Comorbidities among Four Major Clinical Disorders

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Millions of Americans face mental health conditions every year (National Alliance on Mental Illness, 2015). According to the National Institute of Mental Health, one in five Americans has a diagnosable mental disorder, which is about 43 million Americans (Insel, 2015). Many individuals also experience two mental disorders at once, known as a comorbidity. Comorbidities between mental disorders and substance use disorders are common (Barlow & Durland, 2011), particularly comorbidities involving schizophrenia, depression, alcohol use disorder, and smoking. More specifically, as will be discussed, studies have demonstrated that comorbidities of depression and smoking (depression-smoking comorbid disorders), depression and alcohol (depression-alcohol comorbid disorders), schizophrenia and smoking (schizophrenia-smoking comorbid disorders), and schizophrenia and alcohol (schizophrenia-alcohol comorbid disorders) are four common comorbidities (e.g., Kinnunen, Doherty, Militello, & Garvey, 1996; Sher, 2009; Lohr & Flynn, 1992; Drake & Mueser, 2002).

Understanding the epidemiologies and etiologies of these four comorbidities (depression-smoking, depression-alcohol, schizophrenia-smoking, and schizophrenia-alcohol comorbid disorders) is crucial because as will be discussed, the comorbidities are often more detrimental to physical and mental health than having the individual disorders. Also, comorbidities involving smoking and alcohol are particularly crucial to investigate because recent findings suggest that alcohol and smoking tobacco are both ranked among the top ten

risky drugs (Nutt, King, & Phillips, 2010) based on harm caused by the drugs to the users and people in relation to the users.

Thus, the current investigation provides a substantive overview of the epidemiolog and etiological models of four comorbidities involving substance use disorders, depression, and schizophrenia. I first describe the symptoms and prevalence rates of depression and schizophrenia and the incidence of smoking and alcohol use. I then discuss the comorbidities of depression and smoking, depression and alcohol, schizophrenia and smoking, and schizophrenia and alcohol. I subsequently describe the effect of the comorbidities on the prognosis of depression and schizophrenia and treatment difficulties regarding these combined disorders. I close by offering implications and recommendations for treatment and prevention of the four comorbidities.

Depression

The National Institute of Mental Health depression as feelings of sadness that interfere with daily life and cause pain for the individual (National Institute of Mental Health, 2011). Across the world, about 350 million people of all ages suffer from depression, with depression being the leading cause of disability worldwide (World Health Organization, 2015). There are several types of depression, and the current investigation will focus on major depression, which is a mood disorder characterized by persistent feelings of sadness and loss of interest (Mayo Clinic, 2015). Depression can lead to suicide, which is the second leading cause of death in 15-29 year-old individuals (World Health Organization, 2015). The Anxiety and Depression Association of America (2015) reports that at any point in time, to percent of people suffer from

major depression with a lifetime risk of 17 percent (Anxiety and Depression Association of America, 2015).

In addition, symptoms of depression include persistent sad, anxious or "empty feelings, feelings of hopelessness or pessimism, feelings of guilt, worthlessness, thoughts of suicide and suicide attempts, helplessness, and fatigue or decreased energy (National Institute of Mental Health, 2011). More specifically, according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-5,* major depressive disorder is the disorder for people with one or more major depressive episodes (Black & Grant, 2014). A major depressive episode is characterized by having five or more specific symptoms (e.g., depressed mood for most of the day, marked diminished interest or pleasure in all, or most all, activities, feelings of worthlessness or excessive or inappropriate guilt nearly every day) that are unrelated to the effects of another medical condition and include at least one symptom related to depressed mood and one symptom related to loss of interest or pleasure (Black & Grant, 2014).

Schizophrenia

According to the National Institute of Mental Health, schizophrenia is a chronic, severe, and disabling brain disorder that affects about percent of Americans (National Institute of Mental Health, 2009). Schizophrenia is characterized by a broad spectrum of cognitive and emotional dysfunctions, including delusions, hallucinations, disorganized speech and behavior, and inappropriate emotions. The symptoms of schizophrenia can be broken down into positive symptoms, negative symptoms, and disorganized symptoms. Positive symptoms include delusions and hallucinations. Delusions are beliefs that would be seen by most members of a society as misrepresentations of reality, while hallucinations are false sensory experiences in the

absence of external stimuli (Barlow & Durland, 2011). Negative symptoms are abnormalities in normal emotions and behaviors such as flat affect (e.g., emotionless facial expressions or talking in a monotonous voice), lack of pleasure in everyday life, and little speaking (National Institute of Mental Health, 2009). Lastly, disorganized symptoms include disorganized speech and behavior. Schizophrenic individuals exhibiting disorganized speech may jump from one topic to another and other times talk illogically in what is called "word salad" (Barlow & Durland, 2011). Disorganized behavior includes inappropriate affect, such as laughing or crying at improper times, as well as odd and erratic motor movements (Barlow & Durland, 2011).

According to the *DSM-5,* in order to receive a diagnosis of schizophrenia, individuals must satisfy two or more symptoms including delusions, hallucinations, disorganized speech (e.g., incoherence), grossly disorganized or catatonic behavior, and negative symptoms (e.g., diminished emotional expression). At least one of these symptoms must include delusions, hallucinations, or disorganized speech. Additional symptoms include continuous signs of disturbance persisting for at least six months and decreased levels of functioning in major areas such as work, interpersonal relations, or self-care (Black & Grant, 2014).

Nicotine dependence and smoking

Nicotine is a toxic substance found in the tobacco plant is an ingredient in chewing tobacco, cigars, cigarettes, and snuff (Michigan Department of Community Health, 2003). The Mayo Clinic defines nicotine dependence, synonymous with tobacco dependence, to be an addiction to tobacco products caused by the drug called nicotine (Mayo Clinic, 2013), and the Centers for Disease Control and Prevention (2015) records that more people in the United States are addicted to nicotine than to any other drug (Center for Disease Control and Prevention,

2015a). The Centers for Disease Control and Prevention also report that as of 2015, tobacco is the leading cause of preventable disease, disability, and death accounting for about in every deaths in the United States (National Institute on Drug Abuse, 2015b). In fact, for every one person who dies from a smoking-related illness, 30 more suffer from at least one serious tobacco-related illness (National Institute on Drug Abuse, 2015b). Tobacco use has numerous health consequences including cancer, heart disease, and lung diseases (Healthy People 2020, 2015).

Nicotine is the substance in tobacco that makes tobacco addictive, and the toxic effects of tobacco result from other substances in tobacco (Mayo Clinic, 2013). More specifically, people become addicted to nicotine partly because of the nicotine-induced physical and mood-altering effects in the brain that are temporarily pleasing. Nicotine leads to the release of neurotransmitters such as dopamine in the brain that improve mood and activate feelings of pleasure (Mayo Clinic, 2013), and the dopamine released contributes to the addictive properties of nicotine (Action on Smoking and Health, 2013). Paradoxically, even though nicotine is a stimulant drug, individuals can feel both stimulation and relaxation resulting from nicotine (Action on Smoking and Health, 2013).

Alcohol dependence, alcohol abuse, and alcohol use disorder

The two most recent versions of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* have different definitions of alcohol use problems. I will describe both sets of criteria.

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)

According to the Centers for Disease Control and Prevention, alcohol abuse is a pattern of drinking that is harmful to one's health, interpersonal relationships, or ability to work. Indications of alcohol abuse include legal problems related to alcohol, drinking in dangerous situations, and continued drinking despite ongoing relationship problems that are caused or worsened by drinking (Center for Disease Control and Prevention, 2015a). Alcohol abuse can develop into alcohol dependence, and the Center for Disease Control and Prevention defines alcohol to be synonymous with alcohol addiction and alcoholism. Alcohol dependence is a chronic disease with signs and symptoms including strong cravings for alcohol, the inability to limit drinking, and continued use despite repeated physical, psychological, or interpersonal problems (Center for Disease Control and Prevention, 2015b). More specifically, the National Institute on Alcohol and Alcoholics specifies the four main symptoms of alcoholism (alcohol dependence)craving (a need or strong desire to drink alcohol), loss of control (the inability to stop drinking), physical dependence (showing withdrawal symptoms such as nausea, sweating, or vomiting when not drinking) and tolerance (needing more alcohol to meet cravings and to get drunk) (DARA Thailand, 2015).

he Diagnostic and Statistical Manual of Mental Disorders (DSM-)

In May, 2013, the American Psychiatric Association issued the 5th edition of the *Diagnostic and Statistical Manual of Disorders (DSM-5).* Prior to 2013, as previously discussed, the *DSM-IV* described two different criteria for alcohol abuse and alcohol dependence. However, the *DSM-5* integrates alcohol abuse and alcohol dependence into a single disorder called alcohol useisorder mild, moderate, and severe. Rather than having separate criteria for alcohol abuse and alcohol dependence, alcohol use disorder is defined by anyone meeting any two of the 11 criteria

including drinking more or longer than intended and wanting to drink so badly that the person could not think of anything else. The severity of the alcohol use disorder depends on the number of criteria satisfied rather than specific criteria as used in the *DSM-IV* (National Institute on Drug Abuse, 2015b).

In addition, the National Institute on Alcohol Abuse and Alcoholism estimates that about 7.2 percent 17 million adults in the United States 18 and older had an alcohol use disorder in 2012 (National Institute on Drug Abuse, n.d.). More recent findings from the 2014 National Survey on Drug Use and Health indicate that 52.7of Americans age 12 and up reported being current drinkers of alcohol, and of those 176.6 million alcohol users, about 17 million have an alcohol use disorder (Substance Abuse and Mental Health Services Administration, 2015). Because studies analyzed in the current investigation were conducted before and after the newest edition of the *DSM,* alcohol use may refer to individuals having a diagnosis along the alcohol abuse-alcoholism spectrum, or alcohol use may refer to individuals having a diagnosis on the mild to severe alcohol use disorder spectrum.

Comorbidities involving smoking, alcohol use, depression, and schizophrenia

Before investigating the epidemiology and etiology of the depression-smoking, depression-alcohol, schizophrenia-smoking, and schizophrenia-alcohol comorbid disorders, a few terms are of note to the reader. First, although substance use disorders are commonly considered psychiatric disorders, in the current investigation, psychiatric disorders will refer to non-substance use disorders such as depression and schizophrenia. Second, herein, I distinguish between two main categories of etiological models. The first category that I will call “direct prediction” consists of models and hypotheses suggesting that the comorbidity occurs because

the psychiatric disorder (depression or schizophrenia) and substance use disorder (smoking or alcohol) are connected to each other such that one disorder of the comorbidity predicts the other. The second category of models and hypotheses that I will call "common factors" suggests that the psychiatric disorder-substance use disorder comorbidity occurs due to separate risk factors that independently contribute to the development of both disorders rather than interactions between the two disorders.

Epidemiology of Depression and Substance Use

I will now discuss the epidemiology of depression and substance use before addressing the epidemiology and etiology of depression-smoking comorbid disorders in particular. Research suggests that depression and substance use are commonly comorbid with one another (Kilpatrick et al., 2003). The comorbidity has been shown to be more common in certain age groups. For example, the odds ratio of developing comorbid depression and substance use in adolescents compared to adults 1.3, with the odds ratio increasing with age (Kilpatrick et al., 2003). Ethnicity also plays a role in the epidemiology of depression-substance use comorbidities. For example, the risk for depression and substance use dual diagnoses was increased among AfricanAmerican individuals and decreased among Caucasian individuals. AfricanAmerican adolescents show significantly greater risks for comorbid major depression and substance use (odds ratio of 0.2) (Kilpatrick, et al., 2003), while individuals diagnosed with substance-induced depression are significantly less likely to be Caucasian (Schuckit et al., 1997). The discrepancy in rates of the comorbidity between different ethnicities may reflect different ethnicities' attitudes toward smoking (Burgess et al., 2014). Marital status also can influence the rates of comorbidity, as Schuckit et al. (1997) determined that comorbidities between depression and

substance use were higher among unmarried individuals (Schuckit et al., 1997). Lastly, trauma is another factor that can contribute to the frequency of depression and substance use comorbidities. For example, findings indicate that individuals exposed to violence are significantly more likely to have a depression-substance use comorbid disorders compared to individuals who are not exposed to violence (odds ratio of 6) (Kilpatrick et al., 2003). In comparison, individuals who experienced sexual assault showed an increased risk for developing depression comorbid with substance use (odds ratio of 4.4) (Kilpatrick et al., 2003).

Epidemiology of Depression and Smoking

Researchers have determined a high prevalence of diagnosable depression among cigarette smokers and a high prevalence of smoking among individuals with major depressive disorder. For instance, 34of smokers have an untreated diagnosis of major depression (Kinnunen, Doherty, Militello, & Garvey, 1996), and 30of individuals with lifetime major depressive disorder also experience nicotine dependence (Hasin, Goodwin, Stinson, & Grant, 2005). Moreover, findings suggest equal rates of smoking and depression comorbidities in males and females (e.g. Simantov, Schoen, & Klein, 2000), while other findings suggest that the comorbidity is more common in females (Richardson, He, Curry, & Merikangas, 2012). The higher prevalence of depression-smoking comorbid disorders cannot simply be explained by claiming that the higher rates of comorbidity occur because females show higher rates of depression and higher rates of smoking as individual disorders because while females are at a higher risk for depression (National Insitutute of Mental Health, 2013), the prevalence of smoking is higher among men (Centers for Disease and Control, 2015). Thus, components specific to the comorbidity must explain why depression-smoking comorbid disorders are more

common in females. Lastly, evidence suggests that females who are less educated or unemployed are at a higher risk for the dual diagnosis compared to educated or employed females (Weaver & Etzel, 2003).

Etiology of Depression and Smoking

In addition, several models theorize how individuals can develop depression-smoking comorbid disorders. As previously discussed, direct prediction models and common factors models are two main categories of etiological models.

Direct Prediction Models

Researchers highlight how for some individuals, the etiology of depression-smoking comorbid disorders supports a direct prediction model. In other words, studies show how for some individuals, the depression-smoking comorbid disorders occur because depression predicts later smoking. For instance, in a sample of Finnish adolescent twins, early-onset depressive disorders significantly predicted daily smoking 3.5 years later (odds ratio of 2.29) (Sihvola et al., 2008). Similarly, the odds of young adults with a history of major depressive disorder nicotine dependence compared to nondepressed young adults is 2.06 (Breslau, Kilbey, & Andreski, 1993). Other studies also reported depression as a significant predictor of smoking persistence in adults (Edwards, Anda, Gu, Dube, & Felitti, 2007; Kassel, Stroud, & Paronis, 2003) middle school and high school aged adolescents (e.g. Kassel, Stroud, & Paronis, 2003; Simantov, Schoen, & Klein, 2000).

One might suggest that, due to the chronology of depression preceding, depression contributes to the development of smoking. However, it could be that depression does not directly predict smoking, and the comorbidity arises because individuals are predisposed to both

conditions and smoking happens to develop following the depression onset. In other words, just because depression occurs prior to smoking does not necessarily imply that the disorders support a direct prediction model. Thus, more evidence besides chronological data is needed to conclude that the depression-smoking comorbid disorders can arise because depression contributes to smoking. Indeed, researchers have constructed several direct prediction hypotheses to explain how the predictive relationship may signify that depression is a risk factor for smoking.

The self-medication hypothesis proposes that smoking develops among depressed individuals as a way to relieve distressing depressive symptoms (Khantzian, 1997). Numerous studies provide evidence for the self-medication hypothesis. For example,Lerman et al. (1996) reported that smokers who were depressed were more likely to report "self-medication processes" such as smoking in order to reduce negative affect or increase stimulation. Malpass & Higgs (2009) interviewed British smokers who were currently receiving treatment for depression about their reasons for smoking, and participants expressed that one of the main reasons for smoking was to manage negative affect.

Further results provide evidence for the self-medication hypothesis by illustrating how nondepressed individuals report smoking in order to relieve depressive symptoms. For example, when Johnson et al.2003 asked non-depressed adolescent smokers about why they smoked, common responses included that they smoked to obtain feelings of personal pleasure or satisfaction or smoked in order to cope with unpleasant feelings including depression, sadness, fear, anger, and loneliness. More specifically, adolescent smokers reported that smoking helped them cope with unpleasant feelings by soothing them and distracting them from the uncomfortable or unpleasant emotions such as sadness and loneliness. It is important to note that

one limitation to the experimental design of these studies is that they relied on self-report data in an observational setting, which can lead to potential bias in the results.

Studies have further exemplified support for the self-medication hypothesis in an experimental setting. For instance, in an experimental study conducted by Pomerleau et al. (2005), smokers completed a three-day non-smoking withdrawal period, and on the fourth day, the researchers exposed the participants to a controlled dose of smoke. One finding indicated that high-depressed smokers were more likely than low-depressed smokers to show evidence of experiencing pleasurable "buzzes" in response to the smoke exposure. Thus, the findings provided evidence for the self-medication hypothesis because the more severe the depression, the more pleasure the smoking provided. Also, the fact that the researchers utilized an experimental manipulation suggests stronger support for the self-medication hypothesis.

Although one limitation to studying the self-medication hypothesis is that the conclusions often rely on self-report data, there is biological support for the self-medication hypothesis explaining the predictive relationship between depression and smoking. For example, Balfour & Ridley (2000) determined that depression sensitizes patients to the adverse effects of stressful stimuli. These adverse effects can then be relieved by drugs that stimulate dopamine release in the forebrain, which contributes to increased craving to smoke in abstinent smokers exposed to adverse stimuli. The researchers concluded that the dopamine release conditions abstinent smokers to use nicotine to provide fast alleviation of the adverse effects of stress.

In summary, various studies portray support for the self-medication hypothesis through different research methods (e.g., observational data and experimental data from inducing exposure to smoke) and different forms of evidence (e.g. self-report evidence and biological

evidence). In addition, researchers have developed several other direct prediction hypotheses regarding why depression predicts smoking. For example, the risk-taking hypothesis suggests that depression can be a risk factor for smoking because depressed individuals are more likely to take risks (Murphy et al., 2003). More specifically, Murphy et al. (2003) theorizes that depressed individuals are vulnerable to nicotine dependence because their feelings of worthlessness make them prone to take risks like trying tobacco. Another hypothesis suggests that depression may be a risk factor for smoking because social factors mediate the relationship. For example, social factors such as child abuse may also contribute to the pattern of depression predicting smoking. In fact, depressed women who experienced childhood abuse exhibited an increased risk of becoming smokers (Nichols & Harlow, 2004). Similarly, findings indicate that depression mediates the role between child abuse and persistent smoking (Edwards et al., 2007).

A second direct prediction etiological model of the depression-smoking comorbidity suggests that for some individuals, the comorbidity occurs because smoking predicts later depression. For example, numerous studies reported that smoking was a significant predictor for developing depressive symptoms (e.g., Boden, Fergusson, & Horwood, 2010; Choi, Patten, Gillin, Kaplan, & Pierce, 1997; Kassel, Stroud, & Paranis, 2003; Wu & Anthony, 1999). In fact, one study indicated that smokers were three times more likely to become depressed than nondepressed individuals (Murphy et al., 2003).

Studies provide further evidence that smoking can be a significant predictor for depression by showing that smoking is a stronger predictor of depression than other factors. More specifically, findings indicate that compared to other potential risk factors such as social and personality risk factors, smoking was the strongest predictor for developing later depressive

symptoms. For instance, in a sample of adolescents ages 12 to 18, smoking was the most significant predictor of developing depression compared to other risk factors such as involvement in organized athletics, availability of social support, and personality characteristics (Choi et al., 1997). Similarly, among individuals who were nondepressed at baseline, current cigarette smoking was the strongest predictor of developing depressive symptoms (odds ratio of 3.90) (Goodman & Capitman, 2000). Studies further indicate that in addition to predicting depressive symptoms, smoking predicts the onset of major depressive disorder. For example, participants with a history of nicotine dependence exhibited a higher rate of first-incidence major depressive disorder during the follow-up period (odds ratio of 2.45) (Breslau, Kilbey, & Andreski, 1993). Researchers have even concluded a causal link between smoking and depression onset (e.g., Boden, Fergusson, & Horwood, 2010).

studies a predictive relationship between depression and subsequent smoking, it is easy to misinterpret thepredictive relationship between smoking and later depression that depression-smoking comorbid disorders can occur because smoking leads to depression. As mentioned previously, it could be that smoking does not directly predict depression, and the comorbidity develops because the individuals have predispositions for both disorders and depression happens to develop second. Therefore, there must be more evidence besides predictive chronological data to suggest that the comorbidity can develop because smoking is a risk factor for depression. In fact, researchers have proposed a smoking-induced depression hypothesis regarding how the predictive relationship between smoking and later depression may imply that smoking can be a risk factor for depression.

The smoking-induced depression hypothesis suggests that smoking may contribute to the development of depression. Researchers have theorized a biological mechanism in support of the smoking-induced depression hypothesis. For example, Kassel, Stroud, & Paranis (2003) proposed that the neuropharmacological components of nicotine maintain and intensify depression by neural substrates linked to depression. Further evidence suggests that nicotine contributes to depression by interfering with specific neurotransmitter systems. For example, exposure to nicotine causes changes in 5-HT formation and release in the hippocampus, which then contributes to depression (Balfour & Ridley, 2000). In comparison, acetylcholine is the endogenous neurotransmitter for nicotinic acetylcholine receptors, and evidence suggests that nicotine contributes to depressive symptoms and the etiology of major depressive disorder due to dysregulation of the cholinergic system (Mineur and Picciotto, 2010). Other biological evidence supporting the smoking-induced depression hypothesis portrays how smoking may predispose individuals to depression by dysregulating the hypothalamic-pituitary-adrenal (HPA) axis. For instance, Semba, Wakuta, Maeda, & Suhara (2004) concluded that during nicotine-withdrawal, the HPA axis is sub- sensitive to stress, which then contributes to the development of depression during smoking cessation. Lastly, animal models provide further biological evidence to support the substance-induced depression model. For example, in rats, the administration of nicotine induces depression-like behaviors. In particular, after nicotine administration, rats display depressive behaviors such as reduced swimming behaviors on the forced swimming task and reduced mobility (Hayase, 2011).

Overall, when determining which direct prediction etiological models and hypotheses are best supported, it is crucial to keep in mind two ideal characteristics of an etiological model.

First, due to potential biases resulting from self-report data, an ideal etiological model would be supported by additional data besides self-report data (e.g, observed behavioral and biological data). Second, an ideal model would be supported by both observational and experimental methods. Etiological models that are only supported through observational methods should be interpreted with caution because the correlational relationships that result from these studies do not imply causal relationships.

Thus, the direct prediction etiological models and hypotheses, specifically the self-medication hypothesis and smoking induced depression hypothesis, were well supported. More specifically, although some studies provided support for the two hypotheses through the use of self-report data, this limitation was counterbalanced by additional observed biological and behavioral data that confirmed the self-report results. Likewise, although some of the studies on the two hypotheses relied only on an observational research design, experimental studies confirmed the observational results.

Common Factors Models

Another etiological theory proposes that depression comorbid with nicotine dependence may develop due common risk factors such as specific social, personality, and environmental factors that predispose individuals to separately develop the smoking-depression comorbidity rather than one of the disorders directly predicting the other. For example, certain social factors may contribute to the development of the comorbidity. Fleming & Jacobsen (2010) determined that bullied students reported more feelings of sadness, hopelessness, and loneliness and also higher rates of tobacco use, and alcohol use.

Personality risk factors such as high levels of neuroticism may also predispose individuals to develop both depression and smoking separately (Kassel, Stroud, & Paranis, 2003). More specifically, researchers theorize that the high arousal levels characteristic of neurotic individuals contributes to their increased vulnerability to start smoking because smoking can help them achieve lower central nervous system arousal (Kassel, Stroud, & Paranis, 2003). Researchers have determined several mechanisms for neuroticism to predict depression, as well. For example, findings indicate that a gene called the cannabinoid receptor gene that is correlated with neuroticism interacts with life stress to predict depression (Juhasz et al., 2009), while recent findings highlight the potential for emotion dysregulation (e.g., lack of efficient emotion regulation strategies and impulse control) and psychological inflexibility to mediate the relationship between neuroticism and later depression (Paulus, Vanwoerden, Norton, & Sharp, 2016).

Lastly, environmental factors such as socio-economic status and cholesterol level may predispose individuals to develop the smoking-depression comorbidity. For instance, in a sample of former smokers between the ages of 20 and 89, somatic (, cholesterol level, and blood pressure), socio-demographic variables (education level, socio-economic status, and marital status), low physical activity, and alcohol problems were the factors that contributed most to the correlation between anxiety, depression, and smoking (Mykletun, Overland, Aaro, Liabo, & Stewart, 2008).

In addition, the same limitations and strengths applied to the direct prediction models can be applied to interpreting which, if any, of the common factors models are the most supported. For example, one limitation of the social common factors, personality common factors, and

environmental common factors models is that they were all supported through self-report data and observational research designs. However, the personality common factors model appears to be the most supported common factor model for depression-smoking comorbidities because researchers demonstrated through biological and psychological mechanisms how neuroticism (the personality factor) can be a common factor for depression and smoking. Therefore, the model is supported by additional data besides self-report data.

Epidemiology of Depression and Alcohol Use

Studies indicate that depression and alcohol use are another common comorbidity. Although the epidemiologic studies such as the Epidemiologic Catchment Area Study indicate a low rate of comorbid mood disorders and alcohol dependence in the general population (0.1) (Sher, 2009), studies suggest that individuals abusing alcohol are at a high risk of developing major depression. For instance, Greenbaum, Prange, Friedman, & Silver, (1991) reported that alcohol users exhibited an odds ratio of 1.75 to develop diagnosable depression.

Similarly, numerous studies reveal that depressed individuals exhibit an increased risk of developing abnormal alcohol use. More specifically, findings show high odds ratios for depressed individuals to develop abnormal alcohol use. For example, depressed men and women show an odds ratio of 0.65 and 1.65 for developing alcohol abuse (Kessler et al, 1997). Also, depressed men and women exhibit odds ratios for developing alcohol dependence of 2.95 and 4.05 respectively (Kessler et al, 1997). The discrepancies in frequency of depression-alcohol comorbid disorders between males and females could be due the potential for men and women to experience depression differently (National Institutes of Mental Health, 2011). Also, the increase risk for depressed women to develop alcohol use disorders could be due to differences in alcohol

intake patterns between men and women (National Institute on Alcohol Abuse and Alcoholism, n.d.). More specifically, women may be more sensitive to the effects of alcohol because they typically begin to have alcohol-related problems at lower levels than men, they tend to weigh less than men, and they have less water in their bodies than men (alcohol resides mainly in body water) (National Institute on Alcohol Abuse and Alcoholism n.d.). Lastly, Dixit & Crum (2000) studied the odds ratios of depressed women developing abnormal alcohol use and determined that a higher frequency of depressive symptoms correlated with risk for heavy alcohol use (dds ratio of 1.09).

Further findings complement the odds ratios by demonstrating the high risk of depressed individuals developing abnormal alcohol use through reports of prevalence rates. For example, Hasin, Goodwin, Stinson, & Grant (2005) found that among individuals with lifetime major depressive disorder, 40.3 also had an alcohol disorder. Sher (2009) further ied the high prevalence rates of alcohol use disorders among depressed individuals from findings from several epidemiological studies. For instance, the Epidemiologic Catchment Area study reported a lifetime prevalence rate of alcohol dependence among individuals with major depression to be 11.6(Sher, 2009). Also, the Ontario Health Survey observed that 19.8of depressed men and 46of depressed women reported alcohol dependence (Sher, 2009). Lastly, the National Comorbidity Study determined that 24.3of men with major depression and 48.5of women with major depression reported alcohol dependence (Sher, 2009).

Findings indicate that specific groups of individuals may be more prone to develop the depression-alcohol use comorbidity. For instance, findings indicate that young adults are more at risk for the comorbidity compared to older adults (Brière, Rohde, Seeley, Klein, & Lewinsohn,

2014). As previously described, studies also suggest that women exhibit higher risks for the comorbidity. Although the studies previously described odds ratios and prevalence rates similarly suggest that the comorbidity is more common in females compared to males, (e.g., Kessler et al, 1997; Sher, 2009), there are studies that report a higher prevalence of the comorbidity in males compared to females. For example, Nurnberger et al. (2001) observed that the majority (57.4%) of individuals with comorbid alcoholism and depression were male. However, the conclusion that 57.4% constitutes the "majority" should be taken with caution, as this number is incredibly close to 50%.

Etiology of Depression and Alcohol Use

I next discuss etiological models for depression-alcohol comorbid disorders. Similar to depression-smoking comorbid disorders, irect rediction odels and ommon actors odels constitute the two main categories of etiological models.

Direct Prediction Models

Similar to depression-smoking comorbid disorders, researchers have devised direct prediction models that apply to depression-alcohol comorbid disorders, as well. More specifically, findings indicate that depression-alcohol use comorbid disorders may occur because depression predicts the development of alcohol use disorders. For example, depression can be a significant predictor later alcohol problems (Gilman & Abraham, 2001; Simantov, Schoen, & Klein, 2000), and results suggest that 15.2 of alcoholics experience depression onsets before alcohol dependence onsets (Schuckit et al., 1997). More recent studies (e.g., Brière et al. 2014; Sihvola et al., 2008) confirmed that early onset depression significantly predicted later alcohol use disorders. Lastly, one study specifically assessing women revealed that women with a

history of depressive disorder exhibited a significantly greater risk for developing heavy drinking compared to women without a history of major depression (odds ratio of 2.60). (Dixit & Crum, 2000).

As with the depression-smoking models suggesting that depression predicts smoking, just because depression predicts alcohol use does not imply that the depression-alcohol use comorbidity occur due to links between depression and alcohol use. Thus, more evidence is required to demonstrate the linkage between depression and alcohol use.

Several studies (e.g. Johnson et al., 2013) concluded that chronological data provided support for the self-medication hypothesis without taking into account the possibility that depression could have preceded alcohol use simply by chance. Nonetheless, studies do provide results that support the self-medication hypothesis for the depression-alcohol use comorbidity. For example, Hill and Angel (2005) determined that individuals living in stressful poor neighborhoods reported that one of their reasons for consuming alcohol was as an escape and to regulate feelings of depression. In comparison, a study on a group of depressed women illustrated that women reported using alcohol as an attempt to escape difficult emotions or produce positive emotional experiences (Brown & Stewart, 2008). Likewise, data from the National Epidemiologic Survey on Alcohol and Related Conditions indicated that almost one quarter of individuals with mood disorders (including depression) utilized alcohol or drugs to relieve symptoms (Bolton, Robinson, & Sareen, 2009).

As with the depression-smoking comorbid disorders, studies demonstrate the potential for the depression-alcohol use comorbidity to occur because alcohol use predicts depression. For example, one study reported that ave 1 hazardous drinking was associated with Wave 2

depression (Johnson et al., 2013). Other results indicate that individuals with alcoholic use disorder are at a significantly high risk of developing later depression (Gilman & Abraham, 2001). Likewise, Briere et al. (2014) and Brook, Brook, Zhang, Cohnen, and Whiteman (2002) determined that adolescent and young adult alcohol use and alcohol use disorder significantly predicted later major depressive disorder. Further findings reveal that 26.4of alcoholics report at least one substance-induced depressive episode (Schuckit et al., 1997).

Similar to the chronological relationship between depression and later alcohol use, it is easy to conclude that the chronological relationship between alcohol use and later depression indicates that alcohol use contributes to later depression. Indeed, studies (e.g., Preuss et al., 2002) have concluded that the depression of the depression-alcohol use comorbidity is alcohol-induced simply based on the chronology of alcohol use developing first, but further evidence is needed to suggest that alcohol use can predispose individuals to develop subsequent depression.

Similar to depression-smoking comorbidity, researchers have developed the substance-induced depression hypothesis for alcohol use, as well. Researchers have utilized different forms of evidence to support the alcohol-induced depression hypothesis. For instance, Schuckit et al. (1997) demonstrated that in a sample of depressed alcoholics, twothirds of the participants developed depression only during periods of heavy drinking. Thus, it would seem that alcohol was somehow contributing to the development of depression since it would be unlikely that twothirds of these individuals would develop depression only during times of heavy drinking simply by chance.

Researchers also provide support for the alcohol-induced depression hypothesis by utilizing behavioral data. For example, a well-designed experimental study by Foulds et al. (2015) found that individuals with the depression-alcohol use comorbidity as well as individuals with independent depression exhibited improvements in depression when they stopped drinking. Thus, since stopping alcohol use improved depression, the researchers concluded that this finding supports the substance-induced hypothesis since drinking therefore likely worsens depression. In comparison, Gomez and Luine (2014) examined the effects of alcohol administration on the behavior of rats and observed that rats exposed to a combination of stress and alcohol exhibited immobility on the forced swim test, indicating an alcohol-induced depression.

Biological data also provides support for the alcohol-induced depression hypothesis. For example, Pietraszek et al. (1991) conducted a study they assessed the levels of serotonin, a neurotransmitter involved in depression, after a group of nondepressed individuals drank alcohol. The results suggested that compared to the control group, individuals who drank alcohol exhibited similar serotonin levels to depressed patients, leading the researchers to conclude that the mechanism of developing depression following alcohol use may relate to levels of serotonin. Similarly, Getachew, Hauser, Taylor, and Tizabi (2010) assessed the relationship between alcohol and depression in an experimental setting using rats and determined that reduced cortical concentrations of norepinephrine can play a role in alcohol leading to depression. Lastly, findings experimental studies on rats indicate the potential for alcohol to induce depression by reducing derived neurotrophic factors in the hippocampus (Hauser, Getachew, Taylor, & Tizabi, 2011).

among the direct prediction models for depression-alcohol comorbid disorders the alcohol-induced hypothesis is the best supported because the model satisfies the two criteria for an ideal etiological model previously described in the depression-smoking comorbid disorders section. First, the alcohol-induced model is supported by self-report data, behavioral data, and biological data. Second, the alcohol-induced hypothesis is supported through both observational and experimental methods. On the other hand, the self-medication hypothesis for depression-alcohol comorbidities is less supported because the studies in support of the hypothesis relied only on self-report data and data was only obtained through observational studies.

Common Factors Models

Findings suggest the potential for the depression-alcohol comorbidity to develop due to risk factors separate from the depression and alcohol use. Similar to the depression-smoking risk factors, these risk factors include biological, social, and environmental factors. For example, genetics is one potential biological risk factor for developing the depression-alcohol comorbidity. In fact, evidence suggests that depression without alcoholism does not transmit to future generations, while depression and alcoholism comorbidities are transmitted to future generations (Merikangas et al., 1985). In comparison, Prescott, Aggen, & Kendler (2000) calculated that the 50 overlap between depression and alcohol use disorders was attributed to shared genetic factors. Researchers further concluded that specific genes and alleles could predispose individuals to develop the depression-alcohol use comorbidity. For example, Nurnberger et al. (2001) found that an allele located at a locus on hromosome 2 was specific to the comorbid alcoholism and depression phenotype. Other findings indicate that a locus on the CHRM2 gene, a gene involved

in the binding of acetylcholine, is under-transmitted in individuals with alcohol dependence comorbid with depression (Wang et al., 2004). Also similar to the depression-smoking biological risk factors, abnormalities in neurotransmitters constitute a second biological risk factor for the depression-alcohol use comorbidity. For instance, Heinz et al. (1998) determined that alcoholics exhibited a significant reduction in the availability of brainstem serotonin transporters. The significant reduction was significantly correlated with lifetime alcohol consumption and ratings of depression and anxiety. In summary, evidence suggests the potential for specific genetic factors to predispose individuals to both depression and alcohol use.

In addition, social risk factors for the depression-smoking comorbidity are also risk factors for the depression-alcohol use comorbidity. For example, abuse plays a role in the development of the depression-alcohol use comorbidity. More specifically, in adolescents, major depression comorbid with alcohol use disorders is partly attributable to physical abuse and sexual abuse (Clark, De Bellis, Lynch, Cornelius, & Martin, 2003). Roy (1999) determined that depressed alcoholics exhibited significantly higher scores on the Childhood Trauma Questionnaire for childhood emotional abuse, physical abuse, sexual abuse, and emotional neglect. Finally, bullying is a social risk factor for the depression-alcohol use comorbidity. For instance, one finding from a study conducted by Fleming & Jacobsen (2010) revealed that bullied students reported more feelings of sadness, hopelessness, and loneliness and also higher rates of tobacco use and alcohol use.

Other social risk factors shown to contribute to the development of the depression-alcohol use comorbidity include relationships with parents. For instance, Holmes & Robins (1987) determined that unfair, inconsistent, and harsh discipline by parents during the

participant's' life from age 613 significantly predicted both alcohol and depressive disorders independently of the influence of parental psychiatric history, the respondents' gender, and childhood behavior problems. Lastly, bereavement is an additional social risk factor for the depression-alcohol use comorbidity as Vance, Boyle, Najman, & Thearle (1995) reported that males experiencing bereavement showed significant increases in anxiety, depression, and heavy drinking two months following the death.

Lastly, similar to the depression-smoking comorbidity, environmental risk factors can contribute to the development of the depression-alcohol comorbidity. For example, Goodwin, Schulsinger, Knop, Mednick, and Guze (1977) concluded that environmental factors are crucial in the development of both alcoholism and depression in women since both correlated with the psychopathology in the foster parents rather than the biological parents. In addition, other finding specific environmental risk factors that can predispose individuals to develop the depression-alcohol use comorbidity. For instance, Dressler, Ribeiro, Balieiro, Oths, & Santos 2004) proposed that lower incomes lead to lower cultural consonance (a term defined by Dressler and colleagues to describe the inability to act in accordance with ones' cultural ideals), which then contributes to higher rates of depression and alcohol intake. Chronic stress constitutes another potential environmental risk factor as Brennan and Moos (1990) demonstrated how among late-middle aged problem drinkers with depression, drinking behavior and depression was attributed to chronic stressors and social resources even after taking gender, marital status, and negative life events into account. Finally, findings suggest that poor living conditions can be an environmental risk factor for the depression-alcohol comorbidity. For instance, Hill & Angel (2005) concluded that the stress of living a neighborhood characterized by problems with drugs,

crime, teen pregnancy, unemployment, inactive youth, abandoned houses, and unresponsive police can be a risk factor for the depression-alcohol comorbidity. More specifically, Hill & Angel discussed how their findings support the tension reduction hypothesis that proposes that inadequate living conditions are psychologically distressing and lead people to consume alcohol as a way to escape and regulate feelings of anxiety and depression. The tension reduction hypothesis thus parallels the self-medication model in relation to environmental stressors.

Furthermore, all of the common factors models are equally supported. First, the studies in support of the common factors models where biological, social, or environmental factors were the common factors all relied on one form of data. More specifically, the biological common factors models relied on biological observations, while the social and environmental common factors models utilized self-report data. Second, the data that was concluded to support these common factors models was obtained through observational methods. Thus, all common factors models for the depression-alcohol comorbid disorders share the similar limitations of potential bias from self-report and incorrect assumptions about causality based on observational results.

Epidemiology of Schizophrenia and Smoking

In addition, I now will discuss the epidemiology and etiological models for schizophrenia-smoking comorbid disorders. Studies demonstrate that the schizophrenia-smoking comorbidity is a common comorbidity. For instance, Lohr & Flynn (1992) demonstrated that the prevalence of smoking among schizophrenic individuals is extremely high. More specifically, almost 90 of schizophrenic individuals smoke, which is much higher than the 33 smoking rate among the general population and the 45 to 70 smoking rate among individuals with other psychiatric disorders (Lohr & Flynn, 1992). In comparison, other studies report high prevalence

rates such 64.1 of schizophrenic patients currently smoking (Herrán et al., 2000). More recently, Winterer (2010) reported that more 70 to 80 of schizophrenics smoke, and Jeanblanc et al. (2015) noted that more than 80 of schizophrenics smoke. Evidence suggests that specific populations are more vulnerable to develop the comorbidity. For example, schizophrenic individuals who smoke are more likely to have lower educational levels (Tang, George, Mao, Cai, & Chen, 2007). Also, schizophrenic individuals who smoke are significantly more likely to be divorced (Tang et al., 2007).

Moreover, Goff, Henderson, & Amico (1992) found that among schizophrenic individuals, significantly youngerand experienced a greater number of previous hospitalizations. Findings also indicate that smoking among schizophrenic individuals is more common in men (Goff et al., 1992; Herrán et al., 2000). Margolese, Malchy, Negrete, Tempier, and Gill (2004) reported that nicotine was among the top three most abused drugs in a sample of schizophrenic individuals. Among schizophrenics, smokers were significantly younger, more likely to be male, and unemployed, and the rates of smoking among the schizophrenic population were twice the rate seen in the general population. (Krishnadas, Jauhar, Telfer, Shivashankar, & McCreadie et al., 2012). The higher rates of the comorbidity in gender could simply be due to the fact that smoking and schizophrenia are individually more common in men (Centers for Disease and Control, 2015; Iacono, W. G., & Beiser, 1992).

Etiology of Schizophrenia and Smoking

Moreover, similar to the depression-alcohol and depression-smoking comorbid disorders, researchers have devised direct prediction models and common factors models for schizophrenia-smoking comorbid disorders, as well.

Direct Prediction Models

Various studies have assessed the chronological relationship between schizophrenia and smoking. Studies indicate that for some individuals with the schizophrenia-smoking comorbidity, the smoking onset developed following the schizophrenia onset. For example, de Leon (1996) found that 50 of schizophrenia-smoking individuals started smoking after the onset of schizophrenia. In comparison, LLerena, de la Rbia, Penas-Lledo, Diaz, and de Leon (2003) reported that schizophrenia increased the risk of smoking by 2 to 3fold.

Findings indicate that similar to the depression-smoking and the depression-alcohol use comorbidity, the self-medication hypothesis may explain how schizophrenia can be a risk factor for smoking. For example, Esterberg & Compton (2005) and Forchuk et al. (2002) determined that schizophrenic individuals reported smoking in order to relieve schizophrenia symptoms. Other researchers have concluded that schizophrenic individuals smoke to relieve and control psychotic symptoms, particularly negative symptoms, cognitive difficulties, and side effects from antipsychotic drugs (Adler et al., 1993; Esterberg & Compton, 2005; Fisher Anfang and Pope, 1997; Fukui et al., 1995; Glassman et al., 1993; Goff et al., 1992; Janhunen and Ahtee, 2007; Lohr and Flynn, 1992; Srinivasan & Thara, 2002).

Further results reveal that smoking behavior among chronic schizophrenics might function to help the schizophrenic individuals control their anxiety symptoms (Esterberg & Compton, 2005). Findings also indicate support for the self-medication hypothesis by suggesting that higher distress correlates with decreased nicotine use in schizophrenic individuals, which indicates that schizophrenia symptoms increase when cigarette consumption decreases (Hamera, Schneider, & Deviney, 1995). Lastly, findings indicate that smoking may help alleviate

schizophrenic individuals' cognitive difficulties by improving attention deficits and recall (Janhunen and Ahtee, 2007; Sacco et al., 2005), helping to gate out irrelevant stimuli such as auditory hallucinations in order to focus attention (Evans & Drobes, 2008; Kumari and Postma, 2005), and improving visuospatial working memory (Adler, Hoffer, Wiser, & Freedman, 1993; George et al., 2002). Evidence also indicates that schizophrenic individuals smoke to feel more at ease and comfortable when socializing (Hubbard, 2011).

In addition, studies provide a biological basis for the direct prediction model of schizophrenia predicting smoking. More specifically, various studies suggest that schizophrenia predicts smoking because schizophrenic individuals exhibit biological predispositions to become smokers. For example, studies indicate that schizophrenic individuals are more biologically vulnerable to become smokers because they show abnormal neural circuitry involved in drug reward and reinforcement (Chambers, Krystal, & Self, 2001). Studies also schizophrenic individuals may be at risk for smoking due to specific nicotinic acetylcholine receptor genes (Faraone, Taylor, van Eerdewegh, & Tsuang, 2004).

Researchers have zoomed in beyond the level of the gene to demonstrate that abnormalities in receptors encoded by these genes may play a role in schizophrenics being more at risk for smoking. For instance, Winterer (2010) discussed how the molecular and physiologic abnormalities of the central nicotinic system account for the relationship between schizophrenia and smoking, particularly abnormalities related to nicotine binding acetylcholine receptors (nAChRs). More specifically, findings indicate that acetylcholine receptor deficits cause negative and cognitive symptoms in schizophrenia, and this relationship is mediated by smoking (Winterer, 2010). Similar to this finding, Leonard, Mexal, & Freedman (2007) theorized that low

levels of nicotinic receptors in schizophrenia may cause different neurotransmitter release patterns and abnormal gene expressions that are normalized by smoking. In comparison, Freedman, Adler, and Bickford (1994) concluded that schizophrenic individuals exhibit decreased levels of cholinergic nicotinic receptors in the hippocampus and heavily smoke in order to activate these receptors that when activated help the individuals filter out irrelevant stimuli. Luckhaus et al. (2012) determined that schizophrenic smokers exhibited significantly decreased of nicotinic binding compared to healthy smokers.

In addition, researchers have narrowed in even more to identify specific nicotinic receptors that may relate to schizophrenia predicting smoking. For example, findings indicate that decreased amounts of a specific nicotinic receptor known as the α7* nicotinic receptor may predispose schizophrenic individuals to smoking (Adler et al., 1998; Leonard et al., 2000; Leonard, Mexal, & Freedman, 2007). More specifically, Adler et al. (1998) proposed that decreased levels of the α7* nicotinic receptor and the receptor's rapid desensitization present in schizophrenia influence schizophrenic individuals to heavily smoke because a high concentration of nicotine is needed to activate the receptor. Overall, researchers have more broadly demonstrated abnormalities in the nicotinic acetylcholine receptor genes that are implicated in the schizophrenia-smoking relationship and have narrowed in on the specific nicotinic acetylcholine receptor encoded by these genes that may be contributing to the predictive relationship between schizophrenia and smoking.

In addition, researchers have demonstrated that that the activation of these previously described nicotinic receptors functions as biological evidence for the self-medication hypothesis in thatactivation of the nicotc recptors results in improvements in schizophrenic symptoms. For

example, Sacco et al. (2005) demonstrated through an experimental manipulation that stimulating nicotinic acetylcholine receptors by smoking improves visuospatial memory deficits and attention deficits in schizophrenia. In comparison, The activation of the receptors that results from smoking has been shown to improve sensory deficits (e.g., hypervigilance) in schizop, leading researchers to theorize that the increased inhalation of nicotine reflects self-medication of the individuals' sensory deficits (Freedman, Adler, & Bickford., 1994; Olincy, Young, & Freedman, 1997).

In addition, studies show that dopamine irregularities may constitute another biological mechanism that underlies the predictive relationship between schizophrenia and later smoking. For instance, Chambers, Krystal, & Self (2001) determined that the disturbances in drug reward are partly mediated by dysregulated neural integration of dopamine and glutamate signaling in the nucleus accumbens resulting from frontal cortical and hippocampal dysfunction. The altered integration of these signals produces neural and motivational changes that are similar tolong-term substance abuse when there has not been prior drug exposure, which facilitates the schizophrenic individuals to form addictions.

In addition, studies have demonstrated the potential for smoking to predict schizophrenia, as well. One study conducted by de Leon (1996) reported that 50 of the schizophrenic-smokers started daily smoking prior to the onset of the onset of schizophrenia onset, and Riala et al. (2005) reported that smoking preceded schizophrenia onset by an average of 2.3 years. Similarly, Martinez, Gurpegui, Diaz, and de Leon (2004) reported that there was a high prevalence of smoking initiation prior to the development of schizophrenia. Compton et al. (2009) reported a correlation between tobacco use and later schizophrenia onset, as well. Moreover, Beratis,

Katrivanou, & Gourzis (2001) found that in a sample of schizophrenic smokers, 86 of the individuals started smoking before the onset of schizophrenia. Lastly, in a recent thorough meta-analysis of 72 , Gurillo, Jauhar, Murray, and MacCabe (2015) concluded that daily tobacco use correlated with increased risk of psychosis.

In addition, researchers propose hypotheses regarding how smoking could predict schizophrenia. For example, Gurillo and colleagues (2015) theorized that smoking could cause psychosis to develop by increasing the release of dopamine, a neurotransmitter that abnormal hyperactivity in (Barlow & Durland, 2011). It is noteworthy that there is less research on the hypothesis that smoking can predict schizophrenia

Moreover, the self-medication hypothesis is the most supported direct prediction etiological model for the schizophrenia-smoking comorbid disorders because the studies supporting the hypothesis satisfied the two criteria for an ideal etiological model. First, the studies that supported the self-medication hypothesis utilized biological data in addition to self-report data. Second, the studies in support of the self-medication hypothesis provided results based on observational and experimental designs. On the other hand, the smoking-induced schizophrenia hypothesis is less developed, because to my knowledge, researchers have only theorized about the potential for the dopamine from cigarettes to induce schizophrenia and have not found data in support of the hypothesis yet.

Common Factors

Common factors models theorize that specific biological, social, personality, and environmental factors may predispose certain individuals to develop both smoking and schizophrenia without one of the disorders predisposing individuals to develop the other

disorder. Biological common factors may predispose individuals to both schizophrenia and smoking. For example, nicotine acts through a family of nicotinic receptors that either have a high or low affinity for nicotine, and the loci for several of these receptors have been genetically linked to both smoking and schizophrenia. Additional findings suggest that abnormalities in the α7* nicotinic receptor have been shown to relate to both smoking and schizophrenia separately (Leonard et al, 2000; Leonard, Mexal, & Freedman, 2007). In addition, social common factors can also contribute to schizophrenia-smoking comorbidities. For instance, a study conducted by Srinivasan & Thara observed that in a sample of urban male schizophrenic patients in India, the high prevalence of smoking among the schizophrenia patients was related to marital status such that married schizophrenic men displayed both better clinical states of schizophrenia and decreased rates of smoking. In addition, personality common factors such as neuroticism and other psychological traits such as high anxiety may contribute to the development of the schizophrenia-smoking comorbidity (Herrán et al., 2000).

Similar to the aforementioned common factors models for the depression-alcohol comorbid disorders, all of the common factors models are equally supported for the schizophrenia-smoking comorbid disorders. First, the studies in support of the common factors models all relied on one form of data, and second, the data that was concluded to support these common factors models was obtained through observational methods. Therefore, all common factors models for the schizophrenia-smoking comorbid disorders share the similar limitations of potential bias from self-report and incorrect assumptions about causality based on observational results.

Epidemiology of Schizophrenia and Alcohol Use

Studies have illustrated that the schizophrenia-alcohol use comorbidity is another common comorbidity. For example, a meta-analysis conducted by Koskinen, Lohonen, Koponene, Isohanni, & Miettunen (2009) concluded that approximately every fifth patient with schizophrenia had a lifetime alcohol use disorder diagnosis. Similarly, the Epidemiologic Catchment Area study determined that 33.7 percent of people with a diagnosis of schizophrenia also met the criteria for alcohol use disorder at some point in their lives (Drake & Mueser, 2002). Dixon (1999) proposed that as many as half of the individuals with schizophrenia may suffer from comorbid drug or alcohol disorder. Likewise, Barbee, Clark, Crapanzano, Heintz, & Kehoe, (1989) reported that close to half (47) of schizophrenic patients admitted to an emergency psychiatric service exhibited a lifetime diagnosis of an alcohol abuse related disorder.

Recent findings confirm that the alcohol use among schizophrenics is close to 50 (Safak et al., 2015) and that alcohol is the second most commonly consumed drug among schizophrenics (Jeanblanc et al., 2015). Other findings indicate prevalence rates of comorbid alcohol abuse among schizophrenics to be over 50 (Hambrecht & Hafner, 1996), and some researchers have concluded that alcohol use disorder is the most co-occurring disorder in people with schizophrenia (Drake & Mueser, 2002). Findings suggest that the comorbidity rates differ based on gender such that there are a higher proportion of male alcoholic schizophrenics (Dixon, 1999; Pulver et al., 1989), which could reflect the higher prevalence of schizophrenia in males (Iacono & Beiser, 1992). Age also contributes to the comorbidity rates such that male individuals with the comorbidity tend to be younger at first hospitalization compared to individuals with only schizophrenia, while females with the comorbidity are often older than nonalcoholic schizophrenics at first hospitalization (Pulver et al., 1989). Further results indicate that younger

schizophrenics are at a greater risk of developing addictions such as alcohol (Dixon, 1999). Margolese et al. (2004) reported that alcohol was among the top three most abused drugs in a sample of schizophrenic individuals. Alcohol is used by about 4560 of the current and former psychotic patients (Dixon et al., 1001; Drake et al., 1989; Hambrecht & Hafner, 1996). Results also indicate that the comorbidity is common in homeless women living in urban environments (Caton et al., 1995) and individuals with the comorbidity tend perform worse in school (Dixon, Haas, Weiden, Sweeney, & Frances,1991).

Etiology of Schizophrenia and Alcohol

The direct prediction models and common factors models can also constitute etiological models for schizophrenia-alcohol comorbid disorders.

Direct Prediction Models

As with the depression smoking, depression-alcohol use, and schizophrenia-smoking comorbidities, results show the ability for schizophrenia onset to predict subsequent alcohol use disorders. For example, Hays & Aidroos (1986) reported the onset of alcoholism after the onset of schizophrenia.

The self-medication hypothesis is applicable to the schizophrenia-alcohol use comorbidity, as well. For example, evidence suggests that some schizophrenic individuals use alcohol to try to relax (Boschi et al., 2000; Dixon, Haas, Weiden, Sweeney, & Frances, 1991) and relieve depressive symptoms (Dixon, Haas, Weiden, Sweeney, & Frances, 1991). Researchers also concluded that schizophrenic individuals use alcohol with the attempt to decrease the schizophrenic symptoms or side effects of antipsychotic medications (Chambers et al., 2001, from Drake & Mueser, 2002). Likewise, Dixon et al. (1991) observed that

schizophrenic individuals with alcohol use disorder reported using alcohol to relieve the general dysphonia of mental illness and boredom as well as facilitate social interactions and feelings of having an identity, while Khantzian (1997) theorized that schizophrenic individuals use alcohol to relieve negative symptoms of schizophrenia. Khantzian (1997) provides further support of alcohol use relieving social deficits in schizophrenia by discussing a case study of a 48-year-old man who reported that he only could interact with others by being more talkative and involved only when intoxicated. Indeed, the clinical team members confirmed his assertion with their description of him being unusually "affable, warm, friendly, and talkative" when intoxicated (Khantzian, 1997). As with the previously discussed commodities, findings reveal biological evidence in support of the self-medication hypothesis. For instance, the abnormalities in the brain that characterize schizophrenia are believed to facilitate the positive reinforcing effects of alcohol use (Chambers et al., 2001).

Researchers have proposed other psychological mechanisms explaining how schizophrenia can predict alcohol use. For example, Mueser, Drake, and Wallach (1998) proposed that people with schizophrenia are prone to alcohol use disorders because the schizophrenia syndrome produces impaired thinking, impaired social judgment, and poor impulse control that influence even small amounts of psychoactive substances to develop into significant substance use disorders. Further findings provide biological hypotheses regarding how schizophrenia can predict alcohol use. For example, researchers demonstrated the potential for schizophrenia to predict alcohol use through an experimental study on a rat model of schizophrenia. In the study, rats with brain abnormalities resembling theorized schizophrenic brain abnormalities received a small amount of alcohol, and the results indicated that the

"schizophrenic" rats were more likely to self-administer alcohol to the point where the researchers considered their behavior to resemble alcohol use disorder (Jeanblanc et al., 2015). Genetic vulnerabilities may constitute another potential biological mechanism by which schizophrenic individuals are at increased risk for alcohol use disorders. For instance, Ribbe et al. (2011) determined that in a group of schizophrenic individuals, those with specific alleles of the corticotropin-releasing hormone genes CRHR1 and CRHBP were more than twice as likely as other schizophrenic individuals to develop a comorbid alcohol use disorders.

Alcohol use can also predict the onset of schizophrenia. For example, Hambrecht & Häfner (1996) determined that in a group of schizophrenia patients, alcohol abuse more often followed the first symptoms of schizophrenia rather than preceded the first symptoms. Similarly, Welch et al. (2011) observed that alcohol misuse was correlated with a subsequent risk of schizophrenia among people at a high genetic risk for schizophrenia. Lastly, Stewart, Goulding, Pringle, Esterberg, & Compton (2010) reported that in a mainly AfricanAmerican sample with first episode schizophrenia, alcohol use often preceded the onset of psychotic symptoms.

Researchers have theorized about different mechanisms for which substance use, in this case alcohol, can contribute to the development of schizophrenia. For example, based on Zubin and Spring's "Vulnerability Model," individuals may be psycho-biologically vulnerable to schizophrenia, and the schizophrenia becomes triggered by a stressor. In the particular case of alcohol-induced schizophrenia, the stressor is a biological stressor in the form of alcohol use (Mueser, Drake, & Wallach, 1998). Welch et al. (2011) found support for the Vulnerability Model in that individuals biologically vulnerable to schizophrenia due to genetics who experienced alcohol misuse were more likely to develop later schizophrenia.

In addition, one complication to be cautious when assessing alcohol-induced schizophrenia is that alcohol can lead to psychosis in a rare complication known as lcohol allucinosis. Alcohol hallucinosis mimics schizophrenia, and thus, it can be difficult to distinguish between alcohol hallucinosis and alcohol-induced schizophrenia (Bhat et al. 2012).

Moreover, the self-medication model is the most supported direct prediction model for schizophrenia-alcohol comorbid disorders because the studies in support of the hypothesis satisfy the two criteria for an ideal model. First, self-report data and biological data similarly demonstrated the potential for schizophrenia to contribute to alcohol use. Also, the self-medication hypothesis was supported through observational studies and experimental animal studies. On the other hand, although the vulnerability model findings for the alcohol-induced schizophrenia hypothesis consist of biological data in addition to self-report data, the study on the vulnerability model were conducted only through observational methods, leading to potential challenges to assign causality to the findings.

Common Factors Models

Studies demonstrate the potential for separate factors that can predispose individuals to develop the comorbidity. Several biological factors may predispose individuals to develop schizophrenia and alcohol use that are unrelated to schizophrenia or the alcohol use disorder. For instance, Chambers et al.2001 concluded that the dysregulation of dopamine levels in the brain constitutes a common biological factor that may contribute to the risk of developing schizophrenia and alcohol use. Studies also reveal the potential for genetic factors to predispose individuals to the comorbidity. For example, Kendler (1985) compared the prevalence of the schizophrenia comorbid with alcoholism in monozygotic twins and dizygotic twins and

determined that the comorbidity was significantly more common in monozygotic twins, suggesting a genetic predisposition to both disorders. In comparison, Noordsy, Drake, Biesanz, & McHugo (1994) determined that schizophrenic individuals with a family history of alcoholism were significantly more likely to have a comorbid alcohol disorder. Researchers have also determined specific genes that may contribute to the comorbidity. For example, Zuo et al. (2013) determined that specific variations of the alcohol dehydrogenase gene cluster on chromosome 4 that are implicated in alcoholism risk are also correlated with the risk of schizophrenia in AfricanAmericans.

Environmental factors can also contribute to the development of both schizophrenia and alcohol use. For instance, Bruce, Takeuchi, and Leaf (1991) and Mueser, Drake, and Wallach (1998) highlighted how both schizophrenia and higher rates of substance abuse disorder (including alcohol) correlated with lower socioeconomic status and poverty, and concluded thatlower socioeconomic status can be a common factor increasing the risk for both schizophrenia and substance use disorder. Lastly, Mueser, Drake, and Wallach (1998) theorized that poor cognitive functioning might constitute a risk factor for developing schizophrenia and substance use disorders.

Moreover, similar to the depression-alcohol and schizophrenia-smoking comorbid disorders, the common factors models for the schizophrenia-alcohol comorbid disorders are equally supported because the data in support of the models was only obtained through one type of data and through observational study designs. Thus, all of the common factors models share the same limitation of not being able to generalize the correlational findings to causation findings.

In conclusion, researchers have developed direct prediction models and common factors models for all four comorbidities discussed. The self-medication hypothesis and the substance-induced psychiatric disorder hypothesis are two direct prediction hypotheses that have been theorized to apply to all four comorbidities. The discussed comorbidities varied regarding whether the self-medication or the substance-induced hypotheses were better supported. However, the fact that researchers proposed and provided evidence for the self-medication hypothesis for all four further strengthens the idea that individuals with psychiatric disorders like schizophrenia and depression may use substances like smoking and alcohol to regulate their symptoms. Likewise, the fact that all of the discussed comorbidities (except for the schizophrenia-smoking comorbid disorders) provided evidence for the substance-induced hypothesis further strengthens the idea that certain substances, like nicotine and alcohol, can contribute to the development of schizophrenia and depression.

Overall, one common limitation to the etiological models of all four comorbidities is that one might think that chronology implies prediction. However, as previously discussed, it could be that one disorder follows another disorder simply by chance. In addition, it would be difficult to test whether alcohol use can predispose individuals to develop depression because there are so many factors combining to precipitate depression. However, one idea would be obtain a sample of individuals with no genetic predisposition for depression, social predispositions, or environmental and then split these groups into nonalcoholic control, experimental low alcohol, and experimental high alcohol consumption and see over time (maybe over the amount of time studies found it took between alcohol use and depression) and see what the effects on depressive mood are. Alternatively, an animal study could be helpful. The setup could be similar with a

control group receiving no alcohol, an experimental group receiving low alcohol, and an experimental group receiving high amounts of alcohol. Then, animal depressive behaviors could be measured over time. Moreover, another limitation to all of the comorbidities relates to the self-medication is that they do not explain when and why the self-medication effects subside. Eventually, the self-medication effects must subside because otherwise, individuals would not continue to have depression or schizophrenia. However, the self-medication do not address why and when the self-medication affects wear off.

Lastly, as previously mentioned, limitations related to the data used to support the models and methods to obtain data were common among all four comorbidities. More specifically, studies related to all four comorbidities utilized self-report data and observational study designs, both of which introduce potential biases when interpreting the results. Self-report data can lead to inaccurate recall, and observational study designs can lead to incorrect conclusions about causality.

In addition, I am now going to describe how the comorbidities can lead to worse outcomes related to depression, schizophrenia, smoking, and alcohol use.

Depression-smoking

Researchers have determined that individuals with comorbid depression-smoking disorders exhibit worse outcomes from smoking compared to non-depressed smokers (Margolese, Malchy, Negrete, Tempier, & Gill, 2004). Findings suggest that the complex relationship between smoking and depression makes it harder for individuals with the comorbidity to quit smoking, (Covey, Glassman, & Stetner, 1998; Glassman et al., 1990; Murphy et al., 2003). Kinnunen, Doherty, Militello, and Garvey (1996) found that smokers with

major depression were less successful in their attempts to quit smoking compared to non-depressed smokers, likely because the cognitive distortions hinder them from having the that is needed to quit. This could be due to the potential self-medicating effects of smoking contributing to a decreased motivation to quit. Likewise, the cognitive (e.g., defeatist beliefs) and emotional (e.g. feelings of hopelessness) deficits that are characteristic of depression (Black & Grant, 2014) may prevent depressed individuals from being in the proper mindset to quit. Furthermore, Pomerleau, Namenek Brouwer, and Pomerleau (2001) determined that even if depressed women did quit smoking, they were more likely to experience greater difficulty maintaining early abstinence compared to non-depressed women. Thus, findings reveal that individuals depression comorbid with nicotine dependence suffer worse outcomes in that they face more challenges in quitting smoking.

Depression-alcohol

Studies reveal that individuals with depression-alcohol comorbid disorders experience worse outcomes than non-depressed individuals with alcohol-use disorders, such as more severe depression (Preuss et al., 2002 Williams & Adams-Campbell, 2000). In addition, Williams and Adams-Campbell showed that the severity of depression is linked to the amount of alcohol consumed. Self-medication likely contributes to this correlation, because individuals suffering with more severe depression may need a higher dose of alcohol to relieve their symptoms. Alternatively, individuals who consume large quantities of alcohol may exhibit more severe depressive symptoms due to the potential depression-inducing components of alcohol consumption (Williams & Adams-Cambell, 2000).

In addition to severity of depression, individuals with an alcohol-use comorbidity have also been shown to exhibit lower self-esteem (Cornelius et al., 1995) and are more likely to commit suicide (Cornelius et al., 1995; Preuss et al., 2002; McLean, Gladman, & Mowry, 2012; Thase, Salloum, & Cornelius, 2001) compared to depressed individuals who do not have problematic alcohol use. Feelings of worthlessness and suicidal thoughts are two criteria in the *DSM V* for major depression (Black & Grant, 2014). The social and economic consequences of alcohol use disorders could exacerbate the feelings of worthlessness and suicidal thoughts, thus creating a higher prevalence of low self-esteem and suicide among individuals with the comorbidity. More specifically, friends and family may be less likely to support and spend time with depressed individuals who are intoxicated. Likewise, individuals with the comorbidity face financial struggles due to the expenses of purchasing large amounts of alcohol, and economic instability could thus intensify feelings of worthlessness and suicidal thoughts

Schizophrenia-smoking

Results portray how individuals with schizophrenia-smoking comorbid disorders experience worse outcomes compared to nonsmoking schizophrenic individuals. For example, Krishnadas, Jauha, Telfer, Shivashankar, & McCreadie (2012) determined that when comparing schizophrenics with more severe nicotine dependence to schizophrenics with mild or no nicotine dependence, schizophrenics with more severe nicotine dependence exhibited more severe positive schizophrenia symptoms and were prescribed higher doses of antipsychotic medications. It could be that nicotine intensifies positive symptoms that then require a higher dosage of antipsychotic medications to control (Krishnaadas et al., 2012). Also, the more severe positive schizophrenia symptoms correlated with poorer social adjustment, likely because the positive

symptoms (e.g. delusions and hallucinations) escalate social isolation (Krishnadas et al., 2012). Moreover, individuals with the schizophrenia-smoking comorbid disorders exhibit an earlier onset of schizophrenia compared to nonsmoking (Sandyk & Kay, 1991). The earlier onset of in the smoking individuals correlated with abnormal dopaminergic action in the nucleus accumbens, leading researchers to theorize that the onset of schizophrenia among the smoking schizophrenic individuals may be explained by diminished dopaminergic functions (Sandyk & Kay, 1991).

Studies also indicate that individuals with schizophrenia-smoking comorbid disorders display worse outcomes from smoking when compared to non-schizophrenic smokers. For example, face a harder time quitting smokingde Leon, 1996; Shipley, 2004), likely due to the increased ingestion of nicotine (the substance that makes smoking) and self-medicating effects of nicotine (Cite again?). It could also be that the cognitive deficits characteristic of prevent them from understanding the need to quit and having the motivation to quit (cite DSM). Likewise, schizophrenic may have a hard time quitting because as will be discussed, their psychotic symptoms and difficulty pose treatment challenges (Shipley, 2004). Lastly, smoking-related deaths are more prominent among than in the general population (Brown, Barraclough, & Inskip, 2000), which could be due to the increased nicotine intake and difficulties quitting.

In addition, the difficulties quitting smoking can also be explained by the previously described direct prediction models of the schizophrenia-smoking disorders. More specifically, as previously described, schizophrenic individuals exhibit low levels of nicotinic receptors, and evidence suggests that activating these receptors leads to self-medicating effects such as

decreasing social withdrawal (Strand & Nyback, 2005) and improving sensory (e.g.,) deficits characteristic of (Freedman, Adler, & Bickford, 1994; Olincy, Young, & Freedman, 1997). Researchers theorize that these self-medicating effects of activating the nicotinic receptors influence individuals to ingest more nicotine in order to activate the abnormally low levels of nicotinic receptors that are characteristic of schizophrenia (Olincy, Young, & Freedman, 1997; Strand & Nyback, 2005). Indeed,schizophrenic smokers smoke more high-nicotine cigarettes (Leonard, Mexal, & Freedman, 2007; Olincy, Young, & Freedman, 1997; Strand & Nyback, 2005, smoke a number of cigarettes compared to non-schizophrenic smokers (Strand & Nyback, 2005), and inhale a greater amount of nicotine per cigarette compared to non smokers (Olincy, Young, & Freedman, 1997; Williams et al., 2005). The increased levels of nicotine ingested, whether due to smoking high-nicotine , a higher frequency of smoking, or inhaling more nicotine per could then contribute to the schizophrenic individuals' difficulties quitting smoking because nicotine is the substance that makes smoking addictive.

Moreover, the increased challenges to quit smoking then contribute to higher rates of smoking-related diseases and death described in the nicotine dependence section. More specifically, smoking has the potential to lead to cancer in schizophrenic individuals (Masterson & O'Shea, 1984). Likewise, cardiovascular disease resulting from smoking is among the main risk factors for death among schizoprehnic smokers (Hennekens, Hennekens, Hollar, & Casey, 2005).

Schizophrenia-alcohol

Lastly, researchers have determined that individuals with the schizophrenia-alcohol use comorbidity experience worse outcomes, and the diagnosis of an alcohol use disorder is often

missed (Drake et al., 1990). Indeed, various studies report that alcohol use disorders worsen the course of schizophrenia (Green, Burgess, Dawson, Zimmit, & Strous, 2003). For instance, individuals with the schizophrenia-alcohol use comorbidity experience more severeschizophrenia symptoms (Mathalon, Pfefferbaum, Lim, Rosenbloom, & Sullivan, 2003). More specifically, Pulver, Wolyniec, Wagner, Moorman, & McGrath (1989) found that schizophrenics who abused alcohol reported significantly more hallucinations and depressive symptoms compared to nonalcoholic schizophrenics. In comparison, Drake et al. (1989) determined that heavy alcohol use in schizophrenics significantly correlate with paranoia, disorganized incoherent speech, depression, and Bartels, Drake, & McHugo (1992) reported that alcohol use correlated with depression and suicidal behavior in schizophrenic outpatients. A more recent study by Pulver and (2007) confirmed earlier findings from Pulver and (1989) by suggesting that individuals with the schizophrenia-alcohol use comorbidity were more likely to report experiencing hallucinations. The increased hallucinations could be accounted for by the potential for alcohol to lead to schizophrenia . For example, as previously discussed, alcohol can lead to alcohol that is characterized by hallucinations. Thus, who drink alcohol may experience more hallucinations because they are already prone to hallucinations due to the disorder, and the alcohol serves as a trigger of these . Also, as will be discussed, individuals with the -alcohol comorbid disorders may experience more hallucinations because professionals may be reluctant to prescribe antipsychotics that would reduce hallucinations to these individuals due the potential addictive effects of certain drugs (Mueser, Bellack, & Blanchard, 1992). Lastly, individuals with the comorbidity exhibit high mortality ratios likely due to alcohol misuse and suicide (Hjorthøj,

2015; Soyka et al., 1993). Overall, for all four of these comorbidities, the experience of and prognosis is worse than each disorder separately.

Obstacles to treating the comorbidities

In addition, another factor contributing to worse outcomes among individuals with these four comorbidities is the fact that the comorbidities complicate treatments. For example, individuals with these four comorbidities are often less responsive to treatment compared to individuals with only one disorder (Drake & Mueser, 2002; Kessler 2004). More specifically, Kessler (2004) described how one of the challenges of treating psychiatric disorders comorbid with substance use disorders is that the patients typically exhibit greater clinical severity, greater exposure to environmental risk factors, and restricted pharmacological possible treatments due to the potential to abuse the drugs (Kranzler & Rosenthal, 2003 from Kessler). Another challenge to treating the comorbidities relates to how treatment is provided. Kessler (2004) notes how oneobstacle to treating the comorbidities is that there is a lack of knowledge about effective treatments and a shortage of adequately trained professionals to deliver these treatments. Furthermore, there is a shortage of treatment programs that provide integrated treatment of the comorbidities, as most United States reatment systems target drug use disorders and other mental illnesses separately (Kessler, 2004; Merikangas & Gelernter, 1990; National Institute on Drug, 2010). Also, many individuals with the comorbidities are in prisons and jails where adequate treatment is often lacking (National Institute on Drug, 2010).

In summary, evidence portrays how individuals with the four comorbidities face worse outcomes. In addition to the harmful effects of alcohol misuse and smoking discussed, the substance use disorders intensify the schizophrenia and depression. Other findings suggest that

the schizophrenia and depression may also intensify smoking and alcohol misuse such as inhaling more nicotine per cigarette or facing a more difficult time quitting smoking compared to individuals without these disorders.

Treatments for comorbid conditions

Despite these obstacles to treating the comorbidities, several treatments for the four comorbidities exist. Common treatments for all four comorbidities include medications and cognitive behavioral therapies.

Depression-smoking

Several treatments exist for the depression-smoking comorbidity. For example, Torrens, Fonseca, Mateu, and Farre (2005) suggested that evidence supports the efficacy of using antidepressants as a way to try to treat comorbid nicotine dependence with comorbid depression while Mineur and Picciotto (2010) proposed that drugs that reduce acetylcholine signaling through neuronal nAChRs might be useful treatments for depression. Behavioral therapies may also be an effective treatment for depression-smoking comorbidities (Osilla et al, 2009). More specifically, a study conducted by Brown et al. (2001), cigarette smokers with recurrent major depressive disorder received cognitive behavioral treatment for depression, and the results indicated that smokers with recurrent major depressive disorder who received the cognitive-behavioral therapy for depression were significantly more likely to be abstinent than those receiving standard cognitive-behavioral smoking cessation treatment.

A similar study by Haas, Munoz, Humfleet, Reus, and Hall (2004) replicated the results by Brown et al. (2001). Lastly, MacPherson et al. (2010) determined that smokers with elevated depressive symptoms who received behavioral activation treatment for smoking combined with

standard treatment smoking cessation strategies such as nicotine replacement therapy exhibited greater smoking abstinence and greater reductions in depressive symptoms compared to smokers with elevated depressive symptoms who received only the standard smoking cessation treatment.

Depression-alcohol

Findings illustrate the potential for antidepressants to treat the depression-alcohol comorbidity, as well. For example, in a double-blind placebo-controlled study, Cornelius et al. (2009) determined that the antidepressant fluoxetine improved both depression and alcohol use disorder in a group of adolescents with comorbid major depression and alcohol use disorder. However, a meta-analysis by Torrens, Fonseca, Matea, and Farre (2005) concluded that there are not enough studies to suggest that antidepressants are an effective treatment for depression-alcohol comorbidities.

Schizophrenia-smoking

Studies demonstrate the efficacy of antipsychotics in the treatment of the schizophrenia-smoking comorbidity. For example, George et al. (2000) found that atypical antipsychotic agents in combination with the nicotine transdermal patch significantly enhanced the rate of smoking cessation (55.6 in the atypical agent group compared to 22.2 in the typical antipsychotic medications) in schizophrenic smokers. McEvoy, Freudenreich, & Wilson (1999) determined that lozapine, and no conventional antipsychotics, to greater therapeutic responses in schizophrenic smokers compared to nonsmoker schizophrenics. In addition, antidepressants may also be an effective treatment of the comorbidity George et al. (2002) determined that bupropion enhanced smoking abstinence rates compared with placebos in nicotine-dependent schizophrenic smokers.

Other findings demonstrate the potential for combined antidepressants and behavioral therapies in the treatment of the schizophrenia-smoking comorbidity. For instance, Evins et al. (2001) a double-blind placebo controlled study on a group of schizophrenic smokers that the combined treatment of bupropion and cognitive behavioral therapy was associated with improvements in psychotic and depressive symptomstrying to quit smoking. Also, one subjectachieved sustained tobacco abstinence for the 6-month trial.

Schizophrenia-alcohol

Antipsychotics are also utilized in the treatment of the schizophrenia-alcohol use comorbidity. For example, Green, Burgess, Dawson, Zimmet, & Strous determined that in a sample of schizophrenics with alcohol use disorder comorbidities, patients showed significantly higher abstinence rates compared to those treated with risperidone. In comparison, Petrakis et al. (2004) found that alcohol schizophrenics who received the drug naltrexone exhibited significantly fewer drinking days, heavy drinking days, and reported less craving for alcohol compared to placebo treated patients.

Overall, several treatments do exist to effectively treat the comorbidities. However, it is important to note that many of the treatments aim to treat the comordbities by focusing on the treatment of one of the disorders. For example, based on the discussed findings, only antidepressants were used to attempt to treat the schizophrenia-alcohol comorbid disorders. By further embellishing our understanding of the etiological models described, we can progress treatment options. Understanding how the comorbidity developed could help professionals determine whether one disorder should receive more focus in order to maximize chances of successfully treating the comorbidity. For instance, if researchers can determine that smoking is

contributing to depression more than the depression is contributing to the smoking, then the patient may benefit from a treatment that focuses more on depression.

Discussion

Overall, the studies discussed portray the complexity of four common comorbidities: depressionsmoking, depression-alcohol use, schizophreniasmoking and schizophrenia-depression. Findings suggest the potential for all four comorbidities to develop due to interactions between the two disorders constituting the comorbidity (irect prediction models). the psychiatric disorders (schizophrenia and depression) the substance use (smoking and alcohol use)substance use to precede the onset of the psychiatric disorders. Researchers proposed the self-medication hypothesis to suggest that the disorder may precede the substance use because individuals coping with depression and schizophrenia may use alcohol or smoking an attempt to reduce distressing symptoms. The researchers also established the substance-induced hypothesis which indicates the potential for smoking and alcohol use to induce depression and schizophrenia. Other direct prediction hypotheses such as the Risk Taking Hypothesis suggest that individuals with psychiatric disorders like depression may be at increased risk for developing substance use problems because their low self-worth influences them to take more risks like trying smoking. In addition, other findings indicate the possibility for the comorbidities to develop from factors unrelated to the two disorders (common factors models). Common factors implicated in the ommon actors odels for all comorbidities included genetics and environmental factors.

Limitations to interpreting the results

Because these four comorbidities have a high prevalence rate and tend to be associated with more detrimental outcomes for the individuals and there are several obstacles to treatment previously described, it is crucial to continue to advance treatments and preventions of the comorbidities. However, before considering future directions for treatment, itis important to note a few limitations to be cautious of when interpreting results from epidemiological studies, etiolog studies, and treatment studies. These limitations include defining the disorders, sampling challenges, and problems assessing certain limitations can make it difficult to generalize the findings to all individuals with the comorbidities.

Problems defining the disorders

One limitation to the studies discussed is that it can be difficult to define the disorders for several reasons. First, Johnson, Rhee, Chase, & Breslau (2003) propose that one obstacle to studying the comorbidities (specifically depression-smoking) is that there are different ways of defining the disorders. Indeed, the new *DSM* description of alcoholism and alcohol abuse can result in different ways of defining alcohol disorders. In particular, it can be difficult to interpret results from studies utilizing the old diagnosis criteria for alcohol abuse and alcoholism alongside the results from studies using the new diagnosis criteria for alcohol use disorder.

second challenge defining disorders is that certain disorders can present similar symptoms. For example, Mueser, Drake, & Wallach (1998) discussed how it can be difficult to distinguish between substance-induced schizophrenia and schizophrenia-induced substance abuse since they appear with the same symptoms. More specifically, as previously described, researchers can struggle to determine if schizophrenia is alcoholinduced because alcohol hallucinosis mimics schizophrenia. Thus, researchers may incorrectly diagnose individuals due

to these similarities. A third difficulty regarding defining the disorders is that some researchers define the disorders vaguely. For example, researchers may discuss "alcohol consumption" without specifying whether the alcohol consumption is alcohol abuse, alcohol dependency, or alcohol use disorder. Based on the differences between alcohol dependency and abuse in the older *DSM* and the differences between mild and severe alcohol use disorder in the *DSM*, it is important to understand the specific problematic alcohol use diagnosis since the differences in diagnoses could have implications for proper treatment. In comparison, smoking is also often vaguely defined in that researchers often do not specify whether starting to smoke implies becoming addicted to smoking or trying a cigarette for the first time. In addition, another issue regarding defining the comorbidity with alcohol use disorder is that as mentioned before, alcohol hallucinogenic can mimic schizophrenia. Thus, researchers can have a difficult time distinguishing between schizophrenia and alcohol hallucinogenic and may incorrectly infer that schizophrenia was alcohol-induced.

Sampling challenges

A second limitation to the studies examined is that the findings can be hard to generalize to the all individuals with the comorbidities because of several sampling problems that may skew the results. First, one sampling challenge relates to who researchers are able to sample. Oftentimes, the majority of data on psychiatric illness-substance use comorbidities are obtained from clinical samples of patients in treatment, which can lead to an overestimation of the frequency and severity of the comorbidities (Kessler, 2004; Mueser, Drake, & Wallach, 1998; Swendsen et al., 1998). At the same time, researchers highlight how the prevalence and severity of the comorbidities may be underestimated because many individuals who likely have the

comorbidities cannot be studied either due to incarceration or homelessness (National Institute on Drug, 2010). A second sampling challenge is that it can be difficult to obtain accurate measurements from the samples.

For instance, numerous studies rely on self-report data. Relying on self-report data is an obstacle for any stud, and relying on self-report data can be especially problematic when assessing individuals with disorders that characteristically distort reality. Another sampling limitation is that researchers may utilize different methods to obtain data Johnson, Rhee, Chase, & Breslau 2003). Thus, even if two studies collected similar data, it can be difficult to compare the data if the methods used to obtain the data differed. Lastly, variations in sample size constitute another limitation related to sampling (Margolese et al., 2004). For example, researchers may incorrectly conclude that results are significant when the significance is only the result of a small sample size.

A third limitation regarding sampling as discussed throughout the current investigation is that observational design studies can only yield correlational results and thus cannot indicate causation . Experimental studies with a manipulation are the ideal method for determining a causal relationship, but certain hypotheses and models can be difficult to assess in an experimental study. For example, due to ethical reasons, researchers often cannot administer large amounts of alcohol to participants or force nonsmoking participants to start smoking. Thus, certain models and hypotheses are limited to observational study designs.

A fourth limitation related to sampling is the date of obtaining samples. More specifically, the results from some of the studies discussed should be cautiously be interpreted because several of them are from early dates as early as 1977. While it is useful to still examine

the results of these studies, it is crucial to keep in mind that trends change. In other words, over time, the prevalence of the comorbidities in different populations may change and other comorbidities may become more common.

Struggles to assess certain models and hypotheses

A fourth challenge when interpreting the results of these studies is that the models and hypotheses can be difficult to test. For example, as mentioned previously, it can be tempting to conclude that one disorder directly predicts another disorder if it precedes the other disorder. The disorders could be unrelated to each other, and it could be due to chance that one of the disorders preceded the other. Nonetheless, various researchers proposed direct predictive relationships between the two disorders of the comorbidities by using chronological data as evidence (e.g., Grant, 1995). In addition, another obstacle to testing the hypotheses and models is that causality cannot be assigned since most of the studies relied on observational data rather than experimentally manipulating a condition to see the outcome.

Moreover, another challenge to testing certain models is that it can be difficult to assess a bidirectional model. One limitation of the discussed direct prediction models is that they are all unidirectional in that either the psychiatric disorder predicts the substance use disorder or the substance use disorder predicts the psychiatric disorder. It could be that both etiology models are occurring simultaneously, but assessing the potential for bidirectional models could be difficult since it would be hard to distinguish the effects of the comorbidity that originated from the substance abuse, the psychiatric disorder, or both disorders.

Future directions

Future studies could work toward correcting these limitations by constructing a clearer definition of disorders and more standard methods for testing the disorders. Studies could also search for other forms of evidence besides self-report data to support hypotheses. For instance, researchers could examine if self-report data and biological data indicate similar conclusions. Researchers could also utilize experimental animal studies to examine models and hypotheses that are difficult to assess experimentally in humans.

In addition, the comparisons between the four comorbidities have implications for advancing prevention and treatments. For example, evidence for the self-medication hypothesis was found for all four comorbidities. This finding indicates that perhaps treating the psychiatric disorder could prevent individuals from relying on other toxic methods (e.g., alcohol and smoking) to relieve psychiatric symptoms. The evidence supporting the substance-induced schizophrenia and depression indicates that treating the substance disorder could prevent the onset of the psychiatric disorder. Likewise, the similarities in the common factors models for the four comorbidities, particular genetic vulnerabilities, could have implications for preventing and treating the comorbidities. With the up and coming field of genetics, in addition to identifying individuals at risk for the comorbidities based on genetic factors, there may also be methods to reduce expression of certain genes or increase the number of nicotinic receptors that could help prevent the morbidity from developing.

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