. https://doi.org/10.1016/j.jad.2020.01.025

Wichniak, A., Wierzbicka, A., Walęcka, M., & Jernajczyk, W. (2017). Effects of antidepressants on sleep. *Current Psychiatry Reports*, *19*(9), 1-7. https://doi.org/10.1007/s11920-017-0816-4

Williams, A., Mertz, K., & Wilkins, T. L. (2014). Issue brief: Medication adherence and health I.T. *Washington, DC: Office of the National Coordinator for Health Information Technology, Department of Health and Human Services*. https://www.ehidc.org/sites/default/files/resources/files/medicationadherence_and_hit_issue_brief_ONC.pdf

Woldu, H., Porta, G., Goldstein, T., Sakolsky, D., Perel, J., Emslie, G., Mayes, T., Clarke, G., Ryan, N., Birmaher, B., Wagner K. D., Asarnow, J. R., Keller, M., & Brent, D. (2011). Pharmacokinetically and clinician-determined adherence to an antidepressant regimen and clinical outcome in the TORDIA trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(5), 490-498. https://doi.org/10.1016/j.jaac.2011.01.018

World Health Organization (2017). *Depression and other common mental disorders.* WHO Document Production Services, Geneva, Switzerland. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

World Health Organization (2017). Depression and other common mental disorders: global health estimates. *WHO*.

https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?s

World Health Organization (2022). Gender and health. WHO. https://www.who.int/health-topics/gender#tab=tab_1

World Health Organization (2003). Adherence to long-term therapies. Evidence for action. 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pd

Wu, Q., & Kling, J. M. (2016). Depression and the risk of myocardial infarction and coronary death: A meta-analysis of prospective cohort studies. *Medicine, 95*(6). https://doi.org/10.1097%2FMD.0000000000002815

Yu, M., Zhang, X., Lu, F., & Fang, L. (2015). Depression and risk for diabetes: A meta-analysis. *Canadian Journal of Diabetes, 39*(4), 266-272. https://doi.org/10.1016/j.jcjd.2014.11.006

Xu, D., Gong, W., Gloyd, S., Caine, E. D., Simoni, J., Hughes, J. P., Xiao, S., He, W., Dai, B., Lin, M., Nie, J., & He, H. (2018). Measuring adherence to antipsychotic medications for schizophrenia: Concordance and validity among a community sample in rural China. *Schizophrenia Research, 201*, 307–314. https://doi.org/10.1016/j.schres.2018.05.014.

Yap, A. F., Thirumoorthy, T., & Kwan, Y. H. (2016). Medication adherence in the elderly. *Journal of Clinical Gerontology and Geriatrics, 7*(2), 64-67. https://doi.org/10.1016/j.jcgg.2015.05.001

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M.,

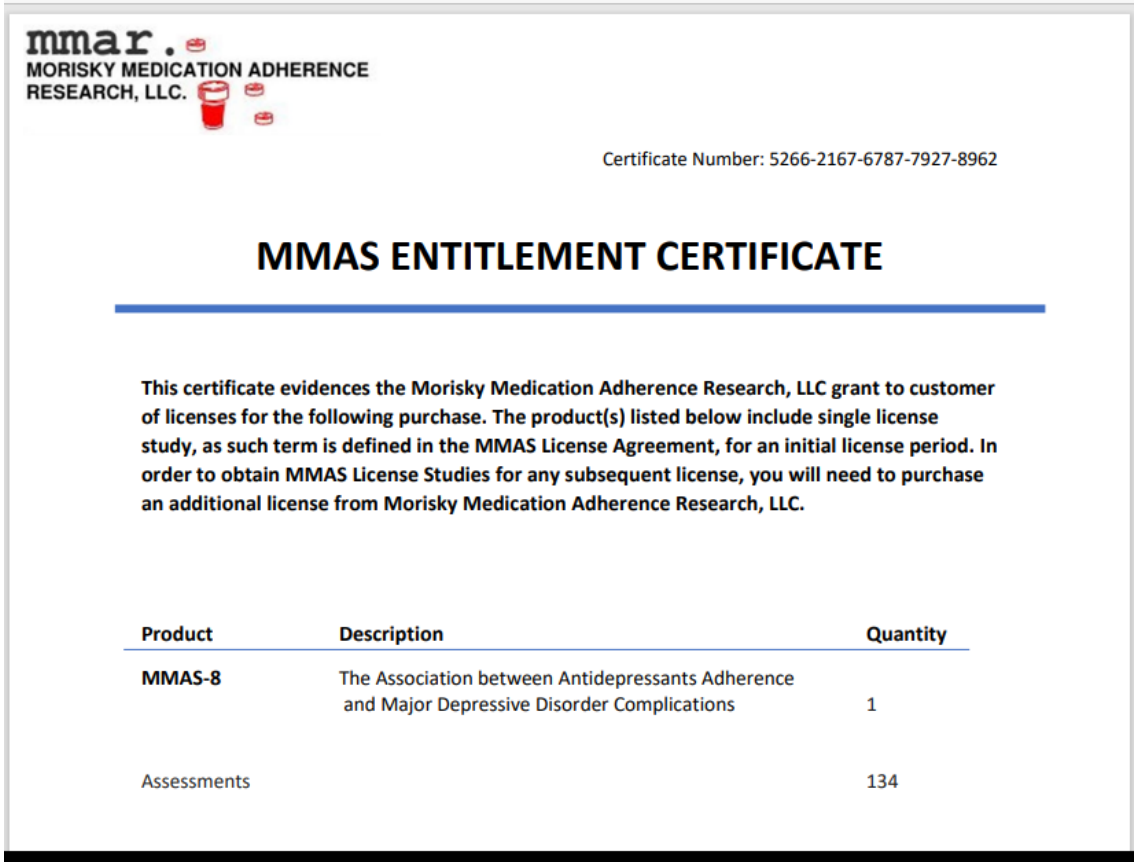
Budaj, A., Pais, P., Varigos, J., Lisheng, L., & INTERHEART Study Investigators. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*, *364*(9438), 937-952. https://doi.org/10.1016/s0140-6736(04)17018-9

Zhang, L. J., Zeng, X. T., Zhao, M. J., He, D. F., Liu, J. Y., & Liu, M. Y. (2020). The important effect of 5-HTTLPR polymorphism on the risk of depression in patients with coronary heart disease: a meta-analysis. *BMC Cardiovascular Disorders*, *20*(1), 1-8. https://doi.org/10.1186/s12872-020-01424-1

Zhou, Q., Wu, Z. G., Wang, Y., Liu, X. H., Chen, J., Wang, Y., Su, Y., Zhang, C., Peng, D., Hong, W., & Fang, Y. R. (2019). Clinical characteristics associated with therapeutic nonadherence of the patients with major depressive disorder: A report on the National Survey on Symptomatology of Depression in China. *CNS Neuroscience & Therapeutics*, *25*(2), 215-222. https://doi.org/10.1111/cns.13030

Zipursky, R. B. (2014). Why are the outcomes in patients with schizophrenia so poor? *The Journal of Clinical Psychiatry*, *75*(Suppl 2), 20-24. https://doi.org/10.4088/jcp.13065su1.05

Appendix: MMAS-8 Authorization



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Product	Description	Quantity
MMAS-8	The Association between Antidepressants Adherence and Major Depressive Disorder Complications	1
Assessments		134