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The Association Between Medication Adherence in Mental Illness and Substance Use Disorder Relapse in Patients with Dual Diagnosis

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THE ASSOCIATION BETWEEN MEDICATION ADHERENCE IN MENTAL ILLNESS AND SUBSTANCE USE DISORDER RELAPSE IN PATIENTS WITH DUAL DIAGNOSIS

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ABSTRACT

THE ASSOCIATION BETWEEN MEDICATION ADHERENCE IN MENTAL ILLNESS AND SUBSTANCE USE DISORDER RELAPSE IN PATIENTS WITH DUAL DIAGNOSIS

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Thesis supervised by Dr. Jordan Covvey

Objectives: The aims of the study were to (1) identify personal, social, and clinical history for patients with substance use disorder (SUD) and mental illness, (2) measure agreeance between patient self-report versus facility record history for mental illness, substance abuse, and psychotropic medication, (3) investigate the specific role of medication adherence and barriers to use for psychotropic medications upon SUD relapse, and (4) assess follow-up changes in mental illness severity and medication adherence in dual diagnosis patients enrolled in a substance abuse rehabilitation program. **Methods:** The pilot study utilized a mixed methodology. Inclusion criteria included male patients at least 18 years of age who were newly admitted at a 90-day residential rehabilitation program with a self-reported diagnosis of SUD, and either major depressive

disorder (MDD), bipolar disorder, generalized anxiety disorder (GAD) or schizophrenia. Patients were evaluated within their first week of treatment and follow-up interviews were conducted at 1 and 2 months. Facility records were accessed to cross-reference patient reported data, using Cohen's kappa coefficient to determine agreement. Patient demographic characteristics, substance abuse characteristics, health-related characteristics, and attitude towards medications stratified by adherence rates and relapse rates utilizing ANOVA and t-tests. Pearson's correlation coefficient was utilized to analyze the relationship between medication adherence and SUD relapse. A multivariable logistic regression model was created to assess the impact of adherence on relapse frequency. Patient and clinical characteristics were stratified according to follow-up interviews completed utilizing ANOVA and t-tests. Lastly, changes in patients' self-reported adherence from interview to interview were analyzed using mean difference. SPSS Statistics (IBM Corp; Armonk, NY) was utilized for all analyses, with a two-tailed level of significance at 0.05.

Results: The final sample consisted of 38 patients. The majority of patients were white (n=27, 71.1%), unemployed (n=32, 84.2%), and homeless (n=30, 78.9%). Heroin was the most common primary drug of use (n=19, 50%), followed by alcohol (n=12, 31.6%), and crack cocaine (n=4, 10.5%). The average length of substance use was 20.3 years. Half of the patients (n=19, 50%) had two or more mental illness diagnoses and the most common was the combination of MDD and GAD (n=9, 23.7%), followed by MDD alone (n=7, 18.4%), and bipolar disorder (n=6, 15.8%). Significant agreeance was found between patient self-reported data to facility records for primary substance of use (κ=0.753, $p<.001$), mental illness diagnosis (κ=0.434, $p<.001$), number of mental illness

comorbidities (κ=0.257, p=0.008), and number of psychotropic medications prescribed (κ=0.094, p<.001). Patients self-reported less comorbid diagnoses and more previous treatment stays compared to facility records. Patients receiving income prior to admission had higher relapse rates (16.9 vs 8.1, p=0.02). Self-reported relapse rate was negatively correlated with the Morisky Medication Adherence Scale (MMAS-8) intentional score (r= -.360, p=.026), MMAS-8 total score was positively correlated with self-reported adherence rates (r=.618, p<.001), the MMAS-8 intentional score (r=.869, p<.001), and the MMAS-8 unintentional score (r=.863, p<.001). MMAS-8 intentional score was positively correlated with MMAS-8 unintentional score (r=.552, p<.001) and self-reported adherence rate (r=.613, p<.001). Lastly, the MMAS-8 score was positively correlated with self-reported adherence rate (r=.481, p<.001). For the regression model, MMAS-8 total score was a significant predictor of relapse rate (stand. beta = -.443, CI= -6.37-0.23, p=.048) but the linear combination of the measures included was not significantly related to self-reported relapse rate (F=2.25, adjusted R2 =.145, p=.073). A total of 12 patients (31.6%) fully completed the study, 15 patients (39.5%) only participated in the first follow-up, and 11 patients (28.9%) only participated in the primary interview. DAI-10 total scores were lower in patients who only completed the primary interview vs. patients who completed the entire study (4.0 vs 7.0, p=.044). There was a significant increase in adherence at the first (mean difference=5.7, p<.001) and second (mean difference=6.5, p<.001) follow-ups compared to the primary interview.

Conclusions: The study provided valuable insight into the relationship between psychotropic medication adherence and SUD relapse in patients with dual diagnosis which can be used by healthcare professionals and drug abuse rehabilitation programs.

DEDICATION

To my parents, Brian and Sue, and my brothers, Brian and Connor.

I would not be where I am today without you.

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Lastly, I would like to thank all of the patients who enrolled in the study. While experiencing a very stressful life event, they gave their time to help shed light on how we can better help patients with dual diagnosis.

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CHAPTER 1 – INTRODUCTION

I. Mental Illness

a. Definition, burden, and impact

Mental illness refers to a wide range of mental health conditions characterized by abnormal thoughts, perceptions, emotions, and behaviors that result in suffering or poor ability to function in life.[1] The Diagnostic and Statistical Manual, 5th Edition (DSM-5) defines mental illness as "*a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning*."[2] A serious mental illness (SMI) is defined as any mental, behavioral, or emotional disorder that substantially interferes with one or more major life activities.[3]

Mental illness has a substantial impact on the population at-large. The World Health Organization (WHO) World Mental Health (WMH) Survey Initiative is a project that aims to obtain and assess accurate data about the worldwide prevalence of mental, behavioral, and substance disorders in 28 counties across 154,000 individuals. The WHM Survey Initiative's most recent data from 2009 found the inter-quartile range (25th–75th percentiles across countries) of mental illness prevalence in the participating countries to be between 18.1% and 36.1%. The worldwide prevalence of SMI was estimated between 4% and 6.8% in half of the countries surveyed, between 2.3% and 3.6% in one-quarter of the countries, and between 0.8% and 1.9% in rest of the countries. A significantly higher 12-month prevalence of mental illness was found in the United States (US; 27.0%), Ukraine (21.4%), Colombia (21.0%), New Zealand (20.7%),

and France (18.9%) while Japan (7.4%), China (7.1%), and Nigeria (6.0%) had a significantly lower prevalence.[4]

The National Survey on Drug Use and Health (NSDUH) is an annual survey of the US population with the purpose of collecting information and identifying trends of behavioral health in citizens 12 years and older. In 2016, NSDUH identified 44.7 million adults over the age of 18 as having a mental illness, accounting for 18.3% of the total population. NSDUH also found that 10.4 million adults had a SMI within the past year (4.2%). The number of adults with mental illness in the population remained stable from 2008 to 2016. Mental illness had a higher prevalence among adults 26 to 49 years old (21.1%) and 18 to 25 years old (22.1%) compared to adults aged 50 or older (14.5%).[5]

Mental illness results in a high economic burden due to its debilitating effect on the patient's capacity to function. Therefore, unlike other common medical conditions, mental illness has higher indirect costs than direct costs. Notable indirect costs include reduced labor force participation, caregiver burden, public disability supplementation, and costs associated with imprisonment and homelessness. The annual loss of earnings alone is estimated to be $193.2 billion per year.[6] When combining indirect and direct costs, mental illness is estimated to cost the US approximately $317 billion per year, or more than $1,000 per capita.[7]

Mental illness has an impact on patient's functioning ability due to its effect on basic activities of daily living, interpersonal relationships, and the ability to function in the workplace. According to the WHO, mental and behavioral disorders account for 13.6% of the total US disability-

adjusted life years (DALYs), ranked third in DALYs in the US, only behind cardiovascular and circulatory disorders and neoplasms.[8] In study of global burden of diseases by Gore *et al*., researchers concluded that 45% of all DALYs of youth between 10 and 24 years old were attributed to psychiatric disorders.[9] It is estimated that there are currently 165,000 homeless people in the US who suffer from a serious mental illness.[10] The debilitating nature of the disease may play a role in this high prevalence rate. The high level of DALYs and rate of homelessness in mentally ill patients shows that not only is mental illness highly prevalent, but also has a significant impact on the functioning ability of those who are affected by it.

b. Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) is the classification and diagnostic tool used by healthcare professionals worldwide to diagnose a clinical mental disorder. The goal of the DSM-5 is to ensure that clinicians can accurately and consistently diagnose patients with mental illness. The DSM is reviewed and revised periodically by the American Psychiatric Association (APA) to adjust to new advances and discoveries in mental health research. The current 5th edition was published in 2013.[11] The DSM-5 is often used to make decisions regarding treatment plans and payments, therefore it provides a uniform tool for healthcare professionals to use to avoid variability that may have a negative impact on the patient.

In addition to DSM-5, other mental health assessment tools are utilized during the mental illness diagnosis process in order to enable an earlier identification of the disease and prevent a misdiagnosis, therefore, leading to a more effective treatment plan. They also provide medical

professionals with a common objective metric that can assure a consistency in diagnoses. Although a medical professional is needed to make a clinical diagnosis, these tools also assist patients with a quick, easy, and low-cost way to determine if they are experiencing mental illness symptoms. Mental health assessments tools can be used as general mental health screening tools or can be disorder specific severity measures.[12]

c. Etiology and risk factors

The exact causation of mental illness is complex and fluctuates from condition to condition. Risk factors for the development of mental illnesses include genetics, environmental factors, social influences, and illicit drug use.

Multiple studies have indicated that genetic factors play a role in the development of mental illness. Sellers *et al*. conducted a longitudinal study to assess if a mother's recurrent depression predicted new-onset psychopathology in their children.[13] The study found that the number of co-occurring mental illnesses in the mother (0, 1, or 2+) predicted new-onset offspring disorders (OR = 1.80, 95% CI 1.17–2.77, p = 0.007), therefore concluding an increased risk of future onset psychiatric disorders in offspring from pre-existing mental illness.[13] Another study conducted by Singh *et al*. set out to assess the link between genetics and mental illness by administering structured interviews among twins, their spouses, and their children; this demonstrated an association between parental and offspring depression (HR 1.52, CI 1.20–3.93, $p \leq .05$). After controlling for measured covariates such as sex, divorce rate, and education level, this association was found to be due to shared genetic liability.[14]

Studies have also shown mental illness to be linked to environmental factors surrounding pregnancy and birth. A population study done in the UK by Dorrington *et al.* found an association between psychosis in offspring and the mother experiencing stressful life events while pregnant (OR = 1.10, CI 1.02–1.18, $p \leq .05$).[15] A wide variety of other prenatal environmental conditions and stressors are correlated with mental illness such as fetal hypoxia,[16] maternal infections,[17] maternal exposure to influenza[18] and maternal malnutrition.[19]

Social influences and external factors have been shown to have an effect on the development and severity of mental illness in those who are genetically and biologically vulnerable to mental illness. Recent studies have linked the development of mental illness to sexual abuse,[20] physical abuse,[21] emotional abuse,[22] domestic violence[23] and bullying.[24] Childhood trauma such as poor parenting and neglect has been found to be a risk factor for both depression and anxiety.[25,26]

Substance abuse, especially long-term use, can increase the risk of mental illness. Heavy alcohol use or dependence has been linked to major depressive disorder.[27] Heavy marijuana use, especially at a young age, has been linked to depression and anxiety.[28] Marijuana users are at double the risk of having a psychotic episode or developing long-term schizophrenia, and children who use marijuana at before the age of 20 have a higher risk of developing bipolar disorder.[29] The use of drugs such as cocaine and amphetamines have been found to put an individual at a higher risk of developing schizophrenia.[30]

d. Treatment modalities

There are different methods to treat mental illness, with the most effective treatment plans being the ones tailored to patient- and condition-specific needs. A variety of different healthcare professionals can provide mental health treatment such as primary care physicians, psychiatrists, psychiatric health nurse practitioners, clinical psychologists, psychiatric pharmacists, and social workers. Facilities that provide mental illness treatments include hospitals, clinics, and a variety of different community mental health services. Mental illness is typically treated through a combination of psychotropic medications and psychotherapies but other complementary treatment modalities can be added to a patient's care plan.[31]

Psychotropic medications play a key role in the treatment of mental illness. The five main psychotropic categories are antidepressants for depression, anti-anxiety or anxiolytics for anxiety disorders, antipsychotics for psychosis disorders such as posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) and schizophrenia, mood stabilizers for bipolar disorder, and stimulants for attention deficit disorders (ADD).[32] If taken as prescribed, psychotropic medications have been shown to be efficacious in treating mental illness. In a meta-analytic study of the short-term efficacy of antidepressants versus a placebo, Storosum *et al.* found significant decrease in symptom severity using the Hamilton Depression Rating Scale.[33] Another meta-analysis conducted by Barbui *et al.* concluded that paroxetine, a selective serotonin reuptake inhibitor (SSRI), was more effective than placebo in increasing the amount of patients who experienced improvement in at least half of their symptoms (RR 0.83, 99% CI 0.77–0.90).[34] The mood stabilizer lithium has been found to be highly effective in treating bipolar disorder, reducing the frequency of symptom relapse by 50% (Hedges- Olkin effect size =0.68, CI =0.60-

0.76).[35] While a majority of studies show psychotropic medications to be efficacious, their outcomes may vary due to factors such as disease severity, duration of disease, and comorbidities.

Psychotherapy refers to a variety of treatment techniques that aim to help a patient overcome the negative effects of the mental illness they are struggling with. Through psychotherapy, a psychologist helps the patient understand their condition and develop healthier and more effective habits of coping with the condition. There are different types of psychotherapies including cognitive behavioral therapy, interpersonal therapy, family therapy, and condition specific therapies.[36] Of the types of psychotherapies, cognitive behavioral therapy (CBT) is the most commonly used in the treatment of mental illness. CBT is short-term and talk-centered psychotherapy that aims to improve the patient's underlying thoughts and actions that result in negative experiences. CBT helps improve the patient's cognitive processes by changing their current thoughts, personal images, beliefs, and attitudes in regard to their emotional problems. CBT is especially effective in the mental illness population due to its focus on teaching patients coping skills and how to apply these skills to their current situation. Those with mental illness experience a decrease in functioning ability and have a higher need for the development of coping skills. For example, a patient with major depressive disorder (MDD) may learn how to pay more attention to their negative thoughts and approach them with a more realistic analysis therefore preventing the patients from experiencing a decrease in mood. CBT is also effective for mental illness treatment due to its focus on improving one's self-beliefs. For example, mental illness patients may feel inferior, mentally flawed, or stigmatized by others. CBT helps patients dispel those beliefs and accept oneself for who they are.[37]

Along with psychotherapy and medications, a patient with mental illness may also consider other treatment options to supplement their care plans. Lifestyle changes such as dietary adjustments, gainful employment, stress reduction, and peer support have been showed to help decrease symptoms in certain conditions such as depression and anxiety.[38] Non-clinical interventions have also been shown to be effective treatment options. A study by Talwar *et al*. found that a combination of music therapy plus standard care can reduce symptom severity in patients with schizophrenia when compared to standard care alone.[39] Yoga has also been found to improve the symptoms of mental disorders. In a meta-analysis conducted by Klatte *et al*., body-oriented yoga was found to lower a patient's mental illness symptom severity (Hedges' g = 0.91; 95% confidence interval 0.55-1.28).[40] In rare cases, psychosurgery treatments can be utilized such as transcranial magnetic stimulation, vagal nerve stimulation, stem cell therapy, deep brain stimulation, and electroconvulsive therapy.[41,42]

e. Specific mental illness conditions

i. Major depressive disorder

Major depressive disorder (MDD), commonly referred to as clinical depression, is the most common mental illness in the US. MDD negatively affects one's emotions, thoughts, and actions causing the patient to be in a state of sadness and disinterest. Characteristics of MDD include depressed mood, loss of interest in activities, changes in appetite, trouble sleeping, fatigue, restlessness, decreased concentration, and thoughts of suicide.[43] In the Global Burden of Disease Study of 2013, approximately 253 million people or 3.6% of the global population were found to be affected by MDD.[44] In 2015, the National Institute of Mental Health (NIMH) estimated that

16.1 million or 6.7% of the US population aged 19 or older suffer from MDD. MDD accounts for 3.7% of all US DALYs, the highest among mental disorders.[45] The annual cost of illness is approximately $210.5 billion with 45-47% accounting for direct costs, 48-50% accounting for loss of productivity, and 5% to suicide-related costs.[46]

A diagnosis of MDD requires a patient to have a depressed mood or loss of interest in nearly all normal activities for at least two weeks duration. The patient must also have at least three of the following symptoms: insomnia or hypersomnia, feelings of worthlessness or excessive guilt, fatigue or loss of energy, diminished ability to think or concentrate, substantial change in appetite or weight, psychomotor agitation, and recurrent thoughts of death or suicide.[47] Not all patients with MDD experience the same symptoms. The severity, duration, and frequency of MDD symptoms vary according to the individual patient and also depend on the stage of the illness.[48] The Patient Health Questionnaire (PHQ-9) is the most commonly used MDD assessment tool, which consists of ten questions assessing the frequency and severity of the patient's MDD symptoms.[12]

Treatment for MDD utilizes a combination of medication and psychotherapy. Medication options for patients with MDD include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Medication choice is based on patient preference, history of prior medication, safety, tolerability, side effects, and cost. Generally, MAOIs are only prescribed to patients who have not responded to previous medications.[49] TCAs and MAOIs are first generation medications that enhance the body's serotonin and norepinephrine production

mechanism but also block histaminic and cholinergic receptors sites therefore resulting in unwanted medication side effects. SSRIs and SNRIs are new generation antidepressants that target specific brain receptor sites therefore resulting in less unwanted side effects.[50] Lifestyle changes such as physical activity and diet change are also recommended to help counteract the symptoms of MDD.[51]

ii. Generalized anxiety disorder

Anxiety disorders are states of abnormal and excessive nervousness, anxiousness, and fear. Generalized anxiety disorder (GAD) is a chronic mental illness in which a patient is in a constant state of worriedness that interferes with his or her daily activities. GAD can also cause physical symptoms such as restlessness, fatigue, lack of concentration, muscle tension, and problems sleeping. Due to the severe symptoms of GAD, patients usually struggle with holding a job or completing everyday activities.[52] Kessler *et al*. estimated that the lifetime prevalence of GAD in the US at 4.3% and the twelve-month prevalence at 2.0%.[53] In general, GAD is more likely to affect females than males.[54] GAD also has a high economic burden on patients, with a mean annual direct medical cost for a patient with GAD estimated at $6,475.[55]

According to the DSM-5, a diagnosis of GAD requires a patient to have excessive anxiety on the majority of the days for at least six months, difficulty controlling their worrying, and three or more of the following symptoms; restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance.[56] A thorough mental health evaluation is essential to a GAD diagnosis due to the high risk of a misdiagnosis. Anxiety can be brought on by other physical health conditions such as hyperthyroidism or hypoglycemia. Certain medications may

result in anxiety as a side-effect. Other untreated mental illnesses such as OCD and MDD can also increase a patient's anxiety level.[57] The Generalized Anxiety Disorder – 7 item scale (GAD-7) is the most commonly used screening tool that helps indicate whether or not a patient requires a complete clinical assessment for GAD. The GAD-7 assess the frequency of common GAD symptoms over the past 2 weeks, ranging from symptoms are not present at all to symptoms are present nearly every day.[12]

Medications are used to relieve the symptoms of GAD but they do not cure the disorder itself. Anti-anxiety medications are used to reduce the symptoms of GAD including excessive anxiety, panic attacks, and extreme fear and worry.[57] Benzodiazepines are the first-line anti-anxiety medications for GAD but should only be used short-term due to their high potential of dependence and abuse.[32] Benzodiazepines treat GAD by inducing relaxation in the patient and reducing muscular tension. Beta-blockers can be prescribed to help relieve the physical symptoms of GAD such as rapid heartbeat, shaking, and trembling. Antidepressants have also been shown to be effective for treating anxiety.[57] Stress management, meditation, and support groups have also been shown to help alleviate the symptoms of GAD.[52]

iii. Bipolar disorder

Bipolar disorder, sometimes referred to as manic-depressive disorder, is characterized by unusual and extreme shifts in mood, energy, activity levels, and ability to function in everyday activities. Patients with bipolar disorder experience shifts in emotional episodes ranging from manic highs to depressive lows. The side-effects of a manic episode include feeling euphoric, high energy, trouble sleeping, and exhibiting risky behavior such as spending money or engaging in unsafe

sexual practices. The side-effects of depressive episodes include extreme sadness, low energy, over sleeping, anxiety, trouble concentrating, and thoughts of suicide.[58] A patient can be diagnosed as either bipolar I or bipolar II. While both of these diagnoses include similar depressive episodes, bipolar I patients experience much more severe mania episodes compared to bipolar II patients. Bipolar II patients experience hypomania, which is a less severe form of mania that would be considered atypical but not abnormal. Bipolar I patients exhibit manic behaviors which are more extreme and abnormal.[59] In the US adult population, the lifetime prevalence of bipolar disorder is estimated to be 3.9% and the annual prevalence is 2.6%. Bipolar disorder is more likely to affect younger patients between 18-29 years old and a lower prevalence is seen in the older population above the age of 60. The average age-of-onset is 25 years old.[60] A systematic review of cost of illness studies for bipolar disorder conducted by Kleine-Budde *et al*. found that the cost per capita in the US ranged from $8,000 to $14,000 per year in direct healthcare costs and $2,000 to $11,000 in indirect costs.[61]

Bipolar disorder is usually diagnosed in adolescence or early adulthood but can occur at any age.[62] Diagnosing a patient with bipolar disorder is difficult due to the various other mental illnesses that share similar symptoms such as MDD, substance-induced mood disorder, ADHD, and conduct disorder.[63] Another reason diagnosing is difficult is because a patient is more likely to seek treatment during a depressive state compared to a maniac state therefore possibly receiving an inaccurate MDD diagnosis.[58] The most common screening tool for bipolar disorder is the Mood Disorder Questionnaire (MDQ), which consists of 13 questions evaluating the presence of common symptoms.[12] Other measures and rating scales used to evaluate bipolar

disorder include the General Behavior Inventory (GBI), the Bipolar Spectrum Diagnostic Scale (BSDS), and the Hypomania Checklist (HCL-32).[64]

While there is no cure for bipolar disorder, medications are used to control the manic and depressive episodes. Mood stabilizers help the patient control mood swings by decreasing abnormal brain activity. Antipsychotics are typically prescribed to help manage the psychosis caused by the manic phases such as delusions or hallucinations. Antidepressants are used to treat the depressive phase of bipolar disorder in the same way they are used to treat MDD. A patient taking medication for bipolar disorder should be heavily monitored by their doctor or pharmacist. When a patient is experiencing a manic phase, they may believe they do not need to take the medication and sudden stoppage of bipolar medication leads to worsening of symptoms and in some cases to potentially fatal withdrawal side-effects.[32]

iv. Schizophrenia

Schizophrenia is defined as a long-term mental illness characterized by a breakdown of thoughts, emotions, and behaviors that cause a patient to have a distorted perception of reality, leading to inappropriate actions and a withdrawal from everyday life. Although schizophrenia is less prevalent than other mental disorders, it is associated with more severe and debilitating symptoms. There are three different categories of symptoms that a patient with schizophrenia experiences: positive symptoms, negative symptoms, and cognitive symptoms. Positive symptoms are psychiatric behaviors that are not present in those without schizophrenia. These symptoms include visual or audible hallucinations, delusions, extreme paranoia, and unusual or dysfunctional thoughts. Negative symptoms are deficits in normal emotional or physical

processes such as extreme reduction in emotional expression, reduced feeling of pleasure, lack of speech, lack of motivation, and lack of desire to engage in social relationships. Cognitive symptoms are deficits impacting the cognitive functioning of the patient. These symptoms include a poor ability to understand information or make decisions, trouble paying attention, and poor memory.[65]

There are currently more than 2.6 million people in the US that suffer from schizophrenia which reflects 1.1% of the population.[65] Of those 2.6 million patients, it is estimated that 40% are untreated.[66] There are significantly more males affected by schizophrenia than females.[67] Schizophrenia has a high economic burden due to the disease's high disability; Chong *et al*. estimated the total economic burden for the US at $102 million, with indirect costs responsible for 50-85% of the total cost of illness.[68]

Schizophrenia is usually diagnosed when the patient is between 16 and 30 years old but in some rare cases, children have also been diagnosed with the disease.[65] According to the DSM-5, a diagnosis of schizophrenia requires a patient to have three of the five following symptoms: delusions, hallucinations, disorganized speech, disorganized or cationic behavior, and negative symptoms.[69] The Brief Psychiatric Rating Scale (BPRS) is a tool used to assess the severity of 18 symptoms that are commonly associated with schizophrenia such as anxiety, grandiosity, hostility, hallucinations, and emotional withdraw. The BPRS can be used to evaluate if a patient is schizophrenic or to assess the efficacy of schizophrenia treatment.[70]

The causation of schizophrenia is relatively unknown; therefore, the treatment of the disease focuses on controlling symptoms. Schizophrenia is treated through a combination of antipsychotics and psychotherapy. Coordinated specialty care (CSC) is a vital part of schizophrenia treatment due to the severity of the disease. CSC is the integration of typical medication and psychotherapy treatment with other supplemental treatments such as case management, family involvement, supported education, and employment services in order to reduce symptoms and improve the patient's quality of life.[65]

II. Substance Use Disorder

a. Definition, burden and impact

Clinicians classify the level to which patients use illicit drugs or alcohol into three categories; substance use, substance abuse, and substance use disorder (SUD). The purpose of using these terms is to help professionals determine the severity of the impact that substance use has on the user's ability to function. Substance use refers to the low frequency and irregular use of illicit drugs. Typically, a person's life is not significantly impacted by substance use until the pattern evolves into substance abuse.[71]

Substance abuse refers to the repeated use of psychoactive substances such as alcohol and illicit drugs, despite known harmful consequences, one or more times in a twelve-month period that leads to significant impairment.[72,73] The results of substance abuse may include struggling with home, work, and school obligations, substance-related legal problems, and interpersonal problems.[73] In 2014, 27 million people in the US were identified as illicit drug users, accounting for 10% of the US population.[3]

Substance use disorder (SUD), commonly referred to as drug addiction, is a distinct medical condition that falls under the mental illness umbrella, but will be discussed as a separate entity in order to establish a clear distinction. SUD is defined by the DSM-5 as "*the recurrent use of alcohol and/or drugs causing clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home*."[74] Substance abuse progresses into SUD when the user develops a tolerance to the drug, uses for an extended period of time, experiences difficulty stopping or controlling use, and experiences withdrawal symptoms when not using.[73] In 2014, 21.5 million people in the US had a SUD in the past year, 8.1% of the total population. Of those 21.5 million, 1.3 million were between the ages of 12 to 17, 5.7 million were between 18 to 25 years old, and 14.5 million were 26 year or older.[3]

Substance abuse and SUD result in a large economic burden to the US due to lost productivity, direct healthcare costs, and crime. It is estimated that the annual cost of substance use is more than $600 billion.[75] According to the National Drug Threat Assessment created by the US Department of Justice's National Drug Intelligence Center, substance use results in more than $120 billion per year in lost productivity. This includes reduced labor participation ($49 billion), loss of productivity due to incarceration ($48 billion), and drug-related deaths ($4 billion).[76] An estimated 67% of current drug users over the age of 18 are employed either part-time or full-time. Another large societal cost due to drug use are criminal justice costs such as criminal investigations, prosecutions, incarcerations, and victim costs, estimated at $61 billion annually.[77]

Substance abuse often leads to other medical problems therefore resulting in more complications and a lower quality of life for the patient. The injection of drugs such as heroin, cocaine, and methamphetamine play a major role in the spread of infection diseases including HIV/AIDS, hepatitis B, and hepatitis C.[78] Injection drug use accounts for roughly 12% of all new AIDS cases.[79] Excessively consuming alcohol damages many vital organs including the brain. Cocaine and other stimulant use can lead to complications of the heart, respiratory system, nervous system, and the digestive system. Due to the intoxicating effect of drug use, many users engage in frequent and unsafe sexual practices, therefore increasing their likelihood of contracting a sexually transmitted disease.[78]

b. Diagnosis

According to the DSM-5, a clinical diagnosis of SUD requires a patient to exhibit a minimum of two of the following symptoms: 1) Overconsumption or consuming more than originally planned, 2) failure to control one's use of the substance, 3) spending extended amounts of time using, 4) failing to fulfill major obligations such as school, work, or home duties, 5) experiencing cravings for the substance, 6) continued use despite physical and mental health problems, 7) continued use despite negative effects on social life, 8) using the substance in a dangerous way such as drinking and driving, 9) withdrawing from regular activities due to use of substance, 10) building a tolerance to the substance, and 11) experiencing withdraw symptoms.[80] A diagnosis of SUD then can be categorized according to severity level, ranging from mild to severe. A diagnosis of mild SUD requires the patient to display two or three of the listed symptoms, moderate requires four to five symptoms, and severe requires six or more symptoms.[81]

c. Etiology and risk factors

While it is still uncertain what exactly causes an individual to be prone to substance abuse, several studies have identified predicting factors. A majority of risk factors for substance abuse are thought to occur during the user's childhood or adolescence. In a study conducted by Kilpatrick *et al*., 4,000 adolescents were interviewed in order to determine risk factors for current substance abuse. The researchers concluded that children and adolescences who experienced or witnessed physical, verbal, or sexual abuse were more likely to develop a drug use habit later in life. The researchers also concluded that children who had a family member with SUD were more likely to use drugs, suggesting either an environmental or genetic link.[82] Another study conducted by White *et al*. found that childhood neglect and abuse play a significant role in the development of substance abuse.[83] In a study of 1,760 young adults, Barrett *et al.* reported that a child who was raised in a single parent household is more likely to use drugs in their lifetime when compared to children raised in a two-parent household.[84] In regards to alcohol, a study conducted by Ohannessian *et al.* found that children with parents who suffer from alcoholism have a higher predisposition to developing alcoholism later in life when compared to children of non-alcoholic parents.[85] Other factors that increase substance use risk include peer substance use, drug availability, early aggressive behavior, and low socioeconomic status.[86]

d. Treatment modalities

As with most mental illnesses, SUD is treated through a patient-tailored combination of psychological therapy and medication therapy. Initial treatment of acute withdrawal often includes medical detoxification, which is a set of medical interventions with the purpose of managing acute intoxication and withdraw symptoms. Through detoxification, harmful toxins in

the bloodstream are eliminated though dieting, drug abstinence, withdrawal management, and medications. The most commonly used medications for detoxification are anxiolytics and methadone.[87] Detoxification is not required for certain drugs, including cocaine, methamphetamine, and marijuana, because the withdraw symptoms are not as severe compared to other drugs. Certain drugs absolutely require detoxification because the withdrawal symptoms are so severe that they may be fatal if not properly treated. These drugs include alcohol, heroin and opioid prescription drugs.[88]

After detoxification, it is recommended that the patient seeks help from a professional psychologist to make a treatment plan tailored to their needs with a focus on health, living situation, the individual's purpose for quitting, and community support.[89] There is currently a wide range of treatment options available including individual counseling and group counseling, inpatient and residential treatment, outpatient treatment, hospital programs, recovery support services, 12-step programs such as Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), and peer support groups. Cognitive-behavioral therapy has been shown to improve outcomes in SUD by helping the user recognize factors that lead to their negative behavioral patterns such as stressors, negative situations, and actions that lead to substance use.[90] Motivational interviewing has also been shown to be effective in implementing behavioral change in those with SUD.[91] Along with psychotherapy, the addition of social and family support has been shown to be critical to helping the patient adhere to their recovery plan.[90]

i. Relapse

SUD is a chronic disease and the recovery stage of the disease lasts for the entire duration of the patient's life. When a patient with SUD quits using for an extended period of time and then resumes using again, it is referred to as a relapse. Similar to most chronic diseases, those with SUD often experience periods of remission and relapse. Relapses are commonly caused by triggers, or external circumstances that cause the patient emotional or psychiatric distress such as anxiety, panic, stress, depression or discouragement.[92] Triggers can be classified into three groups: environmental, re-exposure, and stress. Environmental triggers are circumstances that the patient once associated with drug use such as social events or friends. Re-exposure triggers are events in which the patient is in the presence of drug use therefore leading the patient back to their previous drug seeking behavior. Stress triggers are events that cause intense emotional states such as anger, fear, anxiety, and sadness that lead the patient to returning back to use.[93] Experts suggest patients at risk of relapse identify triggers and develop an action plan of what steps to take when they find themselves in trigger situations.[92]

e. Specific substance use disorders

i. Alcohol

Of the 21.5 million people with a SUD last year, 17 million (6.4% of the total US population) had an alcohol use disorder. Alcohol use is broken down into three different categories: current alcohol use, binge alcohol use, and heavy alcohol use. These are the criteria used by the Substance Abuse and Mental Health Services Administration (SAHMSA) to categorize the levels of alcohol use and do not equate to a diagnosis of SUD. Current alcohol use is defined as a person having any alcoholic drink within the last 30 days. Binge alcohol use is defined as a

person having five or more drinks or drinking to a point of intoxication at least once in the last 30 days. Heavy alcohol use is defined as drinking five or more drinks or drinking to a point of intoxication five or more times in the past 30 days. In 2014, 139.7 million people were current alcohol users, 60.9 million people were binge alcohol users, and 16.3 million were heavy alcohol users.[3] In 2011, Bouchery *et al*. calculated the economic cost of alcohol consumption in the US including healthcare costs, productivity losses, and other miscellaneous costs such as property damage; the total estimated economic costs of excessive drinking were $223.5 billion, with 72.2% in lost productivity, 11% in healthcare costs, 9.4% in criminal justice costs, and 7.5% in other miscellaneous costs. This cost can be broken down to approximately $746 per person or $1.90 per alcoholic drink consumed per year.[94]

ii. Illicit drugs

Of the 21.5 million people with a SUD last year, 7.1 million had an illicit drug use disorder which represents 2.7% of the total population. An estimated 867,000 of those with illicit drug use disorder were between 12 and 17 years old, 2.3 million were between 18 and 25 years old, and 3.9 million were 26 years and older.[64] The most common illicit drug use disorders in the US are cannabis use disorder, stimulant use disorder, and opioid use disorder.[74] While there are many other SUDs prevalent in the population, the following three SUDs will be focused on because they are the most common in the US.

1. Marijuana

Marijuana is currently the most used illicit drug in the US. In 2014, 22.2 million people reported using marijuana within the last month, and 4.2 million met the criteria for a SUD based on their

marijuana use alone.[95] The short-term effects of marijuana include distorted perception, difficulty thinking and problem solving, and reduced motor skill coordination. The symptoms of cannabis use disorder include tolerance to the drug, drug cravings, difficulty sleeping, anxiety, anger, and depression. Long-term use has been proven to cause respiratory infection, impaired memory, and cancer. Early age marijuana use has also been linked to mental illness and poor cognitive functioning.[74]

2. Stimulants

Stimulants are drugs that increase alertness, attention, and energy, and have a high potential for abuse due to the euphoric state the user experiences. The term stimulants can refer to prescription medications such as methylphenidate or illicit drugs such as amphetamines, methamphetamines, and cocaine. In 2014, 1.6 million people were current nonmedical users of non-cocaine stimulants, of which 569,000 were current users of methamphetamine. It is estimated that 1.5 million people are current cocaine users of which 913,000 have a current cocaine use disorder.[3] Symptoms of stimulant use include drug cravings, loss of control of use, tolerance, high blood pressure, increased heart rate and respiration. The withdraw symptoms of stimulants include fatigue, trouble sleeping, increased appetite, and irregular or spastic movements.[74]

3. Opioids

Opioid use and abuse is currently a nationwide problem that is severely impacting the health, social, and economic state of the US. Opioid abuse can refer to the use of prescribed painkillers such as hydrocodone, oxycodone, morphine, and codeine in a manner that does not coincide with a physician's directions. Prescription opioids are prescribed to reduce a patient's pain but may be

taken recreationally due to the intense high and euphoria they induce. Opioid abuse can also occur when the patient takes the medication for pain but not according to physician recommendations. In 2014, it was estimated that 4.3 million Americans used a prescription opioid for nonmedical purpose and 1.9 million had an opioid use disorder due to prescription opioids.[96] In 2014, there were nearly 18,000 reported deaths due to prescription opioids, a 3.4-fold increase from 2001.[97] The most common drugs responsible for overdoses are methadone, oxycodone, and hydrocodone.[98] Experts contribute the severity of the problem to the increase in number of opioids prescribed by physicians, which has increased from 76 million in 1991 to 207 million in 2013. The US is the largest consumer of opioid drugs, prescribing nearly 100% of the world total of hydrocodone and 81% of the world total of oxycodone.[99] Over the past few decades, the U.S. Food and Drug Administration (FDA) has made a priority of solving the problems of opioid misuse, abuse, and addiction by targeting and improving drug development, drug packaging and labeling, prescriber and patient education, and addiction treatment efforts.[100]

In addition to prescription drugs, opioid abuse can also refer to the use of illicit substances such as heroin, a powerful and lethal opiate synthesized from morphine. Many heroin users misuse prescription opioids and then progress to using heroin due to the substantial cost difference. The side effects of heroin use include an intense euphoria, drowsiness, respiratory depression, and nausea. Symptoms of a heroin overdose include trouble breathing, blue lips and fingernails, uncontrollable sweating, convulsions, coma, and death.[96] In 2014, there were 435,000 people in the US who have used heroin in the past month and 586,000 had a heroin use disorder.[3] It is estimated that 4.8 million people have used heroin in their lifetime.[96] There were more than

10,000 deaths involving heroin in the US in 2014, which accounts for a 6-fold increase from 2001.[97]

III. Dual diagnosis

a. Definition, burden and impact

Dual diagnosis is the co-occurrence of a mental illness and SUD. Patients with dual diagnosis exhibit more persistent, severe, chronic, and treatment-resistant symptoms when compared to patients with SUD or a mental illness alone. The presence of a dual diagnosis in a patient results in more severe negative health outcomes such as relapse of psychiatric illness, hospitalization, disruptive behavior, family stress, homelessness, legal problems, decreased functioning status, HIV infections, and low medication adherence.[101]

In 2014, it was estimated that 7.9 million adults had a dual diagnosis, representing 39.1% of the total SUD population, 18.2% of persons with mental illness, and 3.3% of the total US population. It is estimated that there are currently 2.3 million adults (1.0% of the US population) with a serious mental illness and SUD. Of the 7.9 million dually diagnosed patients, 36.0% were between the aged of 18 and 25 years, 42.7% were between 26 and 49 years, and 35.6% were 50 or older.[3]

b. Diagnosis

Accurately diagnosing a patient with a dual diagnosis has been proven to be difficult for physicians. Dual diagnosis is currently not a distinct diagnosis in the DSM-5, therefore there is no standardized diagnosis criteria that can assist physicians to make a proper diagnosis.[102]

Diagnosis is further complicated with symptoms of substance abuse and acute withdrawal being similar to mental illness symptoms. Withdrawal from alcohol in most cases causes patients to exhibit symptoms of depression, and psychedelic drugs cause patients to display symptoms similar to schizophrenia and psychosis. Withdrawal from stimulants cause extreme anxiety in their users. For a patient to truly have a dual diagnosis, the mental illness must still be present in the absence of drug use or after acute withdrawal has taken place, or must have been present prior to establishment of the substance use disorder. Therefore comorbid SUD and mental illness has been problematic to accurately diagnose.[103]

c. Etiology and theories of development

Despite the high prevalence and severity of dual diagnosis, little is known as to why the co-occurrence of these two diseases happens but there are some theories established by previous research. The highly debated causality theory states that heavy and long-term drug use leads to the development of mental illness. For example, a study conducted by Moore *et al*. concluded there was an increased risk of a psychotic event in those who have used cannabis compared to those who have not (adjusted OR =1.41, 95% CI 1.20–1.65, p=0.28). Moore *et al.* also found a dose-response effect, there was an increased risk of a psychotic event in those who used cannabis more frequently compared to those who used less frequently (adjusted OR=2.09, 1.54–2.84; p=0.11).[104] Other studies have also shown that use of stimulants and hallucinogens can lead to long-term psychotic disorders such as schizophrenia or affective disorder.[105]

Another theory to explain the high co-occurrence of these disorders is the self-medicating theory. Patients with mental illness may be in a state of constant discomfort in which the use of illicit

drugs helps alleviate. The presence of a mental illness may cause a patient to experience extreme emotional highs and lows, and the use of illicit drugs may result in temporary alleviation of these feelings or give the patient a perceived control over them.[106] A patient receiving treatment for their mental illness may also use illicit drugs to regulate the side effects of psychotropic medications. For example, a frequent side effect of antipsychotic medications is sedation and lack of energy therefore patients may use stimulants such as amphetamines to counteract the sedation.[107] There are currently multiple diagnostic studies that both support and reject the self-medicating theory.[106]

Another theory used to explain dual diagnosis is the alleviation of dysphoria theory. Dysphoria is a state of severe unease or dissatisfaction and is often experienced by those with depression and anxiety disorders. The theory states that patients with dysphoria are more likely to engage in illicit drug use to alleviate these feelings.[107] In a study conducted on a cohort of inpatients with schizophrenia, it was found that patients with an alcohol-related diagnosis were more likely to cite alcohol use as a relief to their problems and worries.[108]

The overlapping risk factors theory attempts to explain the co-occurrence of SUD and mental illness by crediting the high prevalence to the multiple overlapping risk factors for each disease. These factors include social isolation, low socioeconomic status, lack of adult role responsibility, lack of structured daily activity, and living in areas with high drug availability. There is also evidence that experiencing traumatic life events such as sexual or physical abuse can put a person at a higher risk for both mental illness and SUD.[107]

Lastly, the super sensitivity theory states that patients with mental illness also have biological and psychological vulnerabilities caused by genetic and environmental factors that make it more difficult to cope with negative or stressful life events. For example, a patient with major depressive disorder will not be able to deal with the loss of a love one as well as someone without a mental illness. Therefore, these individuals may not have the capability of sustaining moderate drug use and also be more likely to experience the negative consequences of illicit drug use such as addiction. The super sensitivity theory also provides an explanation to why patients with a mental illness often experience the negative consequences of drug use even while using relatively low levels of the substance.[107]

d. Treatment modalities

The dual diagnosis population often requires intense and patient-specific treatment due to the complexity and severity of their disease. There are many barriers to treatment for those with dual diagnosis and according to the 2015 National Survey on Drug Use and Health only 6.8% of those with a dual diagnosis received treatment for both their mental illness and SUD.[109] While it is not completely clear why there is a lack of dual diagnosis specific treatment, some researchers conclude that it may be due to dual diagnosis patients being more difficult to work with, more likely to be noncompliant to treatment plans, less responsive to typical treatment, and more at risk of violence.[110] A majority of previous research concludes that combining both mental illness and SUD treatment into a single care plan is the most effective way of treating dual diagnosis patients. In a literature review conducted by Drake *et al*., 26 controlled studies of dual diagnosis psychosocial therapy were observed and the most effective treatments were the mental illness and SUD integrated interventions that focused on individualized personal factors.[111]

IV. Medication adherence

a. Definition, burden and impact

The WHO defines adherence as "*the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*."[112] Although the term is most often used in regards to taking prescribed medication, it can also refer to numerous other health-related behaviors.[112] Adherence has a high impact on the health of patients due to its correlation with health outcomes. Low medication adherence can result in adverse effects, increased healthcare costs, patient frustration with disease and treatment, misdiagnosis, unnecessary treatment, increase in disease severity, increase in symptom severity, and death.[113]

It is important to distinguish between the terms adherence and compliance. Until recently, non-compliance was used to describe the degree to which a patient followed the directions given by their medical providers. The term adherence was then introduced to refer to the extent to which a patient's health behavior reflects their health plan which was agreed upon by both the clinician and the patient. Adherence is more patient attitude-centered while compliance is more clinician-centered. Adherence also acknowledges that the patient plays a role in choosing and following their health plan and outcomes.[114]

A patient's non-adherence can be categorized as intentional or unintentional. Intentional non-adherence occurs when a patient deliberately does not take their medications for reasons such as to save on medication costs, lack of motivation, and belief that the medication is not efficacious. Unintentional non-adherence occurs when a patient lacks the capacity to follow their regimen.

For example, an older patient may forget to take their medications or a patient with multiple daily medications may not be able to take all as directed.[115]

Non-adherence can also be categorized as primary or secondary. Primary non-adherence refers to when a patient is prescribed a medication but fails to fill the prescription. Primary non-adherence is common among patients receiving new medications. In a study of 195,930 e-prescriptions, researchers found that only 72% of new prescriptions were ever filled.[116] Secondary non-adherence refers to when a patient fills their prescription but does not take the dosage as recommended. Secondary non-adherence is usually due to patients wanting to save costs, forgetting to take their medications, or believing their medication is not efficacious. Interventions designed to improve adherence must determine which type of non-adherence the patient experiencing in order to effectively improve their behaviors.

In 2003, the WHO concluded that non-adherence is the number one cause of preventable morbidity, mortality, and healthcare costs.[117] It is estimated that the medication adherence rate across chronic diseases in the US is roughly 50%, therefore out of the 3.2 billion prescriptions dispensed in the US, 1.6 billion are not taken by the patients to whom they are prescribed. .[112,118] In a study conducted by Jackevicius *et al*., a cohort of patients with acute myocardial infarction were followed post-hospital discharge and only 74% of the patients filled their prescription after 120 days.[119] Another large study conducted by Vrijens *et al*. found that half of patients who were prescribed antihypertensive drugs completely stopped taking the medication after a year.[120] Each year there are approximately 125,000 deaths in the US that can be attributed to medication non-

adherence.[121] Of the total medication-related hospital admissions in the US, it is estimated that between 33% and 69% are due to low adherence.[118]

Medication non-adherence also results in unnecessary and avoidable healthcare costs. The total annual cost of non-adherence in the US ranges from $100 billion to $300 billion including both direct and indirect costs.[113] In a study of Medicaid patients with heart failure, patients who were adherent to their medications had an overall costs 23% lower than those who were not adherent.[122] In another study of Medicaid patients with diabetes, researchers found that for every 10% increase in medication adherence resulted in a decline of 9-29% in total healthcare costs.[123] Low medication adherence can also result in an increase in indirect costs such as unnecessary caregiver costs and lost work productivity.[118]

b. Risk factors and barriers

Low medication adherence or non-adherence can be attributed to a variety of risk factors and barriers. Poor health literacy or the lack of patient understanding of their treatment plan and medication directions attributes to low adherence rates, demonstrating a need for patient-tailored medication counseling.[124]

Medication costs have been shown to be a barrier to treatment adherence. The US is currently one of the leading countries with the highest pharmaceutical medication prices[125] and increases in medication costs to the patient is associated with a decline in medication adherence.[126] Almost 75% of Americans believe that their prescription drug costs are unreasonably high and 21% find it difficult to pay for their prescriptions.[127] In the past year, 25% of Americans have stated that

they or a family member have not filled their medication prescriptions in order to save money. An estimated 18% reported either cutting their pills in half or skipping a dose in order to save on medication costs.[127]

Another factor that may lead to low adherence is the complexity of a patient's treatment regimen. In a study observing the medication adherence in patients prescribed statins for cardiovascular diseases, researchers found that a greater number of prescribers, visits to more pharmacies, a greater number of daily doses, and less refill consolidations were predictors of low medication adherence.[128] Lower dosing frequencies and a lower number of medications a patient was taking has been found to significantly improve medication adherence.[129]

Low medication adherence can also be attributed to the patient's cognitive beliefs. According to the WHO, low medication adherence has been linked to illness-relevant cognitions, perceptions of disease factors, and treatment beliefs. Other cognitive factors associated with medication adherence include perceived susceptibility of illness, perceived severity of illness, self-efficacy, and perceived control over the disease. Other studies have also found that patients will be more adherent to their medications if it results in a timely and noticeable reduction in symptom severity.[112]

c. Measurements

Medication adherence can be measured in multiple ways including direct measures, secondary database analyses, electronic medication packaging (EMP) devices, pill count, and clinician assessments and self-reports. Direct adherence measuring refers to the process of measuring the

medication concentration in a patient's bodily fluids such as their blood or urine. While direct measures are the most accurate ways to measure a patient's medication adherence, there are some limitations. First, the results only tell the researcher if the medication is present. There is no way to measure the pattern or cause of non-adherence. Direct measures are very intrusive and require full cooperation of the patient. Direct measures are the most expensive adherence measurement techniques and require scientific professionals to conduct the testing.[130]

Secondary database analysis adherence measurement is the process of accurately estimating a patient's adherence levels by observing data patterns from databases such as claims databases and electronic prescription services. This method assumes that the patient's prescription refilling pattern corresponds with their medication-taking behavior. There are three types of secondary database analysis adherence measures: continuous variable analysis, dichotomous variable analysis, and consumption. Continuous variable analysis observes the patient's adherence behavior from the first prescription to the last prescription on record. An example of this method is the medication possession ratio (MPR). This method is a simple calculation of the percentage of days the patient received their medication over the total prescription period. MPR usually overestimates adherence due to its inability to adjust for gaps in refills. Dichotomous variable measurements label a patient as either adherent or nonadherent based on some set criteria. This method is the least used method and has a lower sensitivity due to the lack of a professional consensus of how to determine the cutoff point. Lastly, the consumption method examines the time between prescription refills from the perspective of gaps or periods of non-adherence. Examples of this method includes continuous multiple interval medication acquisition (CMA), continuous multiple interval medication gaps (CMG), continuous single interval medication

acquisition (CSA), and continuous single interval medication gap (CSG). CMA calculates adherence by observing the cumulative days of medication supply obtained over a series of intervals divided by the total number of days. CMG measures adherence by dividing the total number of days in treatment gaps by the total number of days. CSA measures the days of supply obtained in each interval over the total number of days in each interval. CSG is calculated by the number of days without any medication over the total number of days in the interval.[130]

Medication adherence levels can also be measured using electronic medication packaging (EMP) devices. These devices are incorporated into the packaging of the medication and records doses taken, provides patients audio or visual reminders to take a dose, and gives feedback on the patient's adherence.[130] While EMPs are a highly accurate method of measuring adherence, they are rarely used in research due to their high cost and the complex support required for use. In a study on adherence in patients with schizophrenia, the researchers estimated a total cost of $274 per patient to use the devices. The authors also encountered other barriers to use such as encouraging patients to use the devices correctly and coordinating refills with pharmacies.[131]

Pill counting is an indirect measure of adherence in which the number of pills left in a patient's prescription container is counted when they are due for a refill. This number is then divided by the total number of pills received to calculate an adherence ratio. This method is the least costly and most simplistic form of medication adherence measurement but includes several limitations. If a patient does not want to appear nonadherent, they may discard excess medication before refilling. This method also overestimates adherence due to the inability to determine if patients over consumed their medications.[130]

Medication adherence can be measured through clinician assessments and self-reports. This method is the most commonly used form of medication adherence measurement in research due to its relatively low cost, simplicity, and real-time feedback. Medication adherence can be assessed through an interview in which patients are asked to estimate their adherence rate, how many medication dosages they have missed, and the reasons to why they believe they are not adherent. A more structured form of adherence measurement can be done through the use of standardized or condition specific questionnaires and scales. While there is no gold standard measure for medication adherence, a commonly used adherence measurement is the 8-item Morisky Medication Adherence Scale (MMAS-8), which consists of seven yes or no questions related to medication adherence and one Likert scale type question/statement related to the frequency of the patient forgetting to take medication.[132] There are multiple limitations to using clinician assessments and self-reporting. Patients may purposely provide false information to appear more adherent to their medication regimes. There is also a chance for recall bias, in which patients may not be able to remember the extent to their adherence. The researcher must properly decide which measurement to use that will most accurately measure the adherence level in their chosen population.[130]

d. Adherence in the mental illness population

Medication adherence plays a vital role in the treatment of mental illness. As stated, nonadherence often results in poor health outcomes, unnecessary costs, increased symptom severity, and treatment failure, especially in the mentally ill population. In regard to MDD, a retrospective chart review conducted by Sawada *et al.* found that 55.7% of patients with MDD

discontinue their antidepressant medication regimen within the first six months. In the same study, 55.6% of patients were found to be adherent with a MPR $\geq$ 0.8.[133] In a retrospective, observational study using medical and pharmacy claims, Akincigil *et al.* assessed the adherence rates of 4,312 patients with MDD. The researchers found that 51% of the patients were adherent during the first 16 weeks of treatment but only 42% remained adherent within 17 to 33 weeks after the treatment began.[134] In a retrospective study of 22,947 patients receiving a SSRI for MDD, Cantrell *et al.* found that approximately 57% of the patients were not adherent to their medication.[135]

In regard to GAD, medication adherence is essential to controlling a patient's symptoms, especially at the early stages of the disease. Using data collected from a community health survey, Bullock *et al.* estimated the non-adherence rate of patients prescribed anxiolytics to be 38.1%.[136] The current literature on anxiety disorder adherence rates is limited, therefore further research in the area is needed in order to establish accurate estimates of general adherence rates.

For bipolar disorder, medication adherence is a critical part of controlling the extreme highs and lows of the disease. A literature review conducted by Lingam *et al.* observed studies that measured the medication adherence rates of bipolar disorder patients. The non-adherence rates were found to range from 20% to 60% with a median non-adherence rate of 41%. [81] In another large study of 140 patients receiving the mood stabilizers for bipolar disorder, Keck *et al.* found that 51% of the patients were non-adherent during the one year follow-up.[137]

Medication adherence helps prevent patients with schizophrenia from relapsing back into a psychotic state. The rate of relapse in schizophrenia patients who are nonadherent is 55%, which is significantly higher than the relapse rate of 14% for those who are adherent.[138] In a study of 100 who were patients hospitalized for acute mania, Keck *et al.* found that 64% of the patients were non-adherent to their medication the month before admission.[139]

e. Adherence in the dual diagnosis population

Due to the complications related to both diseases, the dual diagnosis population experiences unique barriers to medication adherence. Multiple studies have concluded that substance abuse is associated with poor medication adherence in patients with mental illnesses.[140-142] Evidence shows this correlation may due to a variety of factors. Substance users often lead a disorganized lifestyle that may be intensified by a mental illness therefore resulting in difficulty following a regimented medication schedule. Both mental illnesses and drug use can also impair the cognitive functioning ability of the patient resulting in impaired judgment regarding medical behaviors.[143] As previously stated, the mentally ill patient may be taking illicit drugs instead of psychotropic medications as a form of self-medication in order to subdue the side effects of the disease faster than their prescribed medications. A dual diagnosis patient may attribute their mental illness symptoms solely to drug use, and therefore not feel the need to take medications. The risk of non-adherence to psychotropic medication is also high due to their high risk of adverse events. Low adherence or sudden stopping of the medication may lead to withdraw and an increase in symptom severity, therefore leading the patient back to their drug use tendencies.[144] Lastly, SUD patients may feel a stigma surrounding their mental illness medications, as the medication can still been seen as taking "drugs" [143] It is important to

recognize and treat the factors of non-adherence in the dual diagnosis population because low medication adherence is associated with negative health outcomes such as re-hospitalization, homelessness, and lower quality of life.[145] Currently, there is limited literature on the adherence rates of the dual diagnosis population and the affects psychotropic medication adherence has on the health outcomes of SUD.

V. Problem Statement

Poor medication adherence is associated with negative health outcomes, especially in patients with mental illness and substance use disorder. Currently, there is an incomplete understanding of how medication adherence to psychotropics affects health outcomes of substance use (relapse). SUD and mental illness are two widely co-prevalent conditions with a poor understanding of how one affects the other. Further data on the role that medication adherence plays on SUD outcomes could help interventions target patients more effectively through specific treatment tailoring and therefore improve health outcomes of this vulnerable and stigmatized population.

VI. Hypothesis

The overall hypothesis of the study is that patients with low self-reported adherence rates, negative attitudes toward their medications, and higher severity of mental illness symptoms will have significantly higher relapse rates of substance abuse.

VII. Research Objectives

a. Research Objective 1: Identify personal, social, and clinical history for patients with substance use disorder and either major depressive disorder, bipolar disorder, schizophrenia, or generalized anxiety disorder

b. Research Objective 2: Measure agreeance between patient self-report versus facility record history for mental illness, substance abuse, and psychotropic medication

c. Research Objective 3: Investigate the specific role of medication adherence and barriers to use for psychotropic medications upon substance abuse relapse

d. Research Objective 4: Assess follow-up changes in mental illness severity and medication adherence in dual diagnosis patients enrolled in a substance abuse rehabilitation program

CHAPTER 2 – LITERATURE REVIEW

I. Introduction

a. Rationale

Patients with dual diagnosis, the co-morbid diagnosis of SUD and mental illness, exhibit more persistent, severe, chronic, and treatment resistant symptoms than patients with substance abuse disorder or a mental illness alone. Due to the severity of the disease, patients with dual diagnosis require unique and personalized interventions in order to improve health outcomes. The primary goal of interventions for patients with a substance use disorder is the avoidance of relapse, which is a vital health outcome of dual diagnosis treatment due to the negative consequences associated with substance abuse relapse.

Poor medication adherence is associated with negative health outcomes in many chronic diseases including the dual diagnosis population. Patients with mental illness are at a higher risk of nonadherence due to their lack of awareness of the disease and the significant side effects of psychotropic medication. Patients with SUD are at a high risk of nonadherence due to the interaction between illicit drugs and psychotropics, the patient's lifestyle choices, the effect of drug use on memory, and self-medication with illicit drugs. The combination of both a mental illness and a substance use disorder diagnosis only amplifies the risk of nonadherence therefore leading to poor health outcomes. Therefore, it would be assumed that medication adherence would be an important focus of dual diagnosis treatment yet there is currently an incomplete research understanding of exactly how medication adherence to psychotropic medications impacts the therapeutic outcomes of patients with dual diagnosis, especially substance use relapse.

b. Objectives

The objectives of the literature review were to: (1) identify published studies that evaluate the relationship between substance abuse, psychotropic medications, and medication adherence, and (2) identify gaps in the existing literature.

II. Methods

a. Search strategy

The systematic literature review was conducted according to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Peer-reviewed journals were assessed using the electronic databases PubMed (1996-present), SCOPUS (1990-present), and PsychINFO (2001-present). The last search was run on March 1st, 2017. Articles that were not available online were requested and received through the Duquesne University Gumberg Library. Article eligibility assessment was performed independently by one reviewer and uncertainty in regard to an article's eligibility was resolved by a consensus between the reviewer and the thesis committee chair. A data extraction sheet was developed using Microsoft Excel (Redmond, WA), including the following from each article: (1) study objectives, (2) year published, (3) study population characteristics, (4) study location, (5) methodology, (6) relevant outcomes, (7) self-reported limitations.

b. Eligibility criteria

The inclusion criteria for the literature review were primary research articles assessing the relationship between substance abuse, psychotropic medications, and adherence. Review articles, grey literature, and non-English articles were excluded.

c. Search terms

The search terms used for the PubMED search were as follows:

(Antipsychotic[tiab] OR Antipsychotics[tiab] OR Neuroleptic[tiab] OR Neuroleptics[tiab] OR Psychotropic[tiab] OR Psychotropics[tiab] OR Antischizophrenic[tiab] OR Antidepressant[tiab] OR Antianxiety[tiab] OR "Antipsychotic Agents" [Pharmacological Action] OR "Antipsychotic Agents"[Mesh]) AND (“Drug Dependence”[tiab] OR “Drug Addiction”[tiab] OR “Drug Habituation”[tiab] OR “Substance Use Disorders”[tiab] OR “Substance Use Disorder”[tiab] OR “Substance Abuse”[tiab] OR “Substance Abuses”[tiab] OR “Substance Dependence”[tiab] OR “Substance Addiction”[tiab] OR “Drug Abuse”[tiab] OR “Drug Use Disorders”[tiab] OR “Drug Use Disorder”[tiab] OR "Substance-related disorders"[MH]) AND (Adherence[tiab] OR Non-Compliance[tiab] OR Noncompliance[tiab] OR Non-adherence[tiab] OR Nonadherence[tiab] OR "Patient Compliance"[Mesh:NoExp] OR "Medication Adherence"[Mesh])

The search terms used for the SCOPUS search were as follows:

TITLE-ABS-KEY (Antipsychotic OR Antipsychotics OR Neuroleptic OR Neuroleptics OR Psychotropic OR Psychotropics OR "Antipsychotic Agents" OR "Antipsychotic Agents”)

AND TITLE-ABS-KEY (“Drug Dependence” OR “Drug Addiction” OR “Drug Habituation” OR “Substance Use Disorders” OR “Substance Use Disorder” OR “Substance Abuse” OR “Substance Abuses” OR “Substance Dependence” OR “Substance Addiction” OR “Drug Abuse” OR “Drug Use Disorders” OR “Drug Use Disorder” OR "SUBSTANCE-RELATED DISORDERS”) AND TITLE-ABS-KEY (Adherence OR Non-Compliance OR Noncompliance OR Non-adherence OR Nonadherence OR "Patient Compliance” OR "Medication Adherence”)

The search terms for the PsycINFO search were as follows:

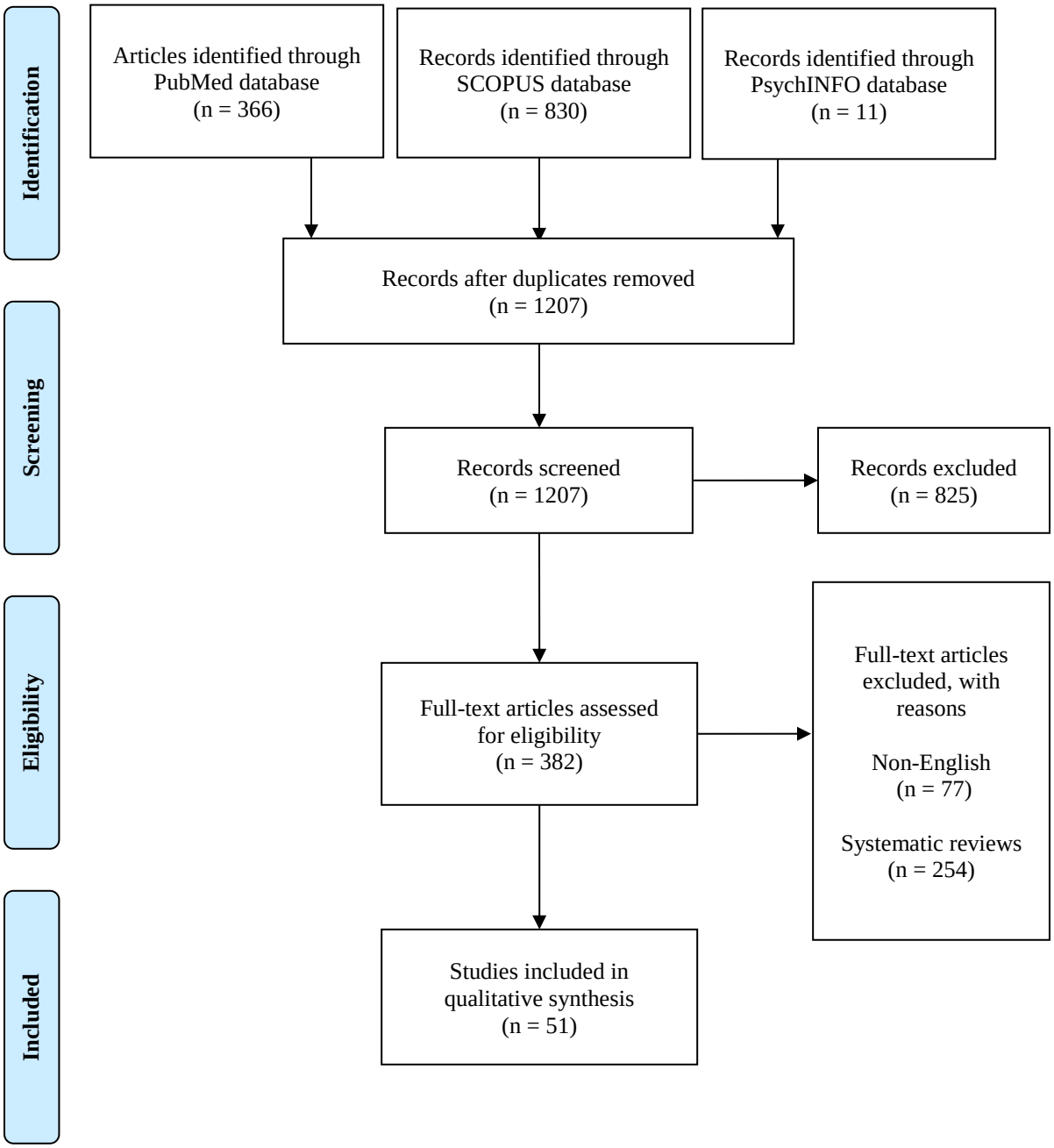
(DE "Neuroleptic Drugs") AND (DE "Drug Abuse" OR DE "Alcohol Abuse" OR DE "Drug Dependency" OR DE "Inhalant Abuse" OR DE "Polydrug Abuse" OR DE "Drug Addiction" OR DE "Heroin Addiction" OR DE "Substance Use Disorder") AND (DE "Treatment Compliance")

III. Results

a. Study selection

The results of the search are shown in the PRISMA flowchart depicted in **Figure 1**.

Figure 1: Results of the Literature Search



b. Study characteristics

A total of 51 studies were included in the synthesis of the literature review. The publication dates of the articles ranged from 1990 to 2017. The largest study contained a sample of 44,026 patients and the smallest study contained a sample of 42 patients. Methods utilized to collect data included structured in-person interviews, self-reported questionnaires, mailed surveys, medical claims database analysis, medical chart reviews, clinical assessments, and randomized clinical trials.

Of the 51 studies included, 32 were conducted in the US (63%), four in Canada (8%), three in Spain (6%), two in Ireland (4%) and two in UK (4%). Other countries with a single article (2% each) included in the review were Germany, Israel, Nigeria, Denmark, Australia, Norway and Italy. One multi-country study (2%) took place in Spain, UK and Greece.

The review contained studies assessing multiple mental illness populations. Schizophrenia was the most reported mental illness in the review (20 articles, 40%). Other mental illnesses studied included bipolar disorder (9, 18%), psychosis (4, 8%), MDD (3, 6%) and post-traumatic stress disorder (1, 2%). Two studies (4%) observed patients with either schizophrenia or bipolar disorder. Two studies (4%) assessed patients with psychotic disorders in general and two other studies (4%) assessed patients with any DSM-IV mental illness. Of the 51 total studies, 8 (16%) specifically observed the dual diagnosis population.

c. Results of individual studies

A summary of studies identified by the systematic literature review are in **Table 1**.

Table 1: Details of Individual Studies Identified in the Systematic Review

Authors, Year	Objective*	Study Population	Location	Methods	Relevant Outcomes	Limitations
Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S 2007 [134]	To describe patient and provider level factors associated with treatment adherence in patients with major depressive disorder	4312 patients who initiated antidepressant treatment	US	Retrospective, claims database analysis	Lower adherence was associated with alcohol abuse (OR=0.49) and other substance abuse (OR=0.72).	Limited generalizability, recall bias, desirability bias
Ascher-Svanum H, Faries D, Zhu B, Ernst FR, Swartz MS, Swanson JW 2006 [146]	To examine the relationship between adherence to antipsychotic medications and functional outcomes among schizophrenia patients	1906 participants with schizophrenia or schizoaffective or schizophreniform disorder	US	Prospective, interview and medical record analysis	Non-adherent patients were more likely to consume drugs or alcohol (OR=1.36)	Adherence measure may be inaccurate
Ascher-Svanum H, Zhu B, Faries D, Lacro JP, Dolder CR 2006 [147]	Identify predictors of nonadherence to psychotropic medication in patients with schizophrenia	1579 patients in the US Schizophrenia Care and Assessment Program	US	Prospective, interview and medical record analysis	Predictors of nonadherence were illicit drug use 4 weeks prior to treatment (OR=1.8) and alcohol use 4 weeks prior to treatment (OR=1.6)	Not all potential factors measured
Baldessarini RJ, Perry R, Pike J 2008 [148]	To determine the risk factors that lead to nonadherence in patients with bipolar disorder	429 adults with bipolar disorder	US	Cross-sectional, questionnaire	Alcohol dependence was a factor significantly associated with nonadherence (RR=2.26)	Recall bias
Coldham EL, Addington J, Addington D 2002 [149]	To measure adherence rates to antipsychotic medications in first episode psychosis patients	200 patients (132 males, 68 females) in the Calgary Early Psychosis Program with a first episode of psychosis	Canada	Prospective, interview	Cannabis is a predictor of nonadherence (OR=0.46). Alcohol use was significantly associated with nonadherence (p=.02)	Recall bias

Colizzi M, Carra E, Fraietta S, Lally J, Quattrone D, Bonaccorso S, Mondelli V, Ajnakina O, Dazzan P, Trotta A, Sideli L, Kolliakou A, Gaughran F, Khondoker M, David AS, Murray RM, MacCabe JH, Di Forti M 2005 [150]	To clarify the contribution substance use and poor medication adherence to poor outcomes after a first episode of psychosis	205 patients with a first episode psychosis	UK	Prospective, interview and database analysis	Nonadherence was significantly associated with nicotine dependence (OR=2.18), cannabis use (OR=2.86), and stimulant use (OR=2.63) but not problem drinking.	Recall bias, social desirability
Cooper D, Moisan J, Grégoire J-P 2005 [151]	To identify determinants of compliance among patients with schizophrenia	6662 individuals with schizophrenia initiated on treatment with atypical antipsychotics	Canada	Prospective, database analysis	Patients without a history of substance-use disorder were more likely to be both persistent (OR=0.70) and compliant (OR=0.63) to their medications	Adherence measurement may be inaccurate
Elbogen EB, Swanson JW, Swartz MS, Van Dorn R 2005 [152]	To examine the effect depressive symptoms and social stability have on nonadherence in psychosis	528 adults with psychotic disorders receiving treatment from public mental health systems	US	Cross-sectional, interview	Substance abuse was a predictor for nonadherence (OR=2.04)	Could not establish temporality
González-Pinto A, Reed C, Novick D, Bertsch J, Haro JM. 2010 [153]	To identify factors associated with medication adherence in bipolar disorder patients	1,831 bipolar disorder patients either starting or switching treatment for a manic/mixed episode	Spain	Prospective, interview	Nonadherence is associated with patients with cannabis abuse/dependence	Adherence measurement may not be accurate
Grunebaum MF, Weiden PJ, Olfson M 2001 [154]	To examine the association between medication adherence and level of supervision along with other environmental and clinical variables	74 adult residents with schizophrenia and related psychotic disorders living in supported housing facilities	US	Cross-sectional, interview	Drug and alcohol abuse was not associated with adherence	Could not establish causation

Herbeck DM, Fitek DJ, Svikis DS, Montoya ID, Marcus SC, West JC 2005 [155]	To examine clinical and non-clinical factors associated with treatment compliance problems in patients with comorbid psychiatric and substance use disorders	342 patients with comorbid psychiatric and substance use disorders	US	Cross-sectional, questionnaire	A comorbid personality disorder (OR=2.6), lower functioning ability (OR-3.6), a current illicit drug problem (OR=4.0), and medication side effects (OR=2.5) were strongly associated with noncompliance	Small sample size, could not establish temporality
Hill M, Crumlish N, Whitty P, Clarke M, Browne S, Kamali M, Kinsella A, Waddington JL, Larkin C, O'Callaghan E 2010 [156]	To examine associations and predictors of nonadherence to antipsychotics four years after a first episode of psychosis	171 patients with a first episode of psychosis	Ireland	Prospective, interview	Alcohol or drug misuse at baseline were predictors of nonadherence at 4 years (OR=6.9)	Adherence measurement may be inaccurate
Hunt GE, Bergen J, Bashir M 2002 [157]	To examine the effect of medication compliance and substance abuse on schizophrenia outcomes	99 patients with schizophrenia receiving acute care in a hospital or a 24-hour community-based crisis teams	Australia	Prospective, medical record analysis	Medication noncompliance (HR=2.46) and current substance abuse (HR=1.83) were predictors of hospitalization	Limited generalizability, small sample size
Iasevoli F, Fagiolini A, Formato MV, Prinzivalli E, Giordano S, Balletta R, De Luca V, de Bartolomeis A 2017 [158]	To evaluate the consistency, reliability, and determinants of two real-world measures of adherence to prescription in schizophrenia patients	57 schizophrenia patients and 61 non-schizophrenia patients	Italy	Cross-sectional, interview	Substance abuse was a significant predictor of lower adherence scores (p=0.027)	Small sample size
Janssen B, Gaebel W, Haerter M, Komaharadi F, Lindel B, Weinmann S 2006 [159]	To evaluate patient-related and treatment-related factors associated with medication compliance in inpatients with a psychotic disorder	670 patients with schizophrenia, schizoaffective disorder, or another psychotic disorder	Germany	Prospective, interview	Substance abuse was a predictor for nonadherence (OR=0.52)	Nonrandomized, adherence measurement not validated
Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Simonsen C, Engh JA,	To investigate potential risk factors for medication non-adherence in patients	255 patients with schizophrenia or bipolar disorder	Canada	Cross sectional, clinical assessments and blood sampling	A previous diagnosis of substance abuse or addiction was associated with nonadherence in both the	Could not establish temporality, Hawthorne effect

Ringen PA, Vaskinn A, Friis S, Sundet K, Andreassen OA 2013 [160]	with schizophrenia and bipolar disorder				bipolar and schizophrenic groups	
Kamali M, Kelly L, Gervin M, Browne S, Larkin C, O'Callaghan E 2001 [161]	To examine factors related to noncompliance to oral antipsychotics in patients with schizophrenia	87 patients with schizophrenia or schizoaffective disorder readmitted to a hospital with acute psychotic relapse	US	Cross-sectional, interview	Comorbid substance abuse is a predictor of noncompliance (p=.003).	Adherence measurement may not be accurate
Kamali M, Kelly BD, Clarke M, Browne S, Gervin M, Kinsella A, Lane A, Larkin C, O'Callaghan E 2006 [162]	To identify factors of first episode schizophrenia that predict adherence at six-month follow-up	100 patients with a diagnosis of schizophrenia	Ireland	Prospective, interview	Alcohol misuse and drug misuse were predictors of non-adherence at six months follow-up	Low follow-up rate, compliance measurements may not be accurate
Keck PE Jr, McElroy SL, Strakowski SM, Bourne ML, West SA. 1997 [137]	To measure the rates of noncompliance in patients with bipolar disorder	140 patients hospitalized for bipolar disorder	US	Prospective, questionnaire	Noncompliance was significantly associated comorbid substance use disorder	Adherence measurement may not be accurate
Krivoy A, Malka L, Fischel T, Weizman A, Valevski A 2011 [163]	To identify the clinical parameters that could predict clozapine discontinuation in patients with schizophrenia	100 patients with schizophrenia who were hospitalized and prescribed clozapine	Israel	Retrospective, medical record analysis	Comorbid substance abuse is a predictor for drug discontinuation	Small sample size, limitations associated with retrospective studies
Lagerberg TVV, Andreassen OA, Ringen PAA, Berg AO, Larsson S, Agartz I, Sundet K, Melle I. 2010 [164]	To investigate the lifetime rates of substance use in bipolar disorder patients and identify clinical outcome differences	125 bipolar disorder patients and 327 population reference	Norway	Retrospective, interview	Bipolar patients were significantly more likely to use illicit substances compared to the general population (OR=3.03). Patients with excessive substance use had significantly lower adherence (p=0.01)	Small sample size, could not establish causation
Lang K, Meyers JL, Korn JR, Lee S, Sikirica M, Crivera C, Dirani R, Menzin J 2010 [165]	To assess adherence rates and predictors of nonadherence and hospitalization among patients with schizophrenia	12,032 Florida Medicaid patients with schizophrenia receiving a long-acting injectable and oral antipsychotic	US	Retrospective, claims database analysis	A substance abuse diagnosis is a predictor of nonadherence (OR=1.54)	Diagnosis not verified, adherence measurement may not be accurate

Lecomte T, Spidel A, Leclerc C, MacEwan GW, Greaves C, Bentall RP 2008 [166]	To assess constructs that may be linked to medication adherence in patients with early psychosis	118 early psychosis patients	Canada	Cross-sectional, interview	No significant link between adherence and substance abuse disorder	Limited generalizability, adherence measurement may not be accurate
Liu X, Chen Y, Faries DE 2011 [167]	To compare adherence of three antidepressants and examine predictors of adherence in patients with major depressive disorder	44,026 patients diagnosed with major depressive disorder and prescribed an SSRI	US	Retrospective, claims database analysis	Alcohol dependence (OR=0.75) and drug dependence (OR=0.66) were associated with decreased adherence	Selection bias, adherence measurement may not be accurate
Lloyd A, Horan W, Borgaro SR, Stokes JM, Pogge DL, Harvey PD 2009 [168]	To determine predictors of medication compliance in psychiatric patients	97 adolescent psychiatric patients	US	Prospective, questionnaire	Post discharge substance abuse is a predictor of nonadherence ($p<0.10$)	Participants taken from previous substance abuse study
Lockwood A, Steinke DT, Botts SR 2009 [169]	To evaluate adherence and its effect on relapse among veterans with PTSD	82 veterans diagnosed with PTSD	US	Retrospective, claims database analysis	Comorbid substance abuse was not associated with drug adherence	Diagnosis not confirmed, adherence measurement may not be accurate
MacEwan JP, Forma FM, Shafrin J, Hatch A, Lakdawalla DN, Lindenmayer JP 2016 [170]	To identify patterns of medication adherence over time for patients with schizophrenia	29,607 patients with an oral atypical antipsychotic	US	Prospective, database analysis	Patients with a history of drug abuse (OR=1.46) and alcohol abuse (OR=1.34) were more likely to be less adherent	Potential coding errors, limited generalizability
Magura S, Laudet AB, Mahmood D, Rosenblum A, Knight E 2002 [171]	To examine associations between self-help meeting attendance, medication adherence, and mental health outcomes in those with a dual diagnosis	240 Double Tree in Recovery (DTR) self-help group participants with both chronic mental illness and a substance abuse disorder	US	Prospective, interview	Living in supported housing, having fewer stressful life events, and having a lower severity of psychiatric symptoms were associated with adherence	Nonstandardized measures, adherence measurement may be inaccurate
Magura S, Mateu PF, Rosenblum A, Matusow H, Fong C 2014 [172]	To examine the risk factors of nonadherence in psychiatric patients with substance misuse history	229 patients with a mental illness, a history of substance misuse, and a current prescription for psychiatric medication	US	Cross-sectional, interview	Lower adherence was associated with medication side effects, excessive alcohol use, and a diagnosis of depression. Schizophrenia was associated with higher adherence	Limited generalizability, could not establish causation

Magura S, Rosenblum A, Fong C 2011 [173]	To measure and determine factors related to nonadherence in psychiatric patients with substance abuse histories	131 patients in a psychiatric continuing day treatment program who had substance misuse histories and are prescribed psychiatric medication	US	Cross-sectional, interview	Factors correlated with lower adherence in the substance misuse population were: lower social support for quitting drug/alcohol, lower recovery-promoting behaviors, nonsatisfaction with medication, medication side effects, lower self-efficacy for drug avoidance, and lower social support for recovery	Limited generalizability, could not establish causation
Manwani SG, Szilagyi KA, Zablotsky B, Hennen J, Griffin ML, Weiss RD 2007 [174]	To examine patterns of adherence to mood stabilizers in patients with bipolar disorder	115 bipolar disorder patients (58 with SUD and 57 without SUD)	US	Cross-sectional, interview	Patients with co-occurring SUD were less adherent than those without	Adherence measurement may be inaccurate
Miller R, Ream G, McCormack J, Gunduz-Bruce H, Sevy S, Robinson D. 2009 [175]	To determine if cannabis use is a risk factor of nonadherence	112 first-episode schizophrenia patients	US	Prospective, interview	Cannabis use significantly increased nonadherence (HR=2.4)	Limited generalizability, use of other substances not observed
Montes JM, Maurino J, de Dios C, Medina E 2013 [176]	Identify factors associated with adherence in patients with bipolar disorder	303 outpatients on oral antipsychotics	Spain	Cross-sectional, interview	Substance abuse/dependence was a predictor of low treatment adherence (OR=1.95).	Could not establish causation, limited generalizability, adherence measures may be inaccurate
Murru A, Pacchiarotti I, Amann BL, Nivoli AM, Vieta E, Colom F 2013 [177]	To compare correlations between adherence and the course of illness in bipolar and schizophrenia patients	50 Patients with bipolar disorder type I and 75 patients with schizoaffective disorder, bipolar type	Spain	Cross-sectional, prospective, and retrospective, interview	No association between poor adherence and substance abuse	Could not establish causation, limited generalizability
Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM 2010 [178]	To assess the predictors of antipsychotic adherence during long-term schizophrenia treatment	6731 outpatients with schizophrenia who were starting or switching antipsychotics for clinical reasons	Spain, UK, Greece	Prospective, interview	Current alcohol dependence (OR=0.63) and substance abuse (OR=0.67) were predictors of nonadherence	Adherence measurement may be inaccurate
Okpataku CI, Kwanashie HO, Ejiofor JI, Olisah VO 2015 [179]	To determine medication adherence behavior in psychiatric out-patients with	208 psychiatric out-patients with psychoactive substance use in a Nigerian Tertiary Hospital	Nigeria	Cross-sectional, interview	No relationship was found between substance use and medication adherence	No limitations reported

	psychoactive substance use comorbidity					
Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ 2000 [180]	To identify predictors of medication noncompliance in patients with schizophrenia	213 adult psychiatric inpatients with a diagnosis of schizophrenia or schizoaffective disorder prescribed antipsychotics	US	Prospective, interview	A substance use disorder was a predictor of medication noncompliance (OR=4.6)	Recall bias, social desirability
Owen RR, Fischer EP, Booth BM, Cuffel BJ 1996 [181]	To examine the effect of medication noncompliance and substance abuse on symptoms of schizophrenia	Short-term inpatients schizophrenia	US	Prospective, interview	Noncompliance was associated with substance abuse	None reported
Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA 2008 [182]	To evaluate predictors of medication nonadherence in patients recovering from a first episode of psychosis	400 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder	US	Prospective, RCT	Ongoing substance abuse was a predictor of poor medication adherence ($p<.01$)	Limited generalizability
Pogge DL, Singer MB, Harvey PD 2005 [183]	To examine antipsychotic medication adherence of adolescents	86 adolescent inpatients prescribed olanzapine or risperidone	US	Retrospective, interview	A diagnosis of substance abuse was significantly related to nonadherence	Limited generalizability
Pristach CA, Smith CM 1990 [184]	To examine the relationship between patterns of alcohol and drug use and compliance to medication among schizophrenia patients	42 schizophrenic patients in an acute care psychiatric unit	US	Cross-sectional, interview	No significant difference in compliance between alcohol users and non-users	Could not distinguish between past and current alcohol use
Quach PL, Mors O, Christensen TØ, Krarup G, Jørgensen P, Bertelsen M, Jeppesen P, Petersen L, Thorup A, Nordentoft M 2009 [185]	To identify predictors of poor medication adherence among patients with first-episode schizophrenia-spectrum disorder	547 patients with first-episode schizophrenia-spectrum disorder	Denmark	Prospective, interview	Substance abuse was a predictor of low adherence (OR=2.03) at 1-year follow-up	None reported

Sajatovic M, Bauer MS, Kilbourne AM, Vertrees JE, Williford W 2006 [186]	To evaluate factors related to treatment adherence among veterans with bipolar disorder	430 veterans diagnosed with bipolar disorder	US	Cross-sectional, interview	A current substance use disorder was a predictor of nonadherence (p=.007) but any past substance use disorder was not	Low sample size, adherence measurement may not be accurate
Sajatovic M, Blow FC, Kales HC, Valenstein M, Ganoczy D, Ignacio RV 2007 [187]	To evaluate patients receiving antipsychotic medication using the medication possession ratio (MPR)	26,530 younger individuals and 6,461 older individuals prescribed antipsychotic medication	UK	Retrospective, database analysis	Substance abuse was a predictor of nonadherence in the older population (OR=1.38) and the younger population (OR=1.30)	Adherence measurement may not be accurate
Sajatovic M, Ignacio RV, West JA, Cassidy KA, Safavi R, Kilbourne AM, Blow FC 2009 [188]	To examine clinical and subjective variables in relation to adherence in bipolar patients	140 patients with bipolar disorder treated with mood stabilizers in a mental health clinic	US	Cross-sectional, interview	Comorbid substance abuse is a predictor of low adherence (p<.01)	Cross-sectional design limitations, small sample size, adherence measurement may not be accurate
Sajatovic M, Valenstein M, Blow FC, Ganoczy D, Ignacio RV 2006 [189]	To examine adherence with psychotropic medications among patients with bipolar disorder	32,993 veterans diagnosed with bipolar disorder	US	Retrospective, database analysis	Comorbid substance abuse associated with treatment non-adherence (p<.0001)	Retrospective design limitations, gender homogeneity, inability to validate medical records
Swanson AJ, Pantalon MV, Cohen KR 1999 [190]	To investigate the effect of motivational interviewing on adherence among psychiatric and dually diagnosed inpatients	121 psychiatric inpatients, 93 with a history of substance abuse/dependence disorder	US	Prospective, assessment of motivational interviewing intervention	Brief motivational interventions improve adherence among dually diagnosed patients	Limited generalizability, no control group
Swartz MS, Swanson JW, Hiday VA, Borum R, Wagner HR, Burns BJ 1998 [191]	To examine the joint effect of substance abuse and medication noncompliance in regard to the risk of violent acts	331 in patients with severe mental illness	US	Cross-sectional and retrospective, interview and other data drawn from a RCT	The combination of noncompliance and alcohol/substance abuse is associated with serious violent acts (p<.01)	Limited generalizability, could not establish temporality
Teter CJ, Falone AE, Bakaian AM, Tu C, Ongür D, Weiss RD 2013 [192]	To examine the impact of substance use disorder among patients with bipolar disorder in regard to medication taking behaviors	54 bipolar I disorder patients at the Schizophrenia and Bipolar Disorder Program at McLean Hospital	US	Cross-sectional, interview	Patients with a past history of SUD are more likely to adhere to their medication regimen as compared to patients with a current SUD	Small sample size, low generalizability

Wilk J, Marcus SC, Westt J, Countis L, Hall R, Regier DA, Olfson M 2006 [193]	To compare clinical characteristics of nonadherence among schizophrenia patients with and without past comorbid substance use disorders	190 patients with schizophrenia and 105 with a comorbidity of SUD and schizophrenia	US	Cross-sectional, questionnaire	Patients with a substance use disorder were less likely to discuss the risks of nonadherence with their provider (p=0.05), link adherence to personal goals (p=.006), or explore the meaning of taking antipsychotic medications with their provider (p=0.01)	Adherence measurement may not be accurate, no clinical diagnosis, limited generalizability
Zivin K, Ganoczy D, Pfeiffer PN, Miller EM, Valenstein M 2009 [194]	To assess predictors of antidepressant adherence among depressed veterans	20,931 and 23,182 veterans registered in the VA who have major depressive disorder and received antidepressants	US	Prospective, database analysis	Patients with a substance abuse disorder were more likely to have poorer adherence at both 3 months (OR=2.18) and 6 months (OR=2.36)	Adherence measurement may be inaccurate

*Objectives directly reported from literature

d. Synthesis of results

Of the 51 studies included in the literature review, 36 studies (71%) concluded that comorbid substance use was significantly associated with psychotropic medication nonadherence.[134,137,146-149,151-153,155,156,158-165,167,168,170,174-176,178,180-183,185-189,194] Eighteen of these studies (35%) identified substance use as a predictor of nonadherence.[149,152,156,158,159,161-163,165,168,176,178,180,182,185-188] The rest simply found an association between the two variables. Of these 35 studies, nine (18%) identified alcohol abuse specifically as a factor associated with nonadherence[134,147-149,156,162,167,170,178] and three (6%) identified cannabis use as a factor.[149,153,175] In regard to negative outcomes, six studies (12%) found no significant relationship between substance use and psychotropic medication adherence.[154,166,169,177,179,184] Of these six studies, 1 (2%) specifically observed alcohol use and found no relationship with nonadherence.[184] One study (2%) included in the review found mixed results of both negative and positive outcomes.[150] This study conducted by Colizzi *et al.* observed 205 patients with a first episode of psychosis in order to identify the effect substance use and poor medication adherence has on health outcomes. The researchers concluded that nonadherence was significantly associated with nicotine dependence (OR=2.18), cannabis use (OR=2.86), and stimulant use (OR=2.63) but was not associated with problem drinking. The remaining eight studies (16%) identified additional conclusions that are further explained below.[157,171-173,190-193]

As stated, eight studies (16%) specifically observed the dual diagnosis population.[155,171-174,179,190,193] Two of these studies found a significant relationship between substance use and nonadherence and one found no significant relationship. The first study, conducted

by Herbeck *et al.*, examined 342 patients with comorbid psychiatric and substance use disorder and concluded that a current illicit drug problem was significantly associated with nonadherence (OR=4.0).[155] The second, conducted by Manwani *et al.*, examined the adherence patterns to mood stabilizers in 115 patients with bipolar disorder, of which 58 had a SUD and 57 did not. The researchers found that lifetime adherence was significantly lower in the SUD group (65.9%) versus the non-SUD group (85.0%).[174] Lastly, Okpataku *et al.* conducted a study in a Nigerian Tertiary Hospital observing medication adherence behaviors in psychiatric outpatients with psychoactive substance use comorbidities. The researchers found no statistically significant relationship between substance use and medication adherence.[179]

Out of the eight studies observing the dual diagnosis population, five studies aimed to identify the factors associated with psychotropic mediation nonadherence in patients with dual diagnosis.[134,171-173,193] The factors found to be associated with a higher level of adherence included living in supported housing, having fewer stressful life events, and lower mental illness symptom severity. Factors associated with lower adherence levels were lower social support for drug and alcohol abstinence, less recovery-promoting behaviors, lower satisfaction with medication, more severe medication side effects, lower self-efficacy for drug avoidance, lower social support for recovery, the diagnosis of a comorbid personality disorder versus other mental illnesses, lower functioning ability, and the current use of illicit substances. The studies specific to the dual-diagnosis population also concluded that these patients were less likely to discuss the risks of nonadherence with their healthcare provider (p=.05), less likely to link adherence to their

personal healthcare goals (p=.006), and less likely to explore the purpose of their psychotropic medications with their healthcare provider (p=.01) when compared to psychiatric patients without a comorbid substance use disorder.

The last study to observe the dual diagnosis population was conducted by Swanson *et al.* The objective of the study was to investigate the effect motivational interviewing has on adherence among the psychiatric and dual diagnosis population. The 121 enrolled patients were split into two groups; one group received a standard treatment using pharmacological and psychosocial methods while the second group received a standard treatment along with an hour-long motivational interview given by a staff therapist. The results showed that a significantly greater proportion of the motivational interview group adhered to their treatment regimen after discharge. The researchers concluded that brief motivational interventions show potential as effective tools for improving adherence in the dual diagnosis population.[190]

The three remaining studies did not observe the dual-diagnosis population but did identify additional conclusions. Swartz *et al.* set out to examine the effect of substance abuse combined with medication nonadherence in regard to the risk of violent acts. 331 patients with severe mental illnesses were recruited from a previous randomized control trial on involuntary outpatient commitment. Through face-to-face and telephone interviews, the patients were asked questions related to violent acts such as whether they have been arrested for physical or sexual assault, have gotten into a physical altercation

that involved violent actions, or done anything that would cause a person to be afraid of being harmed. Serious violent acts were defined as a violent act or a threat involving a weapon or that resulted in an injury of another person. Adherence was measured through self-report or the report of a family member. The researchers concluded that the combination of nonadherence and alcohol or substance abuse is significantly associated with serious violent acts (OR=2.29).[191]

In a study conducted by Teter *et al.,* 54 inpatients who were hospitalized for bipolar disorder were interviewed in order to examine the impact of substance use on medication adherence. Psychiatric symptom rating scaled were administered in order to assess the patient's mental illness severity. Medication taking behaviors were observed daily by the researchers and a standardized medication adherence ratio (SMAR) was calculated. Patients were split into three categories; no substance use history, past substance use history, and current substance use. The results showed that the SMAR of patients in the current substance use group was significantly lower than patients in either the no substance use history group or the past substance use history group.[192]

Lastly, Hunt *et al.* examined the medical records of 99 schizophrenia patients in order to assess the effect of medication adherence and substance abuse on schizophrenia outcomes. A patient was considered to be adherent to their medications if the records suggested that he or she regularly took their medications at least 75% of the time. The results showed that patients who were both non-adherent and abusing substances had the

highest readmission rate per patient (1.45 admissions) and accounted for more than half of the hospital admissions in the cohort (58%). The researchers concluded that the combination of both medication nonadherence and current substance abuse were predictors of hospitalization.[157]

The studies included in the literature review had several self-reported limitations. The most common self-reported limitation was that the measurement technique used to assess adherence levels might be inaccurate (29 studies, 57%), with four studies specifically citing recall bias and three studies citing desirability bias as a limitation. Another commonly stated limitation was that the results from a study could not be generalizable to the general population, which was reported as a limitation in 15 of the studies (29%). Other limitations cited included the inability to establish temporality, the Hawthorne effect due to patient knowledge of observation, possible selection bias, potential coding errors, small sample size, and the inability to verify mental illness diagnoses.

IV. Discussion

a. Summary of evidence

According to the evidence gathered by the systematic literature review, the consensus of previous literature is that alcohol or illicit substance use is significantly associated with psychotropic medication nonadherence. Although some of the included studies failed to identify a significant correlation between the two factors, these studies accounted for a small proportion of the all studies included in the review. As anticipated, no studies found

substance abuse to be a predictor of increased medication adherence. A majority of the studies observed patient populations with one specific mental illness while a limited number more broadly assessed mental illness as a whole. Limited studies observed factors in the dual diagnosis population specifically, even though that was the target population for the review. No studies in the review observed relapse rates or the impact of medication adherence upon substance abuse relapse, which is a vital health outcome of substance use disorder treatment.

b. Limitations

From a review level, there were limitations that require addressing. As in most reviews, the quality of studies varied. The studies included patient populations with various different characteristics, therefore making it more difficult to compare outcomes study to study. Lastly, there was a variation of how substance use was defined from study to study. While some studies required patients to have a clinical diagnosis of substance use disorder, others only required a self-report of substance use.

At the researcher level, multiple limitations could affect the review's results. First, only one investigator was in charge of identifying, collecting, and assessing the data from previous literature, which could result in researcher bias. Another limitation was that non-English studies were not included; therefore, studies written in foreign languages containing relevant data may have been left out of the review.

c. Conclusion

Overall, the literature shows that alcohol and illicit substance use is significantly associated with medication nonadherence in the mentally ill population. The literature review indicates a lack of research into the effect psychotropic medication nonadherence has on the health outcomes of substance use disorder, especially substance use relapse. The logical next step for future research would be to observe adherence factors specifically in the dual diagnosis population and assess the affect adherence has on patient relapse rates. Further data could help interventions tailor treatment to patients more effectively, help overcome barriers to treatment, and improve overall health outcomes.

CHAPTER 3 – METHODS

I. Study Methodology Overview

The study utilized a mixed methodology analysis consisting of a cross-sectional patient interview, a retrospective facility record supplementation and validation, and a prospective follow-up interview. Patients were evaluated within their first week of treatment to assess history of substance abuse, mental illness symptom severity, and adherence patterns prior to admission. Follow-up interviews were conducted at 1 and 2 months to reassess mental illness symptoms and adherence. Facility records were accessed to cross-reference patient reported data.

II. Data Source

a. Location

Participants were recruited from the Salvation Army Harbor Light Center located on the North Side in Pittsburgh, Pennsylvania. The Harbor Light Center is a medically-monitored residential rehabilitation program that provides 90 days of treatment to men 18 years and older who desire recovery from alcohol and/or other substance abuse problems. The services provided to the residents include individual and group counseling, coordination of healthcare and behavioral health needs, education of daily living activity skills, and referral to community supportive services.[195] New admissions to the facility (on average, 5 patients per week) receive an intake appointment where an extensive clinical interview is conducted on relevant medical, psychiatric, and social characteristics. Additionally, a medication interview with the patient is also conducted to ascertain relevant pharmacy history.

b. Participants

Newly admitted patients (within the past week) to the Harbor Light Center were recruited to participate in the study. Due to the intake policies of the rehabilitation center, patients had to be male and at least 18 years of age. Patients eligible for the study further must have had a self-reported diagnosis of a substance use disorder and at least one of the following mental health diagnoses: (1) major depressive disorder, (2) generalized anxiety disorder, (3) bipolar disorder, or (4) schizophrenia. For the purposes of this study, patients were excluded from participation if they have been diagnosed with a substance-induced psychiatric disorder, or if the facility record or patient report is unable to exclude this possibility. If a Harbor Light Center counselor stated that a new intake was experiencing severe withdrawal symptoms or they were having trouble adjusting to the new environment, the researcher postponed the interview until the counselor confirmed they were stable enough to participate in the study. The intake personnel were the first to make the decision of whether or not a newly admitted patient met the exclusion and inclusion criteria, and to make them aware of the ongoing study. This decision was then confirmed by the researcher before initiating the primary interview.

III. Data Extraction

a. Recruitment procedure

Upon admission to the facility and completion of normal intake procedures, potential patients identified to meet inclusion criteria by facility staff were offered the opportunity to participate in the study. If the patient had any questions about the process of the study, they would be answered initially by the intake personnel before enrollment. The intake

facility was given the following study description in order to properly explain the study procedures to the patient before they agreed to participate;

> *"Duquesne University is currently having a study at Salvation Army and is looking for volunteers. We are studying the association between substance abuse and taking your medications for depression, bipolar disorder, anxiety, or schizophrenia. You will be asked questions about your condition once today and again in 1 and 2 months for a follow-up. The first interview will take about 30 mins and the follow-up will take about 5 mins. Participation in this study will not affect your treatment in the Salvation Army program. You will receive $10 for completing the first interview and $10 for each follow-up ($30 total)."*

The researcher then contacted the Harbor Light Center staff once per week in order assess the number of patient that were interested in potential recruitment for the study. The patient recruitment process began in October 2016.

b. Informed consent procedure

After the patient confirmed they were interested in the study, the researcher conducted a face-to-face meeting at the facility in order to explain the study and provide the opportunity for informed consent. At this point the participants were given the *Consent to Participate in a Research Study* form (**APPENDIX 11)** to review and sign. This form, along with verbal guidance from the researcher, explained all the information needed in order for the participant to provide informed consent. The form lists the investigators

involved in the study and their contact information, as well as the contact information for the university IRB chair. The participant was informed that any of the investigators may be contacted in order to explain the study further or answer any questions about the study procedures. The study purpose and participant procedures were then explained in order to provide further clarification of the study. The risks and benefits of the study were listed to explain to the participant that there are minimal risks associated with the participation but are no greater than those encountered in everyday life. The compensation section explains that the patient will receive $10 for completing the first in-person interview and $10 for each follow-up for a total of $30. The study procedure for maintaining patient confidentiality is also explained in the form, stating that their participation in the study and any personal information that is provided will be kept confidential at all times and to every extent possible. Health Insurance Portability and Accountability Act (HIPAA) authorization is explained and states that the patients are aware that they are giving the researchers permission to use their personal health information in their medication records. All health information procedures in this study are HIPAA compliant, which is explained further in the Subject Rights and Ethics section of this chapter. Lastly, the form stated that participation in the study would be completely voluntary and that the participant has the right to withdraw from the study at any time. As a patient at the Harbor Light Center, the participants are under no obligation to participate in the study and choosing not to participate or discontinuing participating will in no way affect the services provided by the center. Once the researcher established with the participant that they clearly understood all aspects of the study, the participants were then required to

provide their signature on the *Consent to Participate in a Research Study* form and orally confirm that they understood what they consented to.

c. Primary interview

After informed consent was obtained, the researcher asked the patient if they wanted to begin the study procedures at that same time. If the patient confirmed they wanted to begin, the researcher then proceeded with the primary interview portion of the study. If the patient requested a delay, a subsequent date and time was arranged. The interview served two purposes: (1) measuring agreeance and supplementing data obtained from the facility record review, and (2) providing additional evaluation through standardized and validated assessment tools to assess medication adherence and psychological symptoms. First, the interviewer utilized the Prospective Patient Interview Form (**APPENDIX 2**) and recorded the patient's responses. This researcher-created instrument was used to collect information on patient-reported factors relating to mental illness, substance use and relapse, medication history and behaviors, and comorbidities. Next, the Morisky Medication Adherence Scale (MMAS-8) (**APPENDIX 4)** and the Drug Attitude Inventory (DAI-10) (**APPENDIX 5)** were given to the patients to fill out themselves. These instruments were used to collect information on the patient's medication adherence tendencies and their attitudes towards their medications. Lastly, depending on the self-reported mental illness diagnosis, the patients were given a questionnaire in order to measure the severity of their mental illness. The Patient Health Questionnaire (PHQ-9) (**APPENDIX 6**) was given to patients with major depressive disorder, the Mood Disorder Questionnaire (MDQ) (**APPENDIX 7**) was given to patients with bipolar disorder, the

Generalized Anxiety Disorder Assessment (GAD-7) (**APPENDIX 8**) was given to patients with generalized anxiety disorder, and the Brief Psychiatric Rating Scale (BPRS) (**APPENDIX 9**) was given to patients with schizophrenia. When filling out each form, the patients were asked to consider their behavior during the month before entering treatment in order to establish a set time period as a reference point. If a patient could not fill out the questionnaires on their own, the researcher administered the questions verbally and recorded the patient's responses. After the interview was completed, the researcher checked all forms for completeness, thanked the participant and processed the reimbursement for their time and participation. The primary interviews took place from November 1st, 2016 to June 20th, 2017.

d. Follow-up interview

Two follow-up interviews were conducted at approximately one and two months post-primary interview. The follow-up time period was chosen due to the program length, rehabilitation goals, and a literature review on relapse rates. Previous studies have found that the largest drop in abstinence occurs within the first month (100% to 70%) and then a leveling out occurs at three months.[196] Before beginning the follow-up interview, the researcher reiterated that the same confidentiality procedures from the primary interview still applied, and asked if the participant had any questions before continuing. During this interview, the interviewer utilized the Longitudinal Follow-up Interview Form (**APPENDIX 3**). Data collected during the follow-up interview included assessment of three key areas: (1) relapse to substance use, (2) status of mental illness symptoms, and (3) status of medication adherence. Any patients who identified symptoms or presented

remarks worrisome for relapse or mental health was offered the opportunity to speak with care coordinators at the facility for intervention. If a patient left the program before completing both of the follow-up interviews, they were coded as a drop-out and information regarding why the patient left was collected from their facility counselors. The primary interviews took place from November 29th, 2016 to June 20th, 2017.

e. Facility record review

After the participant signed the *Consent to Participate in a Research Study* form and gave informed consent, a facility record review was conducted by the co-investigator in order to collect additional data on the patients' risk factors for relapse into substance abuse. The facility record data is initially collected by the Harbor Light center staff through an intake interview along with other information obtained from the patient's medical records. The data collected through the facility record review included demographics, history of substance use and relapse, history of mental illness and treatment, and medical comorbidities. The co-investigator extracted data from the facility record using the Facility Record Data Collection Form (**APPENDIX 1**).

IV. Description of Variables

a. Prospective patient interview form

The prospective patient interview form is a researcher-designed, 13-item instrument consisting of four domains: (1) substance use and relapse, (2) mental illness diagnosis and severity, (3) medication history and adherence behavior, and (4) medical

comorbidities. The form begins by assessing when the patient checked into Salvation Army Harbor Light Center, which was included to determine if the patient was eligible for the study and to collect data on how long the patient has been in treatment prior to the interview. The substance use and relapse section of the instrument assessed what the patient's primary drug of abuse was, how long the patient has been using said drug, and what other illicit drugs the patient had used in their lifetime. The patient was then asked to self-report how many times they have relapsed in their substance use and what factors they believe have contributed to their relapse(s). Finally, the patient was asked how many times they have been in treatment for substance use prior to their current admission to Harbor Light.

The mental illness diagnosis and severity section begins by asking if the patient has ever been diagnosed with a mental illness by a healthcare professional and if so, what the diagnosis was. The patient's mental illness severity was assessed by asking the patient to think back to their mental illness symptoms prior to entering treatment while they were still using alcohol or illicit drugs. This was utilized to provide a baseline prior to treatment. The patient then self-reported their mental illness severity on a scale of 1 to 10, with 1 referring to no symptoms and 10 referring to very severe symptoms. A list of symptoms commonly related to depression, bipolar disorder, generalized anxiety, and schizophrenia was included in order to help the patient assess the symptoms that were particularly relevant.

The medication history and adherence behavior section begins by asking the patient if they have received any medication for their mental illness from a healthcare professional and if so, what medications they currently were taking and what medications have they previously taken. The patient is then asked to self-report their psychotropic medication adherence both a month before coming to treatment while still using alcohol and illicit substance and in their general lifetime. This adherence measure was scored on a scale of 1 to 10, with 1 referring to taking no doses and 10 referring to taking all doses as prescribed. If the patient was unsure of what the term adherence means, the researcher helped explain it to them in more detailed language. The patient was then asked what factors they believe have contributed to them not properly taking their medications.

Lastly, the patients' comorbidities were assessed by asking if they have ever been diagnosed with any other chronic medical condition by a healthcare professional, such as hepatitis C, diabetes, or high blood pressure and if so, what the diagnosis was. The patient was also asked if they are currently taking any prescribed medications for these comorbidities.

b. Morisky Medication Adherence Scale (MMAS-8)

The Morisky Medication Adherence Scale (MMAS-8), a multidimensional self-reported 8-item measure, was utilized to assess the patients' psychotropic medication adherence. The MMAS-8 seeks to measure adherence by identifying the underlying factors that lead to nonadherence such as forgetfulness, side effects, decreasing symptom severity, and

complexity of the patient's medical regimen.[197-199] Each item measures a specific adherence behavior and cannot be used individually as a determinant of adherence. The first seven items of the MMAS-8 are dichotomous responses requiring a yes or no response and the last item is a five-point Likert-scale. The items utilize reverse wording resulting in both positive and negative questioning about adherence behaviors in order to avoid desirability bias or patients giving only positive yes responses.[200] The MMAS-8 scoring system is copyright protected and available for licensing from the originator. A patient's final score can be categorized low adherence, medium adherence, or high adherence. As for psychometric properties, a 93% sensitivity and 53% specificity was reported while validating the tool in a cohort of low income patients treated for hypertension in an out-patient setting. The same study also reported a Cronbach's alpha value of 0.83, which is above the acceptance threshold of acceptability.[200] The MMAS-8 was chosen as the adherence measurement for the study due to its popularity, common usage in various clinical settings, widespread use in different diseases, populations, and countries, high level of concordance with pharmacy fill data and electronic adherence monitoring devices, and low response burden due to its conciseness. [201] The current study utilized the general MMAS-8, although other condition and medication-specific forms of the measure are available.

c. Drug Attitude Inventory (DAI-10)

The Drug Attitude Inventory (DAI-10) (**APPENDIX 5)** was utilized to measure patient attitudes and beliefs in regard to their prescribed psychotropic medications that may contribute to their adherence levels. The DAI is a 10-item, true/false, self-reported

measure that analyzes a patient's subjective feelings towards medication. For example, the DAI assesses if a patient believes that it is unnatural to take medication, if the good things about medication outweigh the bad, or if they stop taking medication once they feel better. In regard to scoring the DAI, questions that reflect a positive attitude towards medication are scored as +1 if the patient answers true and -1 if the patient answers false, whereas questions that reflect a negative attitude are scored as -1 if answered true and +1 if answered false. The total scoring of the DAI ranges from -10 to +10 with a total score greater than 0 representing a positive attitude towards medications, a total score less than zero representing a negative attitude towards medications and a total score of 0 representing a neutral attitude towards medication.[202] Previous research has shown that the reliability and validity of the DAI is similar to or greater than other common medication adherence screening instruments when used within the mentally ill population.[203] The DAI was used in the study due to its ease of administration and low response burden.

d. Condition specific measures

i. Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ-9) (**APPENDIX 6**) is a self-reported, 9-item instrument designed to screen, diagnose, monitor, and measure the severity of major depressive disorder (MDD). The PHQ-9, which was generated from the full 3-page PHQ questionnaire, incorporates both DSM-IV diagnostic criteria along with other common symptoms of depression. As stated, the PHQ-9 can be used as a diagnosis tool as well as a severity measure. For a patient to be diagnosed with MDD, he or she must answer

"More than half the days" or "Nearly every day" to question 1 and 2, must have 5 or more of the symptoms present on more than half the days, and must have not checked "not difficult at all" for question 10. When being used as a severity measure, the PHQ-9 score ranges from 0 to 27. A score of 5 represents mild, 10 represents moderate, 15 represents moderately severe, and 20 represents severe depression.[204] The PHQ-9 has been shown to have strong psychometric properties, with an internal reliability of 89% and a test-retest reliability of 84%. The PHQ-9 has also been validated for criterion validity and construct validity within the mental illness population.[205] The PHQ-9 was chosen to be used in the study due to its low response burden, simple scoring and common usage in clinical settings.

ii. Generalized Anxiety Disorder Assessment (GAD-7)

The Generalized Anxiety Disorder Assessment (GAD-7) (**APPENDIX 8**) is a 7-item self-reported screening instrument for patients with generalized anxiety disorder. The scale consists of 7 items related to the DSM-IV symptom criteria for GAD. The patients reported how often they have experienced these symptoms over the past two weeks with the options of selecting "Not at all", "Several days", "Over half the days", and "Nearly every day". In order to score the GAD-7, each answer is given a weighted score (not at all = 1, several days = 2, over half the days = 3, nearly every day = 4) and the scores are added together to get a total score. Similar to the PHQ-9, the GAD-7 can be used as both a diagnostic tool and a symptom severity measure. A score of 10 or more can be interpreted as a probable diagnosis of GAD, which can be confirmed by further psychiatric evaluation. As for severity, a score of 5 refers to mild anxiety, 10 refers to

moderate anxiety, and 15 refers to severe anxiety.[206] In a study conducted by Spitzer *et al.,* the psychometric properties of the GAD-7 were measured in a population of 2,740 adult patients in 15 primary care clinics. The researchers found a high internal consistency of 92% and a test-retest reliability of 83%. In addition, the researchers also concluded the GAD-7 had good criterion, construct, factorial, and procedural validity.[206] The GAD-7 was chosen for this study due to its conciseness, ease of scoring, and strong psychometric properties. While the GAD-7 was intended for screening, the study used it as a measurement for severity. The GAD-7 has been established in previous literature as a valid and efficient tool for assessing GAD severity in clinical practice and research.[206]

iii. Mood Disorder Questionnaire (MDQ)

The Mood Disorder Questionnaire (MDQ) (**APPENDIX 7**) is a 15-item self-reported screening instrument for patients with bipolar disorder. The instrument consists of five questions, of which the first lists 13 items related to the DSM-IV symptom criteria for bipolar disorder. The MDQ then assess if these symptoms occurred in the same period, the impact of the symptoms on the patient's life, whether the patient has a family history of bipolar disorder, and if the patient has been previously diagnosed with bipolar disorder. In order to receive a positive screening for bipolar disorder, the patient must exhibit 7 of the 13 symptoms listed in question 1, must have experienced more than one of these symptoms at the same time, and must report these symptoms have resulted in either moderate or serious problems in their life.[207] In a study conducted by Hirschfeld *et al.,* the psychometric properties of the MDQ were measured using a cohort of 198 patients at five outpatient psychiatric clinics. The results showed the MDQ has a high

internal consistency of 90%. The researchers also found that the MDQ has a good sensitivity (0.73; 95% CI: 0.65- 0.81) and a good specificity (0.90; 95% CI: 0.84-0.96).[208] The MDQ was chosen for this study due to its timely and accurate evaluation of bipolar disorder. Similarly, to the GAD-7, the MDQ was intended for screening but the study used it as a measurement for severity which has been reported in previous literature.[209]

iv. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS) (**APPENDIX 9**) is a widely utilized, 18-item instrument used to assess the positive, negative and affective symptoms in patients with psychotic disorders, especially schizophrenia. Each item of the instrument gives a description of a specific symptom related to psychotic disorders and the patient assigns a number to each symptom that correlates with their self-reported severity, ranging from 1 (not present) to 7 (extremely severe). While there is no established total scoring criteria for the BPRS, the scores of the 18 items can be added together and compared to other patients or measured for change over time.[210] While there is a lack of research into the BPRS's psychometric properties, one study conducted by Anderson *et al.* found that the instrument has both adequate reliability (78%) and validity (66%) in the psychotic population.[211] The BPRS was chosen for this study due to its wide use in the psychiatric field in order to assess patients with schizophrenia.

e. Longitudinal follow-up interview form

The Longitudinal Follow-up Interview Form (**APPENDIX 3**) is a researcher-designed, 6-item instrument consisting of three domains: (1) substance use relapse, (2) mental illness symptom severity, and (3) psychotropic medication adherence. The form begins by asking the patient if he resumed the use of any alcohol or drugs since the last interview. If the patients answered yes, the interviewer assessed when the relapse occurred and if the patient has sought help. Then the patient was asked to report how their mental illness symptoms have changed since the last interview, with the options of "no current symptoms," "symptoms decreased," "symptoms increased," and "symptoms remained the same." Similar to the Prospective Patient Interview Form, a list of symptoms commonly related to depression, bipolar disorder, generalized anxiety, and schizophrenia is included in order to help the patient assess their symptom severity level. Lastly, the patients were asked to assess their adherence levels since the last interview on a scale of 1 to 10, with 1 referring to taking no doses and 10 referring to taking all doses as prescribed. If the patient has not taken their medications as prescribed, they were asked what factors they believed contributed to the nonadherence.

f. Facility record data collection form

The Facility Record Data Collection Form (**APPENDIX 1**) is a 19-item form created by the researchers to collect information on newly admitted patients from the facility intake form. The form consists of four sections, which are patient demographics, history of substance use and relapse, history of mental illness treatment and adherence, and medical comorbidities. The data collected on patient demographic and social characteristics

include age, race/ethnicity, employment status, income level, education background, housing situation, and family support. The data collected on the patient's substance use and relapse history include the patient's primary substance of use and other substances used, age of first use, length of use, longest time clean, and number of admissions at Harbor Light Center and other rehabilitation programs. Other rehabilitation program stays were defined as any time a patient received inpatient or outpatient treatment for their SUD outside of the Harbor Light Center. The data collected on patient mental illness history include both patient-reported and medically-assigned mental illness diagnosis, age of diagnosis, severity, pharmacological or non-pharmacological treatment both current and previous, and medication adherence levels. The intake faculty determines the patient's mental illness severity level by assessing their signs of withdraw, the presence of post-acute withdraw syndrome, visible SUD symptoms, psychological and emotional drug cravings, mood stability, and presence of auditory or visual hallucinations. Patient adherence levels are determined through the intake faculty assessing the patient's external and internal motivation. Lastly, the patient's other medical comorbidity diagnoses are assessed and reported.

V. Data and Statistical Analysis

a. Research objective 1

The first objective of the study was to identify personal, social and clinical histories for patients with substance use disorder and either major depressive disorder, bipolar disorder, schizophrenia or generalized anxiety disorder. Data for this objective was collected from both the primary interview and the facility records. This objective was

accomplished through a descriptive analysis of the following variables: age, race (Caucasian and African American), employment status (unemployed, employed, disabled), socioeconomic status (monthly income level), educational background (less than high school, high school, more than high school), housing situation (homeless, living with family, other), number of incarcerations, primary substance of use, number of previous relapses, number of previous treatment stays, number of previous times at Harbor Light, age of first substance use, mental illness diagnosis, mental illness severity level, number of other medical comorbidities, and number of psychotropic medications prescribed. The variables were broken down into the categories listed above in order to make a proper analysis and compare the information. The data for this analysis was primarily gathered through the facility data record collection with some supplementation from data collected through the primary interviews. Data gathered from the facility data record collection included age, race, employment status, socioeconomic status, educational background, housing situation, number of incarcerations, number of previous times at Harbor Light, and age of first substance use. Data collected through primary interviews included primary substance of use, number of pervious relapses, number of previous treatment stays, mental illness diagnosis, number of other medical comorbidities, and number of psychotropic medications prescribed. Results were reported using frequencies, means with standard deviations, and medians with ranges.

b. Research objective 2

The second objective of the study was to identify discrepancies between patient self-reported data versus facility record data in regard to mental illness traits, substance abuse

history, and psychotropic medication. This objective was accomplished through two analyses of the following variables: primary substance of use, mental illness diagnosis, number of mental illness comorbidities, number of psychotropic medications prescribed, number of other comorbid diagnoses, and number of previous treatment stays. These variables were chosen for this analysis due to them being collected at both the primary patient interview and the facility data record collection. The above variables also play a vital role in study's other statistical analysis, therefore the accuracy of the patient self-reported should be confirmed. Cohen's kappa coefficient was utilized to determine agreement between self-reported and facility record data. This statistical analysis was chosen over a simple percent agreement calculation due it being a more robust measure that takes into account agreement occurring by chance.[212]

c. Research objective 3

The third objective was to investigate the specific role of medication adherence and barriers to use for psychotropic medications upon substance abuse relapse. Data for this objective was collected from both the primary interview and the facility records. This objective was completed through five separate analyses. First, patient demographic characteristics were stratified by self-reported adherence rates, MMAS-8 total score, and number of self-reported relapses. The variables observed in this analysis included age (18-29, 30-39, 40-49, 50+), race/ethnicity, employment status, socioeconomic status, education background, housing situation prior to entry, and number of incarcerations (0, 1, 2, 3+). The mean and standard deviation of adherence scores and relapses

corresponding with each variable were reported then mean scores were assessed for significant differences.

The patients' substance abuse characteristics were then stratified by self-reported adherence rates, MMAS-8 total score, and number of relapses. Substance abuse characteristics included the variables of primary substance of use (heroin, alcohol, crack cocaine, other), number of distinct drugs used (≤3, 4-9, 10+), and length of use (less than 10 years, 10 to 29 years, 30+ years). If there was a discrepancy between patient reported data and facility records, patient reported data was used in the analysis.

The patients' health related characteristics were then compared according to self-reported adherence rates, MMAS-8 total score, and number of relapses. The mental illness characteristics included in this analysis were mental illness diagnosis (MDD, GAD, bipolar disorder, schizophrenia, more than 1 mental illness), self-reported mental illness severity level (1-6, 7-9, 10), number of psychotropic medications prescribed (1-2, 3-4, 5+), presence of more than one mental illness (yes, no), PHQ-9 score (not present, mild, moderate, moderately severe, severe), MDQ score (negative, positive), and GAD-7 (not present, mild, moderate, severe). The BPRS scores were excluded from this analysis due to only two patients having schizophrenia and both patients received similar scores for severity level. Similar to the substance abuse characteristics, if there was a discrepancy between patient reported data and facility records, patient reported data was used in the analysis.

The patients' attitudes towards medications were then analyzed by stratifying the DAI results by self-reported adherence rate, MMAS-8 total score, and number of relapses. The total scores of the DAI were first compared according to adherence and relapses then each question was broken down individually.

Patients' adherence scores were correlated with the self-reported number of relapses in order to assess the overall relationship between psychotropic medication adherence and substance use relapse. Pearson's correlation coefficient was utilized for this statistical analysis. The four adherence measurements included were the MMAS-8 total score, MMAS-8 intentional score, MMAS-8 unintentional score, and self-report adherence rate.

A multivariable logistic regression model was then created in order to assess the direct impact psychotropic medication adherence has on relapse frequency. Patient characteristics that were hypothesized to be a predictor of relapse were included in the model. Said characteristics were MMAS-8 total score, self-reported mental illness symptom severity level, mental illness type, length of substance use and DAI total score. All variables except for mental illness type were classified as continuous variables. Mental illness type was classified as a nominal variable composed of the following groups: MDD, GAD, Bipolar, Schizophrenia, 2+.

In regard to statistical analyses, t-test and ANOVAs were utilized for continuous variables and chi square tests for categorical variables. When t-tests were used, Levene's test for equality of variance was utilized to assess variance within the data. For ANOVAs, a test of homogeneity of variance was run to assess variance within the data. If there was no significant variance, Tukey's post hoc was then used to determine between which variables the significant difference had occurred. If significant variance was present then the Dunnett T3 statistic was used. As stated, Pearson's correlation coefficient was utilized for the correlation analysis. An *a priori* p-value of <0.05 was considered statistically significant for all statistical assessments and effect sizes will be reported when applicable, using Cohen's d and odds ratio with a 95% confidence interval.

d. Research objective 4

The fourth and final research objective was to assess follow-up changes in mental illness severity and medication adherence in dual diagnosis patients enrolled in a substance abuse rehabilitation program. Data for this objective was collected from both the primary interview and the follow-up interviews. This was accomplished through three analyses. First, the frequency and percentage of patients was reported according to which interview they completed (primary interview only, 1st follow-up, 2nd follow-up). Second, patient characteristics including age, MMAS-8 total score, MMAS-8 intentional score, MMAS-8 unintentional score, self-reported adherence rate, mental illness type, mental illness symptom severity, substance of choice, DAI-10 total score, receiving income, and housing situation were stratified according to follow-up interviews completed. Lastly, changes in patients' self-reported adherence from interview to interview were analyzed in

order to assess for significant change in adherence over time while enrolled in the rehabilitation program. The results in this analysis were reported in mean difference.

e. Missing data

Missing data was not adjusted for in the statistical analysis of the study results. Due to the methodological design of the study, the researchers concluded that missing data would have no impact on the results of the study. The interviewer checked each form for completeness during the primary interviews and follow-up interviews before the interview concluded. If the patient missed any question, they were simply asked to complete it before leaving, therefore there was no missing data from the primary data collection step of the study. Patients who dropped out of the study were not considered missing data. They were moved to the drop-out group of the study sample and analyzed from that perspective. As for the facility data, only one patient had missing data for their mental illness diagnosis. The patient self-reported a MDD diagnosis and the facility data confirmed that the patient was prescribed the SSRI Prozac® and the antidepressant Remeron®. Therefore, the researchers safely assumed that the patient was diagnosed with MDD. Two patients had not reported their previous living status during their intake interview but this played an insignificant role in the overall analysis. There were no other cases of missing data prevalent in the data included in the statistical analysis.

VI. Data Capture

During the primary and follow-up patient interviews, information was collected using paper data collection forms and was then transferred to a SPSS datafile. Data collected through the facility record reviews were entered directly into an excel spreadsheet. The Morisky Widget (MMAS Research LLC) was utilized in order to score and record the results of the MMAS-8. Permission for use and a license agreement was obtained from MMAS Research LLC. SPSS Statistics 22 (IBM; Armonk, NY) was utilized for all statistical comparisons and modeling.

VII. Subject Rights and Ethics

Due to the vulnerable nature of the study participants, enhanced care was given to research ethics and subject rights. The study underwent and received a full board approval by the Duquesne University Institutional Review Board, and the thesis committee included a faculty member with specialized expertise in psychology, addiction and research ethics for supervision. Before beginning any data collection, the researcher confirmed that the participants fully understood the confidentiality protocol, their right to withdraw, and HIPAA authorization, using both verbal and written explanations. All health information procedures in the study were HIPAA compliant and no protected health information (PHI) was recorded in any data collection procedure. Patient names never appeared on any research instrument and their responses were only reported through statistical data summaries. Each patient was given a study ID number in order to keep their identity anonymous. A study ID log that matched each ID number to their corresponding patient's name was kept in a Harbor Light Center facility member's office

and was only removed in order to conduct the patient record review process. All other patient data collected throughout the study were kept confidential at all times and were protected to every extent possible.

After completing patient interviews, the data collected was uploaded onto a password protected computer located in the graduate student office located on Duquesne University's campus. The researchers had the sole access to the protected data. All materials with personal or health information will be maintained for three years. Electronic data will be manually deleted from the computer's hard drive and all physical material will be shredded by the researchers at the completion of the study.

CHAPTER 4 – RESULTS

I. Objective 1

Identify personal, social, and clinical history for patients with substance use disorder and either major depressive disorder, bipolar disorder, schizophrenia, or generalized anxiety disorder

a. Demographics

The final study sample consisted of 38 patients. The study data collection period took place from November 1st, 2016 to June 20th, 2017. A majority of the patients were white (n=27, 71.1%) and the rest were African American. The mean age of the patients was 40.8±11.4 years old. A total of 32 (84.2%) patients were unemployed and 7 (18.4%) patients were receiving any form of income before entering treatment, with an approximate monthly income level of $145.08 which includes those receiving no income. Patients' education level was somewhat evenly distributed, with 15 patients (39.5%) having less than a high school education, 15 (39.5%) having a high school degree, and 8 (21.1%) having more than a high school education. The median number of incarcerations was 1 with a range of 0 to 4. A majority of the patients were homeless before entering treatment (n=30, 78.9%). The frequencies and percentages of patient demographics are outlined in **Table 2**.

Table 2: Demographic Characteristics

Demographic Characteristics **n (%) unless specified otherwise**	**Study Sample** **(n=38)**
Age (mean, st dev)	40.8 (11.4)
Race/ethnicity:	
Caucasian	27 (71.1)
African American	11 (28.9)
Employment status prior to treatment:	
Unemployed	32 (84.2)
Disabled	4 (10.5)
Employed	2 (5.3)
Approximate monthly income level ($) prior to treatment (mean, st dev)	145.08 (318.65)
Receiving any income prior to treatment:	
Yes	7 (18.4)
No	31 (81.6)
Educational background:	
Less than high school	15 (39.5)
High school	15 (39.5)
More than high school	8 (21.1)
Housing situation prior to treatment:	
Homeless	30 (78.9)
Living with family	2 (5.2)
Other	4 (10.5)
Missing	2 (5.3)
# of incarcerations	
Mean, st dev	1.2 (1.2)
Median, range	1.0 (0-4)

b. Substance use characteristics

In terms of substance use characteristics, heroin was the most common primary drug of use among patients (n=19, 50%), followed by alcohol (n=12, 31.6%), and crack cocaine (n=4, 10.5%). Other substances used by patients included marijuana, methamphetamines, cocaine, benzodiazepines, hallucinogens, opiates, buprenorphine/naloxone, amphetamines, Robitussin®, and research chemicals. The average number of substances used was 5.4 and the average length of substance use was 20.3 years, with the average age of first substance use being 13.1 years old. The average number of rehabilitation treatment center stays before entering Harbor Light was 6.1 stays. Lastly, the average number of previous relapses was 9.7 among the patient population. The frequencies and percentages of patient substance use characteristics are outlined in **Table 3**.

Table 3: Substance Use Characteristics

Substance Use Characteristics n (%) unless specified otherwise	**Study Sample (n=38)**
Primary substance of use:	
Heroin	19 (50.0)
Alcohol	12 (31.6)
Crack cocaine	4 (10.5)
Alcohol/cocaine	1 (2.6)
Marijuana	1 (2.6)
Methamphetamines	1 (2.6)
# of distinct substances used	
Mean, st dev	5.4 (2.8)
Median, range	4 (1-10)
# of previous relapses	
Mean, st dev	9.7 (14.1)
Median, range	6 (0-75)
# of previous treatment stays	
Mean, st dev	6.1 (6.0)
Median, range	4 (0-25)
Length of substance use (mean, st dev)	20.3 (13.7)
Age of first use (mean, st dev)	13.1 (3.0)

c. Health-related characteristics

In regard to health characteristics, half of the patients (n=19, 50%) had two or more mental illness diagnoses. The most common mental illness was the combination between MDD and GAD (n=9, 23.7%), followed by MDD alone (n=7, 18.4%), and bipolar disorder (n=6, 15.8%). Four patients had a combination of MDD, GAD, and bipolar disorder. This combination of mental illness was the only instance of patients having three or more comorbidities. On a scale from 1 to 10, the average self-reported mental illness severity level was 8.39±1.93. Patients were prescribed an average of 2.3 psychotropic medications and the number of other comorbid diagnoses was 2.3. The frequencies/percentages of patient health-related characteristics are outlined in **Table 4**.

Table 4: Health-related Characteristics

Health-related characteristics n (%) unless specified otherwise	**Study Sample (n=38)**
Co-morbid mental illness:	
Major depressive disorder (MDD)	7 (18.4)
Generalized anxiety disorder (GAD)	4 (10.5)
Bipolar	6 (15.8)
Schizophrenia	2 (5.4)
Comorbidity (2+ conditions)	19 (50.0)
MDD and GAD	9 (23.7)
Bipolar and Schizophrenia	2 (5.4)
MDD, GAD, and Bipolar	4 (10.5)
GAD and Bipolar	2 (5.3)
MDD and Bipolar	2 (5.3)
Self-reported mental illness severity	
Mean, st dev	8.39 (1.93)
Median, range	9.0 (1-10)
# of other comorbid diagnoses	
Mean, st dev	2.3 (1.8)
Median, range	1 (0-3)
# of psychotropic medications prescribed	
Mean, st dev	2.3 (1.40)
Median, range	2 (0-6)

II. Objective 2

Measure agreeance between patient self-report versus facility record history for mental illness, substance abuse, and psychotropic medication

a. Patient-report and facility record comparison

Results from the patient interviews were compared to the facility medical records in order to identify discrepancies and to test the agreeance of the patient self-reported data. Cohen's kappa, which measures the extent of agreement among data collected by two different collectors, showed a significant agreeance in the reporting of primary substance of use (κ=0.753, p<.001), mental illness diagnosis (κ=0.434, p<.001), number of mental illness comorbidities (κ=0.257, p=0.008), and number of psychotropic medications prescribed (κ=0.094, p<.001). Cohen's kappa showed an insignificant agreeance between patient self-report and facility records for number of other comorbid diagnoses (κ=0.094, p=0.176) and number of previous treatment stays (κ=0.107, p=0.05). Patients reported less comorbid diagnoses (median 1.0 vs 2.0) and more previous treatment stays (median 4.0 vs 3.0) when compared to facility records. The results of the patient-report and facility record comparison are outlined in **Table 5**.

Table 5: Patient Report vs Facility Record Data

Variables	Patient interview N (%)	Medical record N (%)	Cohen's κ	p-value
Primary substance of use:				
Alcohol	12 (31.6)	17 (44.7)		
Alcohol and cocaine	1 (2.6)	0 (0.0)		
Crack cocaine	4 (10.5)	1 (2.6)		
Heroin	17 (44.7)	19 (50.0)	0.753	<.001*
Heroin and opiates	1 (2.6)	0 (0.0)		
Marijuana	1 (2.6)	0 (0.0)		
Methamphetamine	1 (2.6)	1 (2.6)		
Opiates	1 (2.6)	0 (0.0)		
Mental illness diagnosis				
GAD	4 (10.5)	4 (10.5)		
GAD and Bipolar	2 (5.3)	0 (0.00		
GAD, Bipolar, and MDD	4 (10.5)	7 (18.4)		
GAD and MDD	9 (23.7)	10 (26.3)		
Bipolar	6 (15.8)	6 (15.8)		
Bipolar and MDD	2 (5.3)	4 (10.5)	0.434	<.001*
Bipolar, MDD and Schizophrenia	0 (0.0)	1 (2.6)		
Bipolar and Schizophrenia	2 (5.3)	1 (2.6)		
MDD	7 (18.4)	2 (5.3)		
MDD and Schizophrenia	0 (0.0)	1 (2.6)		
Schizophrenia	2 (5.3)	1 (2.6)		
Missing	0 (0.0)	1 (2.6)		
# of mental illness comorbidities (median, range)	2.0 (1-5)	2.0 (1-4)	0.257	<.001*
# of psychotropic medications prescribed (median, range)	2.0 (0-6)	3.0 (1-7)	0.240	<.001*
# of other comorbid diagnoses (median, range)	1.0 (0-3)	2.0 (0-9)	0.094	0.176
# of previous treatment stays (median, range)	4.0 (0-25)	3.0 (0-8)	0.107	0.052

III. Objective 3

Investigate the specific role of medication adherence and barriers to use for psychotropic medications upon substance abuse relapse

a. Measurement scores breakdown

i. MMAS-8

The Morisky Medication Adherence Scale (MMAS-8) was utilized to measure patient's adherence. The patients' average score was 3.5±2.0, considered low adherence. A total of 33 (86.6%) of patients had low adherence, 4 (10.5%) had medium adherence, and only 1 patient (2.6%) had high adherence. Patients received similar average scores for both intentional and unintentional adherence. The results for each individual question of the MMAS-8 is shown in **Table 6**.

Table 6: MMAS-8 Breakdown

MMAS-8 Question	Response N (%)
Total score (mean, st dev)	3.5 (2.0)
1. Do you sometimes forget to take your pills?	
Yes	30 (78.9)
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?	
Yes	22 (57.9)
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?	
Yes	23 (60.5)
4. When you travel or leave home, do you sometimes forget to bring along your medication?	
Yes	27 (71.1)
5. Did you take your medicine yesterday?	
Yes	30 (78.9)
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	
Yes	23 (60.5)
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	
Yes	20 (52.6)
8. How often do you have difficulty remembering to take all your medications?	
Never	1 (2.6)
Almost Never	14 (36.8)
Sometimes	15 (39.5)
Frequently	6 (15.8)
Always	2 (5.3)

ii. DAI-10

The Drug Attitude Inventory (DAI-10) was given to the patients in order measure patient attitudes and beliefs in regard to their prescribed psychotropic medications that may contribute to their adherence levels. The cutoff point for the DAI is 0; therefore, a negative score reflects a negative attitude, a score of 0 reflects a neutral attitude, and a positive score reflects a positive attitude. The mean total score was 5.4±3.0 which reflects a positive attitude towards medications. Almost all of the patients received a score above 0 (n=34, 98.5%), while three patients (7.9%) scored 0 and only one patient (2.6%) scored below zero. The results for each individual question of the DAI-10 along with the total scoring is shown in **Table 7**.

Table 7: DAI-10 Breakdown

Drug Attitude Inventory (DAI-10)	**Response N (%)**
Total score (mean, st dev)	5.4 (3.0)
Total score rating	
Negative attitude (<0)	1 (2.6)
Neutral (0)	3 (7.9)
Positive attitude (>0)	34 (98.5)
1. For me, the good things about medication outweigh the bad	
True	34 (89.5)
False	4 (10.5)
2. I feel strange, “doped up”, on medication	
True	12 (31.6)
False	26 (68.4)
3. I take medications of my own free choice	
True	33 (86.8)
False	5 (13.2)
4. Medications make me feel more relaxed	
True	31 (81.6)
False	7 (18.4)
5. Medication makes me feel tired and sluggish	
True	19 (50.0)
False	19 (50.0)
6. I take medication only when I feel ill	
True	8 (21.1)
False	30 (78.8)
7. I feel more normal on medication	
True	32 (84.2)
False	6 (15.8)
8. It is unnatural for my mind and body to be controlled by medications	
True	13 (34.2)
False	25 (65.8)
9. My thoughts are clearer on medication	
True	27 (71.1)
False	11 (28.9)
10. Taking medication will prevent me from having a breakdown	
True	27 (71.1)
False	11 (28.9)

b. Results stratified by adherence and relapse

i. Patients characteristics

Patient characteristics including age (18-29, 30-39, 40-49, 50+), race/ethnicity (Caucasian, African American), employment status (unemployed, employed, disabled), receiving income (yes, no), educational background (less than high school, high school, more than high school), housing situation (homeless, living with family, other), incarcerations (0, 1, 2, 3+), and number of comorbid health conditions (0, 1-2, 3-4, 5+) were stratified according to total MMAS-8 score, self-reported adherence on a scale from 1-10, and self-reported relapse rate. The results showed that the group of patients who were receiving income prior to admission had significantly higher mean relapse rates compared to the group of patients who were not receiving income (16.9 vs 8.1, p=0.02). The results of this analysis are shown in **Table 8**.

Table 8: Patients Characteristics Stratified by Adherence and Relapse

Demographic Characteristic	Adherence (MMAS-8 score; mean, st dev)	Adherence (self-report; mean, st dev)	Relapses (self-report; mean, st dev)
Age			
18-29	3.6 (2.5)	3.3 (4.6)	6.3 (3.1)
30-39	3.9 (1.5)	3.6 (3.3)	5.7 (7.3)
40-49	3.9 (2.4)	2.9 (3.2)	11.5 (13.7)
50+	2.4 (1.2)	2.1 (3.3)	15.5 (24.2)
Race/ethnicity:			
Caucasian	3.5 (1.9)	2.9 (3.4)	11.7 (16.3)
African American	3.7 (2.1)	3.6 (3.4)	4.8 (3.2)
Employment status:			
Unemployed	3.5 (1.9)	2.8 (3.2)	8.9 (13.5)
Disabled	5.2 (1.9)	5.5 (5.2)	7.3 (2.5)
Employed	1.5 (0.0)	2.0 (00)	29.0 (29.7)
Receiving income			
Yes	4.1 (2.6)	2.7 (3.0)	16.85 (25.7)*
No	3.4 (1.8)	4.6 (4.8)	8.1 (9.9)*
Educational background:			
Less than high school	4.2 (1.9)	3.1 (3.8)	8.5 (12.0)
High school	3.5 (1.8)	3.7 (3.6)	7.4 (5.6)
More than high school	2.5 (2.1)	1.6 (1.1)	16.1 (25.3)
Housing situation			
Homeless	3.5 (2.0)	2.7 (3.1)	10.1 (15.7)
Living with family	2.4 (0.2)	2.0 (1.4)	5.5 (0.7)
Other	3.9 (2.7)	5.0 (4.7)	11.0 (6.2)
Incarcerations			
0	3.2 (2.1)	2.0 (2.5)	13.8 (22.4)
1	4.0 (2.1)	3.6 (4.1)	7.9 (6.7)
2	4.3 (1.6)	3.5 (3.0)	7.3 (8.4)
3+	2.3 (1.6)	4.2 (4.5)	6.8 (3.6)
Number of comorbid health conditions			
0	4.5 (1.7)	3.3 (3.4)	7.0 (6.3)
1-2	3.5 (2.2)	2.7 (3.8)	6.3 (5.1)
3-4	3.6 (1.7)	2.3 (2.9)	16.3 (22.1)
5+	1.3 (1.1)	6.0 (4.2)	4.3 (2.1)

**Significant difference at p<0.05*

ii. Substance use characteristics

Substance use characteristics including primary substance of use (heroin, alcohol, crack cocaine, other), number of distinct drugs used (≤ 3, 4-9, 10+), and length of use (less than 10 years, 10 to 29 years, 30+ years) were stratified according to total MMAS-8 score, self-reported adherence, and self-reported relapse rate. The results showed that there were no significant differences among these groups. The results of this analysis are shown in **Table 9**.

Table 9: Substance Use Characteristics Stratified by Adherence and Relapse

Substance Use Characteristic	Adherence (MMAS-8 score; mean, st dev)	Adherence (self-report; mean, st dev)	Relapses (self-report; mean, st dev)
Primary substance of use:			
Heroin	3.8 (2.1)	3.2 (3.7)	6.4 (5.9)
Alcohol	3.3 (1.7)	2.3 (2.6)	16.6 (22.6)
Crack cocaine	4.4 (1.8)	4.3 (4.4)	9.8 (7.6)
Other	1.7 (1.7)	3.3 (4.0)	3.0 (1.7)
# of distinct drugs used			
≤ 3	3.9 (2.4)	4.2 (4.1)	15.5 (24.1)
4-9	3.4 (1.9)	2.6 (2.9)	7.8 (7.0)
10+	3.3 (1.5)	2.5 (3.4)	5.7 (2.3)
Length of use			
Less than 10 years	4.0 (2.0)	2.4 (2.4)	4.3 (3.1)
10 to 29 years	3.4 (1.9)	3.6 (3.6)	7.2 (6.7)
30+ years	3.4 (2.2)	2.7 (3.7)	17.0 (22.4)

 Pertinent citations include: (1) Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354. (2) Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66. (3) Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

iii. Mental illness characteristics

Mental illness characteristics including mental illness diagnosis (MDD, GAD, bipolar disorder, schizophrenia, more than one mental illness), self-reported mental illness severity level (1-6, 7-9, 10), number of psychotropic medications prescribed (1-2, 3-4, 5+), presence of more than one mental illness (yes, no), PHQ-9 score (not present, mild, moderate, moderately severe, severe), MDQ score (negative, positive), and GAD-7 (not present, mild, moderate, severe) were stratified according to total MMAS-8 score, self-reported adherence, and self-reported relapse rate. The BPRS scores were excluded from this analysis due to only two patients having schizophrenia and both patients received similar scores for severity level. The results showed that there were no significant differences among these groups. The results of this analysis are shown in **Table 10**.

Table 10: Mental Illness Characteristics Stratified by Adherence and Relapse

Mental Illness Characteristic	Adherence (MMAS-8 score; mean, st dev)	Adherence (self-report; mean, st dev)	Relapses (self-report; mean, st dev)
Diagnosis			
MDD	3.6 (2.0)	2.5 (3.3)	5.9 (3.8)
GAD	3.4 (2.3)	2.3 (1.0)	11.0 (10.9)
Bipolar Disorder	4.0 (2.5)	4.7 (4.1)	9.0 (8.6)
Schizophrenia	6.3 (2.5)	5.5 (6.4)	8.5 (2.1)
More than one mental illness	3.1 (1.6)	2.6 (3.3)	11.2 (18.8)
Self-reported severity			
Low (1-6)	2.2 (2.0)	2.6 (2.5)	4.0 (2.5)
Medium (7-9)	3.7 (1.7)	3.1 (3.8)	8.0 (5.3)
High (10)	3.8 (2.1)	3.2 (3.4)	13.3 (20.8)
Number of psychotropic medications prescribed			
1-2	2.9 (1.4)	2.6 (3.5)	7.3 (5.5)
3-4	3.9 (1.7)	3.1 (3.4)	10.4 (17.0)
5+	3.6 (2.9)	3.4 (3.6)	10.8 (14.9)
Presence of more than one mental illness			
Yes	3.6 (1.8)	3.4 (3.7)	8.7 (7.3)
No	3.5 (2.2)	2.4 (2.7)	10.2 (16.7)
PHQ-9			
Not present (0-4)	3.5 ( )	0.0 ( )	9.0 ( )
Mild (5-9)	-	-	-
Moderate (10-14)	4.0 (1.3)	5.0 (4.0)	5.0 (2.2)
Moderately severe (15-19)	3.2 (2.2)	0.8 (1.0)	5.2 (4.0)
Severe (20-27)	3.0 (1.8)	2.6 (3.6)	16.0 (23.9)
MDQ			
Negative screen	3.8 (1.7)	3.3 (2.6)	18.3 (22.9)
Positive screen	3.2 (2.1)	3.1 (3.6)	6.3 (5.1)
GAD-7			
Not present (0-4)	3.5 ( )	0.0 ( )	9.0 ( )
Mild (5-9)	4.5 ( )	1.0 ( )	1.0 ( )
Moderate (10-14)	2.9 (1.7)	0.7 (1.2)	7.0 (1.7)
Severe (15+)	3.4 (1.9)	3.6 (3.5)	14.0 (22.1)

iv. DAI-10

Patients' total score on the DAI-10 along with each individual item were stratified according to total MMAS-8 score, self-reported adherence, and self-reported relapse rate. While there were no significant differences in terms of total scores, there was significance at the individual item level. Patients who answered "True" to the statement "For me, the good things about medication outweigh the bad" had significantly higher self-reported adherence rate compared to those who answered "False" (3.3 vs 1.0, p=.001). Patients who answered "True" to the statement "I feel strange, or doped up, on medication" had significantly lower MMAS-8 scores (2.5 vs 4.0, p=.024) and significantly lower self-reported adherence scores (1.3 vs 3.9, p=.030). Patients who answered "True" to the statement "I take medications on my own free choice" had significantly higher self-reported adherence (3.3 vs 1.6, p=.033). Patients who answered "True" to the statement "It is unnatural for my mind and body to be controlled by medications" had significantly lower MMAS-8 scores (2.3 vs 4.2, p=.004). Lastly, patients who answered "True" to the statement "Taking medication will prevent me from having a breakdown" had significantly higher MMAS-8 scores (4.0 vs 2.5, p=.035). There were no significance differences in relapse rates for any questions in the DAI-10. The results of this analysis are shown in **Table 11**.

Table 11: DAI-10 Stratified by Adherence and Relapse

Drug Attitude Inventory (DAI-10)	Adherence (MMAS-8 score; mean, st dev)	Adherence (self-report; mean, st dev)	Relapses (self-report; mean, st dev)
Total score			
Negative (<0)	0.5 ( )	1.0 ( )	10 ( )
Neutral (0)	3.1 (1.9)	6.3 (4.7)	26.3 (42.1)
Positive (<0)	3.7 (1.9)	2.8 (3.2)	8.2 (9.4)
1. For me, the good things about medication outweigh the bad			
True	3.6 (2.0)	3.3 (3.5)*	9.7 (14.7)
False	3.1 (1.8)	1.0 (0.0)*	9.3 (8.3)
2. I feel strange, “doped up”, on medication			
True	2.5 (1.5)*	1.3 (1.1)*	11.6 (20.2)
False	4.0 (2.0)*	3.9 (3.8)*	8.8 (10.6)
3. I take medications of my own free choice			
True	3.5 (2.0)	3.3 (3.6)*	10.6 (14.9)
False	3.7 (1.4)	1.6 (0.9)*	3.4 (2.6)
4. Medications make me feel more relaxed			
True	3.7 (1.9)	3.2 (3.4)	7.9 (9.5)
False	2.8 (2.3)	2.3 (3.8)	17.4 (26.2)
5. Medication makes me feel tired and sluggish			
True	3.2 (1.9)	3.5 (3.7)	7.5 (6.50
False	3.9 (2.0)	2.6 (3.0)	11.9 (18.9)
6. I take medication only when I feel ill			
True	2.8 (1.4)	3.1 (2.9)	5.6 (3.4)
False	3.7 (2.1)	3.0 (3.6)	10.8 (15.7)
7. I feel more normal on medication			
True	3.8 (1.9)	2.9 (3.3)	8.2 (9.7)
False	2.2 (1.6)	3.7 (4.2)	17.8 (28.2)

8. It is unnatural for my mind and body to be controlled by medications			
True	2.3 (1.5)*	2.6 (3.0)	15.4 (22.6)
False	4.2 (1.9)*	3.3 (3.6)	6.7 (5.0)
9. My thoughts are clearer on medication			
True	3.7 (2.0)	3.0 (3.5)	8.3 (9.6)
False	3.0 (1.9)	3.3 (3.3)	13.1 (21.9)
10. Taking medication will prevent me from having a breakdown			
True	4.0 (2.0)*	3.1 (3.5)	10.7 (16.1)
False	2.5 (1.5)*	3.0 (3.2)	7.1 (7.2)

**Significant difference at p<.05;* Pertinent citations include: (1) Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354. (2) Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66. (3) Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

c. Adherence measurements and relapse correlation coefficients

Correlation coefficients were computed among the four different measurements of adherence and patients' self-reported relapse rate. The four adherence measurements included were the MMAS-8 total score, MMAS-8 intentional score, MMAS-8 unintentional score, and self-report adherence rate. The results of the correlation analyses, presented in **Table 12**, showed that self-reported relapse rate was negatively correlated with the MMAS-8 intentional score ($r = -.360$, $p = .026$). MMAS-8 total score was positively correlated with self-reported adherence rates ($r = .618$, $p < .001$), the MMAS-8 intentional score ($r = .869$, $p < .001$), and the MMAS-8 unintentional score ($r = .863$, $p < .001$). MMAS-8 intentional score was positively correlated with MMAS-8 unintentional score ($r = .552$, $p < .001$) and self-reported adherence rate ($r = .613$, $p < .001$). Lastly, the MMAS-8 score was positively correlated with self-reported adherence rate ($r = .481$, $p < .001$).

Table 12: Correlation Between Adherence and Relapse

Pearson Correlation Coefficient (r)	Self-report Relapse Rate	MMAS-8 Total Score	MMAS-8 Intentional Score	MMAS-8 Unintentional Score
MMAS-8 Total Score	-.296			
MMAS-8 Intentional Score	-.360*	.869**		
MMAS-8 Unintentional Score	-.139	.863**	.552**	
Self-reported Adherence Rate	-1.23	.618**	.613**	.481**

***Significant at p<.001; *Significant at p<.05;* Use of the ™©MMAS is protected by US and International trademark and copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research) LLC; 14725 NE 20th St.; Bellevue, WA 98007. Pertinent citations include: (1) Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354. (2) Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66. (3) Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

d. Linear regression model

A multiple regression analysis was conducted to evaluate how well certain study measures predicted self-reported relapse rate. The predictors were MMAS-8 total score, self-reported mental illness symptom severity level, mental illness type, length of substance use and DAI total score. All variables except for mental illness type were classified as continuous variables. Mental illness type was classified as a nominal variable composed of the following groups: MDD, GAD, bipolar disorder, schizophrenia, 2+ mental illnesses. The assumptions for linear regression models were assessed before running the model. The Shapiro-Wilk Test was utilized to assess normality and the VIF collinearity statistic was utilized to assess collinearity. The linear combination of the study measures included in the model was not significantly related to self-reported relapse rate ($F=2.25$, adjusted $R^2=.145$, $p=.073$). **Table 13** shows the relative strength of each individual predictor. The regression model shows that MMAS-8 total score is a significant predictor of relapse rate when adjusting for the other included study measures (stand. beta = -.443, CI= -6.37-0.23, p=.048).

Table 13: Linear Regression Model

	Self-report Relapse Rate (n=38)		
	Stand. beta	**95% CI**	**p-value**
Constant		-25.84 to 17.14	
MMAS-8 total score	-.443	-6.37 to -0.23	0.048*
Mental illness symptom severity (self-reported)	.314	-0.41 to 5.00	0.093
Mental illness type	-.141	-2.90 to 1.26	0.429
Length of substance use	.287	-0.30 to 0.62	0.074
DAI total score	.173	-0.98 to 2.37	0.402

**Significant difference at p<.05;* Use of the ™©MMAS is protected by US and International trademark and copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research) LLC; 14725 NE 20th St.; Bellevue, WA 98007. Pertinent citations include: (1) Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354. (2) Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66. (3) Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

IV. Objective 4

Assess follow-up changes in mental illness severity and medication adherence in dual diagnosis patients enrolled in a substance abuse rehabilitation program

a. Follow-up rates

As stated in previously, follow-up interviews were conducted with patients at one-month and two months post-primary interview. A total of 12 patients (31.6%) fully completed the study with two follow-ups, 15 patients (39.5%) participated in the first follow-up then dropped out of the study, and 11 patients (28.9%) only participated in the primary interview before dropping out. Reasons for patient drop-out included being caught using drugs on the Harbor Light Center premises, not complying with center rules, not believing that their addiction was severe enough to warrant treatment, overdosing on the premise and being admitting to the hospital, being found in possession of illicit substance, leaving the program to be with a significant other, leaving the program with intention to continue substance use, completing the program early, testing positive for illicit substances, using illicit substance while on leave, and simply leaving the program without giving a reason.

b. Patient and clinical characteristics by follow-up

Patient characteristics were stratified according to follow-up interviews completed. The characteristics included in this analysis were age, MMAS-8 total score, MMAS-8 intentional score, MMAS-8 unintentional score, self-reported adherence rate, mental illness type, mental illness symptom severity, substance of choice, DAI-10 total score, receiving income, and housing situation. The results of this analysis are shown in **Table 14**. The DAI-10 total score was significantly lower in patients who only completed the primary interview vs. patients who completed the study entirely (4.0 vs 7.0, p=.044). All other comparisons were statistically insignificant.

Table 14: Patient and Clinical Characteristics by Follow-up

Characteristics Mean, st dev unless specified	Primary (n=11)	1st Follow-up (n=15)	2nd Follow-up (n=12)	p-value
Age	41.2 (11.5)	40.5 (11.1)	40.8 (12.7)	0.990
MMAS-8 total score	3.2 (1.5)	3.2 (1.8)	4.3 (2.0)	0.300
Adherence (self-report)	3.8 (3.5)	2.6 (3.3)	2.9 (3.6)	0.667
Mental illness type, n (%)				0.670
MDD	1 (2.6)	2 (5.3)	4 (10.5)	
GAD	1 (2.6)	1 (2.6)	2 (5.3)	
Bipolar	2 (5.3)	3 (7.9)	1 (2.6)	
Schizophrenia	1 (2.6)	0 (0.0)	1 (2.6)	
2+	6 (15.8)	9 (23.7)	4 (10.5)	
Symptom severity	8.2 (1.5)	8.3 (2.5)	8.8 (1.4)	0.748
Drug of choice, n (%)				0.634
Heroin	4 (10.5)	9 (23.7)	6 (15.8)	
Alcohol	4 (10.5)	4 (10.5)	4 (10.5)	
Crack cocaine	2 (5.3)	1 (2.6)	1 (2.6)	
Alcohol and crack	0 (0.0)	0 (0.0)	1 (2.6)	
Marijuana	1 (2.6)	0 (0.0)	0 (0.0)	
Methamphetamine	0 (0.0)	2 (5.3)	0 (0.0)	
DAI total score	4.0 (2.8)*	5.1 (2.3)	7.0 (3.4)*	0.044*
Relapse rate (self-report)	8.5 (8.0)	10.6 (18.5)	9.7 (13.0)	0.933
Receiving income, n (%)				0.117
Yes	0 (0.0)	3 (7.9)	4 (10.5)	
No	11 (28.9)	12 (31.6)	8 (21.1)	
Housing situation, n (%)				0.272
Homeless	9 (25.0)	13 (36.1)	8 (22.2)	
Living with family	0 (0.0)	0 (0.0)	2 (5.6)	
Other	1 (2.8)	1 (2.8)	2 (5.6)	

**Significant difference at p<.05;* Pertinent citations include: (1) Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354. (2) Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66. (3) Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

c. Changes in adherence

At each interview, patients reported their adherence on a scale from 1 to 10. These self-reported adherence rates were analyzed in order to assess for significant change in adherence over time while enrolled in the rehabilitation program. The results showed a significant change in adherence during the first follow-up interview compared to the primary interview (mean difference=5.7, $p<.001$) and a significant change in adherence during the second follow-up interview compared to the primary interview (mean difference=6.5, $p<.001$). There was no significant change in adherence between the first follow-up interview and the second follow-up interview. The results of this analysis are shown in **Table 15**.

Table 15: Changes in Adherence

Adherence (self-report)	Mean difference (st dev)	p-value
Primary interview vs. 1st follow-up	5.7 (3.7)	<.001*
Primary interview vs. 2nd follow-up	6.5 (3.7)	<.001*
1st follow-up vs. 2nd follow-up	0.17 (0.9)	0.551

**Significant difference at p<.05*

CHAPTER 5 – CONCLUSION

I. Discussion

The overall goal of the study's first objective was to gain better insight into the dual diagnosis patient population. The demographic data collected through the study demonstrated that the study population is an extremely vulnerable population who need both mental health and substance use treatment. The study population is characterized as predominately indigent, of lower educational status, homeless, white, middle-aged men. The majority of these men were engaging in the use of drugs such as heroin or crack cocaine, and have been using drugs since they were young teenagers. The results of this long-term use are highlighted by the high amount of comorbid health conditions in the patients. The high rate of previous substance use treatments and relapse rates may lead one to extrapolate that these patients are somewhat aware that they are engaging in an unhealthy and dangerous lifestyle but they lack the ability to stop even if they are actively trying to. While the previous statement is a plausible conclusion, it is important to be cognizant of the fact that SUD is a defined mental illness driven by addiction and characterized by irrational behavior.

The population also suffers from severe mental illnesses, and in most cases more than one diagnosis. During the primary interviews, patients were given both mental illness severity measurement tools and asked to self-report their symptom severity on a scale from 1 to 10. The results from the mental illness severity measurements and patient self-report show that not only are the patients suffering from severe mental illnesses but they

are also aware of the severity of their symptoms. Yet, patients in this population are not taking the medications prescribed to them to aid in the treatment of their diagnoses. Both the patient's self-report and the MMAS-8 show that adherence to psychotropic medications is severely low within this population. The overwhelmingly positive results of the DAI-10 show that patients are fully aware of the benefits of psychotropic medications yet still lack the ability to take them as prescribed. When asked why they were not taking their medications properly, a majority of patients cited reasons related to their drug habits such as 'being too inebriated to remember' and fearing dangerous drug interactions. Many patients even displayed an awareness that they are self-medicating their mental illness with illicit drugs. The concepts of cognitive impairment and self-medicating may offer an explanation of why there is a gap between patients knowing their condition yet not taking their medications. Cognitive impairment is a common symptom of both SUD and mental illness that harms certain areas the patient's mental functioning including critical thinking, memory, attention, and motivation.[213] Therefore, patients in the study may lack the cognitive ability to maintain a prescription regimen even when they are actively trying. In regard to self-medicating, previous literature has proven that this is a common problem within the dual diagnosis population. In a large nationally representative survey of 43,093 adults with mental illness, Bolton *et al.* found that 25% of individuals with mental illness used drugs or alcohol to relieve their symptoms.[214] Therefore, it can be concluded that patient within our study may be actively choosing to relieve their mental illness symptoms using illicit drugs even if they are aware of the benefits of psychotropic medications. In other words, the patients may simply prefer drugs of abuse over psychotropic medications.

Outside of mental impairment and self-medicating, another way to explain the conflicting beliefs of patients being aware of their mental illness and wanting to recover from their substance abuse problem yet not taking their medications is to conclude that patients are not aware of how properly treating their mental illness will benefit their goal of quitting substance abuse. Patients may believe that their mental illness and SUD are two unrelated diseases that are to be treated separately. Therefore, they may be currently attempting to treat their SUD through rehabilitation while not properly treating their co-occurring mental illness.

The results from the study's first objective are on par with previous literature. First our study concluded found that the study population suffered from a high level of mental illness symptom severity. Previous studies have also concluded that patients with SUD are likely to suffer from more severe mental illness symptoms compared to those who do not have a SUD. For example, a study conducted by Ries *et al.* measured the mental illness severity in 104 patients admitted to an acute voluntary psychiatric unit. The study concluded that patients with a current SUD had significantly more severe symptoms compared to those who did not.[215] Secondly, our study found that the patients included in the study displayed an extremely low level of adherence. As discussed in the literature review, psychotropic medication nonadherence is common in patients with SUD. Our literature review found that 36 of the 51 studies (71%) concluded that comorbid substance use was significantly associated with psychotropic medication nonadherence.[134,137,146-149,151-153,155,156,158-165,167,168,170,174-176,178,180-183,185-189,194] [134,137,146-149,151-153,155,156,158-165,167,168,170,174-176,178,180-183,185-189,194] Of these 36 studies, 18 (35%) identified substance use

as a predictor of nonadherence. Yet, these studies vary in adherence measurement methods when compared to our study. In a previous study conducted by Dunn *et al.,* the MMAS-8 scale was used to measure medication adherence in 316 patients with co-occurring psychiatric disorders and SUD enrolled in an addiction treatment program. It appears that this is the only other study that has utilized the MMAS-8 scale in the dual diagnosis population. The researchers concluded that 80.4% of the patients enrolled in the study scored as adherent on the MMAS-8.[216] These results are contrary to both the results found in our study and the results found in the majority of the studies within the literature review. Lastly, our study's first objective found that patients displayed an overall positive attitude towards their psychotropic medications according the DAI-10 results. In a previous study conducted by Cuevas *et al.,* 270 psychiatric outpatients were given the DAI-10 along with 292 citizens with no history of mental illness or psychotropic medications. The psychiatric patients showed an overall more positive attitude compared to the general population, with a mean DAI-10 score of 3.6 compared to -0.7.[217] These DAI-10 scores are similar to the overall DAI-10 mean of 5.4 that was measured in our study population.

The goal of the study's second objective was to measure agreeance between patient-self reported data using facility records in order to determine if the dual diagnosis population is a reliable source of data for research. While the majority of the data collected from the facility records was patient self-reported, the patients' mental illness diagnosis and medications prescribed were supplemented by medical records. It is important to test this relationship not only to confirm the agreeance of the data but also to test patients' disease

insight, which is the ability to understand the nature of their illness. Patients with low disease insight are more difficult to treat and experience worse health outcomes.[218] Before conducting the study, it was hypothesized that the data gathered from patients would be somewhat inaccurate due to the mental state of the patients who are providing the data. Multiple previous studies have measured disease insight in patients with heroin-use disorder,[219] bipolar disorder,[220] schizophrenia,[221] depression[222] and mental illness in general.[223] These studies have unanimously concluded that patients in their respective population exhibit significantly low disease insight or awareness. Contrary to our hypothesis and previous research, the patients in our study displayed a high awareness and knowledge of their current health status by accurately reporting information about their mental illness diagnoses and psychotropic medications. The high correlation between patients' report of adherence and all three MMAS-8 scores also highlights the accuracy of the adherence information provided by patients. This finding may be due to the Harbor Light intake protocol and the other processes the patients go through before admission. The majority of patients come to Harbor Light from detoxification or other health care settings such as hospitals emergency departments. In these settings and through Harbor Light intake procedures, patients may have been reminded of their disease states. Since the primary interview took place within a week of admission, the patients were more likely to remember their mental illness compared to others in the dual diagnosis population. It is important to note that agreeance was higher for primary substance of use compared to the other variables. The researchers hypothesize that this outcome occurred due to substance use history being the only patient controlled variable included in the analysis.

The goal of the study's third objective, which was the primary objective of the study, was to investigate the specific role of medication adherence and barriers to use for psychotropic medications upon SUD relapse. The results of the DAI-10 stratification showed that low adherence is a result of patients having negative attitudes towards their psychotropic mediations or not believing that these medications play a vital role in their mental illness treatment yet it was found that these attitudes and beliefs do not play a role in patients relapsing back to substance use. The researchers hypothesize that the insignificant relapse outcome was caused by large standard deviations due to only one patient expressing negative attitudes and 34 expressing positive attitudes. The conclusion that negative attitudes towards psychotropic medication leads to low adherence is supported by previous literature. In a study conducted by Brown *et al,* attitudes and beliefs about antidepressant medications were measured in patients in a primary care setting. Patients' attitudes were measured using the Beliefs about Medicines Questionnaire (BMQ), the measurement that the DAI-10 is based on. The researchers concluded that positive beliefs about medications were significantly associated with self-reported adherence.[224] Another study conducted by Brain *et al.* observed the effect of drug attitude on medication adherence in 112 outpatients with schizophrenia and schizophrenia-like psychosis. The DAI-10 was utilized to measure drug attitudes and a medication event monitoring system was utilized to measure adherence. A univariate regression model showed that a negative DAI-10 score was a predictor of non-adherence.[225]

The study's third objective also found that there was a significant correlation between patients' nonadherence to psychotropic medications and SUD relapse. This relationship was then analyzed further using a regression model, which concluded that the linear combination of the included variables was not significant. The researchers hypothesized that this outcome was due to the influence of the underpowered study sample size on the model's F statistic, even though all 38 patients were included in the model and no missing data was prevalent. Yet, the model concluded that adherence is a significant predictor of substance abuse relapse when other study variables were incorporated into an adjusted analysis. Therefore, the results of the study can lead one to conclude that dual diagnosis patients' nonadherence to psychotropic medications is related to substance abuse relapse. Our study is currently the first study in the literature to observe this specific relationship within the dual diagnosis population and to make this conclusion.

While there may be multiple explanations as to why a relationship was found, the act of self-medicating may explain the gap between psychotropic medication nonadherence and SUD relapse. Patient were not adherent their psychotropic medications due to multiple factors including negative attitudes towards their medications. As discussed in the background section, nonadherence leads to increased mental illness symptom severity. As their symptoms increase, patients may be choosing to treat their mental illness with illicit drugs instead of prescribed medication therefore leading them back to SUD relapse. A study focused on patients self-medicating would need to be conducted in the future in order to confirm this hypothesis.

The goal of the study's fourth and final objective was to assess differences between patients who stayed in the study versus those who did not and to observe changes in behavior while in rehabilitation. This was done by following patients over three months through follow-up interviews. Less than one third of the total participants continued the study to its completion. This high drop-out rate was initially expected due to the nature of the study population. All patients who dropped out of the study also dropped out of the rehabilitation program, therefore no patient specifically chose to discontinue study participation while still pursing treatment. Patient drop-outs were simply a secondary result of patients not continuing drug addiction treatment and was not due to the study itself. The drop-out rate within our study is similar to substance abuse treatment program dropout rates found within previous literature. The typical treatment drop-out rate within the first month of treatment is 30% and the rate rises to 50% at 3 months.[226] Our study had a drop-out rate of 28.9% within the first month and a drop-out rate of 68.4% at three months. The study found that patients who completed the entire study displayed more positive attitudes and beliefs towards the psychotropic medications they are prescribed. Since all patients who dropped out of the study also discontinued their substance abuse treatment, this relationship offers valuable insight into the importance of patients fully understanding why they should be taking their medications and the vital role it plays in rehabilitation. Lastly, the study found that patients' adherence increased over time while in the rehabilitation center. Harbor Light Center's staff does not force patients to take their mediations nor do they monitor medication taking behavior at a clinical level. Therefore, one can conclude that the drug abuse rehabilitation intervention played a

significant and vital role in increasing psychotropic adherence which, as the study has shown, decreases their likelihood of substance abuse relapse.

II. Study Implications

The results of the study provide valuable insight into the relationship between psychotropic medication adherence and substance abuse relapse in patients with dual diagnosis. It is evident from the study findings that dual diagnosis patients' adherence and attitudes towards their psychotropic medication play a significant role in substance use relapse. The results of the study can be applied to real-world treatment of dual diagnosis in the following ways.

First, the study results provide a better understanding into the dual diagnosis population and can be used by drug abuse rehabilitation programs in order to target patients more effectively and increase treatment outcomes. Interventions can now identify patients that are at a higher risk of substance use relapse therefore giving them the ability to provide more centralized and individually tailored treatment to those who need it the most. Since the main outcome of most rehabilitation interventions is preventing substance use relapse, an increased understanding of what causes that outcome is extremely valuable. Interventions should incorporate education about the importance of psychotropic medication adherence and mental illness treatment into their programs therefore helping patients attain their cessation goals. While Harbor Light does encourage their patients to take their psychotropic medications, adherence should become an integral part of their treatment program. Periodic assessments of adherence should take place while patients

are in treatment in order to guarantee that patients are staying adherent. Harbor Light should also provide adherence counseling and adherence motivational interviewing to their patients. As discussed in the literature review, standard SUD treatment combined with motivational interviewing has been shown to significantly increase adherence among dual diagnosis patients.[190] The most noteworthy challenges of working within this population was the patients' lack of accuracy and reliability when reporting health-related variable. Therefore, these counseling sessions should also focus on improving health literacy in order to increase disease awareness and improve outcomes. Since our study found that negative attitudes towards medications are related to nonadherence, these counseling sessions should also educate patients on the short-term and long-term effects of medication, how the medication works, and the role adherence plays in SUD treatment.

Second, the results from the study can be utilized by healthcare professionals. The study highlights the importance of physicians integrating the treatment of mental illness and SUD in dual diagnosis patients due to the negative effect each disease has on the other. SAMHSA has recently published a report, titled *Integrated Treatment for Co-Occurring Disorders: The Evidence*, which highlights the importance of integrated dual diagnosis treatment along with previous evidence that concluded combined treatment results in more positive outcomes.[227] The third objective of our study found that nonadherence is related to SUD relapse. Therefore, physicians should provide adherence counseling to patients with a history of SUD before they are prescribed psychotropic medications and continuously through their treatment. These counseling sessions should consist of

adherence strategies, expected side effects, potentially dangerous drug-drug interactions, and the benefits on staying adherent. Phone counseling can be utilized to ease the burden on patients who are unable to or not willing to return to the physician's office. Since self-reported adherence may not be accurate in this population, physicians could use electronic pill bottles to measure adherence behaviors more accurately between appointments. Since these patients are uniquely difficult to treat using typical mechanism such as primary care, social and case workers may also be more effective in implementing these changes.

The results of our fourth objective highlight the importance of following-up with patients after they leave treatment in order to guarantee the continuation of adherence. While follow-ups may be more difficult to conduct in this population, many techniques can be utilized. Short message service (SMS) based interventions have been shown to both improve adherence in patients with mental illness [228] and improve drug abstinence in dual diagnosis patients.[229] Significant others or family members without SUDs could also be included to help prevent patients discontinuing the interventions. The use of mobile interventions will result in a faster detection of nonadherence therefore giving interventions the ability to provide help before the patient reverts back to illicit drug use.

III. Limitations

The study contains some potential limitations that may have impacted the results, and need to be addressed in order for the study outcomes to be properly interpreted. First, due to some study characteristics, the results may not be generalizable. The study finished

data collection with low sample size due to it being intentionally designed as a feasibility study. Also, the study only contained males in the sample since Harbor Light Center is a male only facility. Therefore, the results may not be generalizable to females with dual diagnosis. The study only included patients with major depressive disorder, generalized anxiety disorder, bipolar disorder, and schizophrenia. Although these are among the most prevalent mental illnesses, the results may not be generalizable to patients with other mental illnesses such as attention-deficit disorder or post-traumatic stress disorder.

Second, the information reported by patients may be subject to recall bias. Almost all of the information collected from the patients is retrospective and the patients may have been cognitively impaired during that time period. For example, one patient was required to recall the number of relapses he experienced during a 40-year history of substance use. The inclusion of facility records attempted to minimize this effect since the patients' mental health information was supplemented by health records.

Third, the results may be subject to social desirability bias. Since all patients were interviewed within their first week of treatment, patients may have embellished their adherence levels or restrained from revealing all of their past substance use in order to exhibit their ability to succeed in the program. Also, question #9 of the PHQ-9 asked the patients if they have ever had "Thoughts that you would be better off dead or of hurting yourself in some way." One patient expressed a concern that there would be consequences if he answered that question honestly. The impact of social desirability bias should be minimal due to the study design. The researcher began each interview by

reiterating to the patient that no information would be shared with the Harbor Light Center staff and that the interview would have no effect on their treatment in the program. If the patients were aware that the information they gave during interviews was completely confidential, there would be no reason to embellish or lie about their adherence levels or substance use characteristics.

Fourth, the patients' low health literacy may have affected the accuracy of the self-reported data. Multiple patients showed signs of not fully understanding the concept of adherence, even after it is explained to them. For example, patients often self-reported a '10' on adherence but then admitted to occasionally missing doses. One patient self-reported a '10' on adherence but admitted to breaking all of his pills in half for every dose so the medication lasted longer. He also saw nothing wrong with doing this since it was saving money. In reality, this would be classified as extremely low adherence or even considered zero adherence. The researcher thoroughly explained the concept of adherence to each patient and expressed willingness to explain any material to patients during all interviews. The interviewer also attempted to assess if the patient understood all of the questions included in the self-reported assessments. Therefore, the impact of this limitation should not be significant. Similar future research should consider measuring patient health literacy and adjusting for it within the statistical analysis.

IV. Opportunities for Future Research

Based on the results of the study, one can conclude that psychotropic nonadherence plays a significant role in regard to substance abuse relapse in the dual diagnosis population.

While this is a significant and impactful finding, further research is needed in order to gain a more in-depth understanding in regard to the connection between adherence and SUD relapse. The researchers suggest that future studies take the following approaches. First, a larger study with a greater sample size and wider geographic coverage observing the same relationship would produce a better understanding of the relationship. Second, while the study established nonadherence as a predictor of relapse, a more in-depth study analyzing the causation of nonadherence within the dual diagnosis population would better help interventions improve adherence therefore preventing relapse. The researchers suggest a more in-depth qualitative study surrounding patients self-medicating in order to discover why patients are choosing illicit drugs over psychotropic medications for treating their psychiatric symptoms. These studies should also establish a more accurate approach to measuring symptom severity across the sample. While our study used established tools such as the PHQ-9 and the MDQ, these results could not be compared across disease states. Third, while the study established that adherence improved while in treatment, no information was gathered on patients after they completed the program or dropped out. Patients' adherence levels were established during the primary interview and measured through the 90-day treatment period. While the study concluded that adherence improved during this period, this conclusion cannot be assumed to hold true after the patient leaves the program since they are going from a controlled environment to an uncontrolled environment. A future study should follow patients for a longer amount of time, even after rehabilitation completion, collecting substance abuse and relapse information in order to assess if the changes in adherence made during treatment are permanent. This may prove to be difficult since a majority of the patients were homeless

before admission. We suggest researchers conduct phone interviews or invite patients to return back to the facility after completing the program and establish a way to pay the patients for their time. A future study should also conduct exit interviews with patients who completed the program in order to assess variables that influenced successful treatment. Lastly, a future study should assess the impact of a rehabilitation centers educating patients on the importance of adherence in order to determine if interventions that focus on increasing patient knowledge in regard to adherence would indeed lead to a decrease in relapse.

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APPENDICES

APPENDIX 1: Facility Record Data Collection Form

1. Patient ID:
2. Year of birth:
3. Race/ethnicity (Caucasian, Black/African American, Hispanic, other):
4. Employment status prior to relapse:
5. Approximate income level prior to admission:
6. Educational background (less than high school, high school, more than high school):
7. Housing situation prior to admission:
8. Description of family support:
9. Primary substance of abuse/choice:
    a. Other substances utilized:
10. Age at substance use initiation:
11. Length of use reported:
12. Number of previous admissions to Harbor Light facility:
13. Number of other admissions to rehabilitation programs:
14. Mental illness diagnoses:
    a. Patient-reported:
    b. Medically-assigned:
15. Age at mental illness diagnosis:
16. Severity of mental illness prior to admission:
17. Mental illness treatments (pharmacological or non-pharmacological):
    a. Previously utilized:
    b. Currently prescribed:
18. Level of medication adherence:
19. Medical comorbidity diagnoses:

APPENDIX 2: Prospective patient interview form

1. What is your primary drug of abuse? What other drugs have you utilized in addition to your primary drug of abuse?

2. How long have you been using your primary drug of abuse?

3. How many times have you relapsed in your substance use prior to this facility?

4. How many times have you been in treatment for substance use prior to this facility?

5. What factors do you believe have contributed to your relapse this time?

6. Have you ever been diagnosed with a mental illness by a healthcare professional? If so, what diagnoses?

7. Think back to your mental illness symptoms prior to entering treatment (excluding withdrawal symptoms). On a scale of 1 to 10 (1 = no symptoms and 10 = very severe symptoms), how would you rate the severity of your mental illness symptoms (insert appropriate example below)?

    a. Depression – e.g. low energy, lack of appetite, lack of motivation
    b. Bipolar disorder – e.g. mood swings, periods of excessive energy or depression
    c. Generalized anxiety – e.g. persistent worrying, inability to relax, distress
    d. Schizophrenia – e.g. hallucinations, delusions

8. Have you received any medication for your mental illness from a healthcare professional?

    a. If so, what medications are you currently taking?
    b. If so, what medications have you previously taken?

9. Often times, people do not take their medication as prescribed. On a scale of 1 to 10 (1 = taken no doses and 10 = taken all doses as prescribed), how would you rate adherence to your medication for your mental illness?

10. What factors do you believe have contributed to you not taking your medication?

11. Have you ever been diagnosed with other long-term medical conditions by a healthcare professional, such as hepatitis C, diabetes, high blood pressure? If so, what diagnoses?

APPENDIX 3: Longitudinal follow-up questions

1. Since leaving the Harbor Light facility, have you resumed use of any alcohol or other drugs of abuse (for example, prescription opioids, cocaine, marijuana, or heroin)?

2. If relapsed, how long after leaving the Harbor Light facility did this occur?

3. If relapsed, have you sought treatment for your substance use?

4. Since leaving the Harbor Light facility, how have your symptoms of your mental illness changed (insert appropriate example(s) of symptoms below) – (1) no current symptoms, (2) symptoms deceased, (3) symptoms increased, (4) symptoms remained the same? Please explain.

    a. Depression – e.g. low energy, lack of appetite, lack of motivation
    b. Bipolar disorder – e.g. mood swings, periods of excessive energy or depression
    c. Generalized anxiety – e.g. persistent worrying, inability to relax, distress
    d. Schizophrenia – e.g. hallucinations, delusions

5. Often times, people do not take their medication as prescribed. Since leaving the Harbor Light facility, on a scale of 1 to 10 (1 = taken no doses and 10 = taken all doses as prescribed), how would you rate adherence to your medication for your mental illness?

6. If you have not taken your medication as prescribed, what factors do you think have contributed to you not taking your medication?

[Offer for contact with care coordinator at Harbor Light if patient expresses increased symptoms or reports relapse to substance use]

APPENDIX 4: The Morisky Medication Adherence Scale (MMAS-8)

Pertinent citations include:

- Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. Journal of Clinical Hypertension 2008; 10(5):348-354.
- Krousel-Wood MA, Islam T, Webber LS, Re RS, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care 2009;15(1):59-66.
- Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: Final response. J Clin Epidemi 2011; 64:258-263.

APPENDIX 5: The Drug Attitude Inventory (DAI-10)

Name **Date**

	Question	Answer (True/False)*
1	For me, the good things about medication outweigh the bad	**T** / F
2	I feel strange, "doped up", on medication	T / **F**
3	I take medications of my own free choice	**T** / F
4	Medications make me feel more relaxed	**T** / F
5	Medication makes me feel tired and sluggish	T / **F**
6	I take medication only when I feel ill	T / **F**
7	I feel more normal on medication	**T** / F
8	It is unnatural for my mind and body to be controlled by medications	T / **F**
9	My thoughts are clearer on medication	**T** / F
10	Taking medication will prevent me from having a breakdown	**T** / F
If you have any further comments about medication or this questionnaire, please write them below		

T = True, F = False

*Answers shown in **bold** are scored +1; answers in normal font are scored -1

Hogan TP., Award AG., Eastwood R. A self report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med. 1983;13:177–183.

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APPENDIX 6: The Patient Health Questionnaire (PHQ-9)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Column Totals	_____ +	_____ +	_____	
Add Totals Together	_____			

10. If you checked off any problems, how difficult have those problems made it for you to Do your work, take care of things at home, or get along with other people?

Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. Journal of General Internal Medicine. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x.

APPENDIX 7: The Mood Disorder Questionnaire (MDQ)

Hirschfeld RMA. The Mood Disorder Questionnaire: A Simple, Patient-Rated Screening Instrument for Bipolar Disorder. Primary Care Companion to The Journal of Clinical Psychiatry. 2002;4(1):9-11.

APPENDIX 8: The Generalized Anxiety Disorder Assessment (GAD-7)

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of Internal Medicine. 2006;166(10):1092–1097. https://doi.org/10.1001/archinte.166.10.1092

APPENDIX 9: The Brief Psychiatric Rating Scale (BPRS)

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Patient Name _____ **Today's Date** _____

Please enter the score for the term that best describes the patient's condition.

0 = Not assessed, 1 = Not present, 2 = Very mild, 3 = Mild, 4 = Moderate, 5 = Moderately severe, 6 = Severe, 7 = Extremely severe

Score		
☐	1.	**SOMATIC CONCERN** Preoccupation with physical health, fear of physical illness, hypochondriasis.
☐	2.	**ANXIETY** Worry, fear, over-concern for present or future, uneasiness.
☐	3.	**EMOTIONAL WITHDRAWAL** Lack of spontaneous interaction, isolation deficiency in relating to others.
☐	4.	**CONCEPTUAL DISORGANIZATION** Thought processes confused, disconnected, disorganized, disrupted.
☐	5.	**GUILT FEELINGS** Self-blame, shame, remorse for past behavior.
☐	6.	**TENSION** Physical and motor manifestations of nervousness, over-activation.
☐	7.	**MANNERISMS AND POSTURING** Peculiar, bizarre, unnatural motor behavior (not including tic).
☐	8.	**GRANDIOSITY** Exaggerated self-opinion, arrogance, conviction of unusual power or abilities.
☐	9.	**DEPRESSIVE MOOD** Sorrow, sadness, despondency, pessimism.
☐	10.	**HOSTILITY** Animosity, contempt, belligerence, disdain for others.
☐	11.	**SUSPICIOUSNESS** Mistrust, belief others harbor malicious or discriminatory intent.
☐	12.	**HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence.
☐	13.	**MOTOR RETARDATION** Slowed, weakened movements or speech, reduced body tone.
☐	14.	**UNCOOPERATIVENESS** Resistance, guardedness, rejection of authority.
☐	15.	**UNUSUAL THOUGHT CONTENT** Unusual, odd, strange, bizarre thought content.
☐	16.	**BLUNTED AFFECT** Reduced emotional tone, reduction in formal intensity of feelings, flatness.
☐	17.	**EXCITEMENT** Heightened emotional tone, agitation, increased reactivity.
☐	18.	**DISORIENTATION** Confusion or lack of proper association for person, place or time.

Overall JE. Gorham DR. The brief psychiatric rating scale. Psychological reports. 1962 10:799-812.

APPENDIX 10: Patient screening tool

For Salvation Army Harbor Light facility staff:

If during an intake interview, a new patient meets ALL of the following criteria (check off):

- ☐ Male sex
- ☐ At least 18 years of age
- ☐ Admitted to Salvation Army Harbor Light
- ☐ Dual diagnosis of substance abuse disorder and either:
    - Major depressive disorder
    - Bipolar disorder
    - Generalized anxiety disorder
    - Schizophrenia

If a patient has evidence of a substance-induced psychiatric disorder, they are **NOT ELIGIBLE**.

If the patient meets these above criteria, please make the following offer:

> "*There is currently a research study being conducted here at the Salvation Army Harbor Light facility that is looking to determine if adherence to medications for mental health conditions has any connection to relapse in substance use. Would you be interested in speaking with someone regarding participating in this study?"*

If the patient expresses interest after this offer, please contact one of the study investigators.

APPENDIX 11: Consent to Participate in a Research Study Form

DUQUESNE UNIVERSITY

600 FORBES AVENUE ♦ PITTSBURGH, PA 15282

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Non-adherence to psychotropics and risk for substance use disorder relapse among patients with dual diagnosis

INVESTIGATORS:

Tyler Dunn	Masters student Duquesne Univ Mylan School of Pharmacy	
Minha Choi	Bachelors/Pharm.D. student Duquesne Univ Mylan School of Pharmacy	
Jordan R Covvey, PharmD, PhD, BCPS	Assistant Professor Duquesne Univ Mylan School of Pharmacy	412.396.2636
Khalid M Kamal, MPharm, PhD	Associate Professor Duquesne Univ Mylan School of Pharmacy	412.396.1926
Lauren Jonkman, PharmD, MPH, BCPS	Assistant Professor Univ of Pittsburgh School of Pharmacy	412.648.8563
Vincent Giannetti, PhD	Professor Duquesne Univ Mylan School of Pharmacy	412.396.6379

SOURCE OF SUPPORT:

This study is being performed as partial fulfillment of the requirements for the Masters degree in Pharmacy Administration (Dunn) and a Bachelors degree in Pharmaceutical Sciences (Choi) at the Duquesne University Mylan School of Pharmacy.

PURPOSE:

You are being asked to participate in a research study that is evaluating whether medication adherence (taking your medication as directed) for depression, bipolar disorder, generalized anxiety or schizophrenia and substance use disorder has a connection to substance abuse relapse.

To participate in the study, you must be male, at least 18 years of age and part of the residential program at the Salvation Army Harbor Light facility. You must also report a diagnosis of a substance use disorder and either major depressive disorder, bipolar disorder, generalized anxiety or schizophrenia. The study aims to determine if adherence to medications for these conditions is connected with lower rates of relapse in substance use.

PARTICIPANT PROCEDURES:

To participate in this study, you will be asked (1) to provide permission to access to your Harbor Light record to collect information about you and your health and medication history, (2) to participate in an interview with one of our study investigators to answer questions about medication, substance use and your mental health, and (3) permission to contact you at one (1) and (2) months after the interview for follow-up questions regarding medication, substance use and your mental health. The in-person interview is expected to take approximately 30-45 minutes and the follow-up phone calls should take approximately 5-10 minutes each. Study investigators will take notes on paper during your interview and phone calls. These are the only requests that will be made of you.

RISKS AND BENEFITS:

For the interview and phone calls, you will be asked questions regarding your mental health history. If you experience any stress or become tired while talking with the study investigator, you will be allowed to stop and take a break. You do not have to answer questions that you do not want to answer. The study investigators will also view and collect more data from your Harbor Light record. However, at no point will you receive any physical or mental treatment within the study. You are only providing information to the study investigators.

You are free to stop study participation at any time. There are minimal risks associated with this participation but no greater than those encountered in everyday life. There are no direct benefits to you, but the information from the study could help to provide better support and treatment to others with substance abuse in the future.

COMPENSATION:

Your time and participation in the study will be reimbursed in cash based on your level of participation. If you are enrolled in the study, you will receive $10.00 for completing your in-person interview, and $10.00 for follow-up phone calls at 1-month and 2-months (a total of $30.00 maximum per person). This payment will be provided as the study continues. Participation in the project will require no monetary cost to you.

CONFIDENTIALITY:

Your participation in this study and any personal information that you provide will be kept confidential at all times and to every extent possible.

Your name will never appear in any data entry and will only be used to conduct interviews and follow-up. Instead, you will be given a study number (Patient 1, 2, 3…) which will keep your identity anonymous in all recorded data. All written and electronic forms and study materials will be kept secure. After completion of the study, the information collected will be uploaded and stored on a secure computer until the data analysis is complete. Your response(s) will only appear in statistical data summaries. Any study materials with personal identifying information will be maintained for three years after the completion of the research and then destroyed.

If while during the study or follow-up you express concerns that require clinical help (such as suicidality), study investigators will be required to inform facility personnel.

HIPAA AUTHORIZATION:

You understand that by participating in this study, you are giving us permission to use your personal health information in your medical record and information that can identify you. The health information procedures in this study are HIPAA compliant. Any health protected information obtained will be stored by the researcher for six years after the completion of the study.

RIGHT TO WITHDRAW:

You are under no obligation to participate in this study and may stop participation at any time. Initial enrollment or any subsequent discontinuation from the study will in no way affect services provided or accessed within the Harbor Light Center. You are free to withdraw your consent to participate at any time by communicating your wish to your study investigator or any Harbor Light staff member.

SUMMARY OF RESULTS:

A summary of the results of this research will be supplied to you, at no cost, upon request.

VOLUNTARY CONSENT:
I have read the above statements and understand what is being requested of me. I also understand that my participation is voluntary and that I am free to withdraw my consent at any time, for any reason. On these terms, I certify that I am willing to participate in this research project.

I understand that should I have any further questions about my participation in this study, I may call Dr Covvey at 412.396.2636, Dr Kamal at 412.396.1926 or Dr Giannetti at 412.396.6379. Should I have questions regarding protection of human subject issues, I may call Dr. David Delmonico, Chair of the Duquesne University Institutional Review Board, at 412.396.1886.

_____ _____
Participant's Signature (Patient ID =) Date

_____ _____
Researcher's Signature Date