CLINICAL OUTCOMES AMONG PATIENTS WITH AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS AND THE ROLE OF SUBSTANCE USE

by

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Abstract

Substance use is common among individuals experiencing psychosis and has important implications for clinical outcomes, symptomatic course, and treatment considerations. While research has largely focused efforts towards understanding the impact of cannabis in this population, insufficient attention has been paid towards alcohol in the existing literature. In addition, conclusions about the impact of substance use on patients with psychosis may be limited given that most research includes patients with affective and non-affective psychosis. There is some debate in the literature regarding the clinical utility of this dichotomy and further exploration is warranted. The aims of the current study were to: 1) examine the differences and similarities between patients with affective and non-affective psychosis; and 2) investigate whether substance use differentially impacts patients diagnosed with affective or non-affective psychosis. Patients were recruited from an early psychosis intervention program in St. John's, NL and were diagnosed with either schizophrenia or bipolar disorder. Patients' clinical characteristics (i.e., substance use, positive symptoms, overall functioning, illness severity, and overall improvement) were assessed at three time points: admission, 12 and 24 months. A significant interaction between diagnostic group and time was found and suggested that patients with schizophrenia tended to show greater levels of improvement over the course of 24 months compared to patients with bipolar disorder. Further, patients with schizophrenia who abused cannabis tended to improve over the same time while patients with bipolar disorder who abused cannabis tended to show a decline. The interaction between diagnostic group and time was not significant for positive symptoms, overall functioning, or illness severity. Patients with bipolar disorder were also rated as having higher overall levels of global functioning and lower levels of illness severity compared to patients with schizophrenia. Lastly, alcohol abuse was a significant

predictor of various clinical outcomes, including overall functioning and illness severity. The current study highlights the clinical utility of the dichotomy between affective and non-affective psychosis, and the need to further examine the impact of substance use, particularly alcohol, in this population.

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Table of Contents

List of Tables

List of Figures

Chapter 1: Substance Use, Affective Psychosis, and Non-affective Psychosis: An Overview

Overview

Substance misuse can be defined as the use of any substance at high doses or in inappropriate situations and has the potential to cause health or social problems, immediately or over time (McLellan, 2017). Individuals experiencing a first episode of psychosis (FEP) are frequently using substances, with cannabis (i.e., current misuse prevalence estimate of 11.3% and lifetime misuse estimate of 22.5%) and alcohol (i.e., lifetime misuse estimates ranging from 16 – 34%) being the most widely misused substances within this population (Archie et al., 2007; Green et al., 2005; Margolese et al., 2004). The deleterious impact of substance misuse on the course of psychosis has been the focus of many studies, with cannabis being the most widely studied substance. By and large, research demonstrates a consistent harmful relationship between cannabis and psychosis, especially for younger populations (McHugh et al., 2017; Schubart et al., 2011). For example, research has shown that cannabis misuse was significantly associated with increased severity of psychotic symptoms, mania, depression, and poorer psychosocial functioning in a population of patients with FEP at 12-month follow-up (Seddon et al., 2016). Studies have also demonstrated that continued cannabis misuse following FEP places individuals at a greater risk of experiencing a relapse of psychosis during periods of cannabis use relative to periods of no use (*OR* = 1.13; 95% CI 1.03 – 1.24; Schoeler et al., 2016a).

Despite occurring at similar rates as cannabis misuse, the effects of alcohol misuse on clinical outcomes in populations of individuals experiencing a FEP has received less attention (Green et al., 2005; Wisdom et al., 2011), with the literature demonstrating variable findings. For example, there appears to be less of a consensus regarding alcohol's effect on positive symptoms than there is for cannabis. Though most studies have reported no difference in positive symptoms between patients who misuse alcohol and those who do not misuse alcohol (Barrowclough et al., 2013; Sorbara et al., 2003), other studies, have demonstrated some negative effects such that

alcohol was associated with more positive symptoms (Compton et al., 2007; Lv et al., 2023). Research has more consistently demonstrated that alcohol misuse has been linked with lower social and general functioning (Ouellet-Plamondon et al., 2017) and increased depressive symptoms and suicidal ideation/attempts (Barak et al., 2008; McLean et al., 2012). It is possible that alcohol misuse may uniquely impact different clinical outcomes, with its influence more clearly seen on overall general functioning, as opposed to psychotic symptoms.

In a systematic review and meta-analysis, consisting of 20 studies and a sample size of 2024 patients, Gupta et al. (2013) highlighted several important methodological limitations in the existing literature examining the relationship between substance misuse and functional and symptomatic outcomes in FEP populations. First, most studies were cross-sectional in design, with only a small number providing longitudinal data after a period of follow-up. Second, definitions of "substance use" as defined by the type and amount of substance, varied between studies. For example, the severity of substance use was assessed using specific self-report measures, as well as clinical judgment, using differing criteria including use, misuse, or dependence, although patterns of use were considered clinically significant in all studies and met criteria for a substance use disorder (SUD) in most. Additionally, the type of substances examined included any form of psychoactive substance, including alcohol, cannabis, stimulants, and other drugs. Gupta et al. (2013) further note a failure to control for the effect of concomitant drug misuse. More specifically, the authors noted that they were unable to differentiate the effects of alcohol from other drugs as no primary research reported on this difference (Gupta et al., 2013).

Although research has addressed some of the limitations highlighted by Gupta et al. (2013) since its publication, research in the field often continues to integrate patients

experiencing both affective and non-affective psychosis (e.g., patients diagnosed with bipolar disorder and schizophrenia, respectively). There is debate within the literature regarding the current dichotomous classification system and its utility for both clinical and research purposes (Craddock & Owen, 2007; Jauhar et al., 2018; Linscott et al., 2010). While the dichotomous view remains the cornerstone of modern psychiatric classification, other proponents have suggested the idea of a psychosis spectrum (Guloksuz & Van Os, 2018). Essentially, it has been proposed that schizophrenia and bipolar disorder fall somewhere along the same dimension, with no sharp demarcation between affective psychosis and schizophrenia (Jablensky, 2010). Despite some similarities between the two, emerging research has begun to document the differing clinical features more systematically, including how the illnesses may be impacted differently by various environmental factors (Ramain et al., 2020). Given this, it is possible that substance misuse may also differentially affect patients with affective and non-affective psychosis (i.e., patients with bipolar disorder and schizophrenia).

The aim of this study is to examine whether patients with bipolar disorder and schizophrenia demonstrate different clinical trajectories over a 24-month period, and how cannabis and alcohol use may play a role in the relationships. This chapter will provide an overview of the features of affective and non-affective psychosis, the differences and similarities between clinical profiles of patients with affective and non-affective psychosis, and a brief discussion of some of the theories in the field which attempt to synthesize the research. A general overview of substance misuse in patients with FEP will follow. Finally, review of cannabis misuse in patients with schizophrenia and bipolar disorder, as well as alcohol misuse in both patient groups will also be presented.

Affective versus Non-Affective Psychosis

Affective and non-affective psychosis refers to the dichotomy used to distinguish the experience of psychotic symptoms in the presence and absence of clinically significant mood concerns. The classification of affective psychosis applies to forms of psychoses marked by a severe disturbance in mood and encompasses individuals with bipolar disorder with psychotic features, major depression with psychotic features, and schizoaffective disorder. Non-affective psychosis has clinically been reserved to refer to individuals experiencing psychotic features in the absence of significant mood concerns. Individuals in this category may be diagnosed with schizophrenia and schizophreniform disorders. The utility of this dichotomy has proved useful in clinical environments; however, the similarities and distinctions are just beginning to be explored through systematic research. There is some evidence for cognitive, neuropsychological, and genetic overlap between bipolar disorder and schizophrenia, suggesting the existence of a psychosis spectrum; however, there are also unique differences between the two. The general findings on both sides are reviewed below.

There is some evidence to support the inclusion of patients experiencing non-affective and affective psychosis in a single cohort, based on epidemiological and biological evidence indicating overlap in schizophrenia and bipolar disorder. For example, both bipolar disorder and schizophrenia occur at approximately equal rates, have similar ages at onset, and follow an episodic course (Berrettini, 2000). Research also suggests shared genetic determinants (Lichtenstein, 2009), with twin, family, and adoption studies showing a genetic concordance between the two disorders of approximately 0.60 (Cardno & Owen, 2014). Strong evidence that identifies common specific susceptibility genes (O'Donovan et al., 2009) and polygenic variation (Purcell et al., 2009) that contribute to the risk of developing both disorders has also emerged.

Studies have also demonstrated substantial overlap in neuroanatomical regions impacted in schizophrenia and bipolar disorder, including regions in the prefrontal cortex, thalamus, left caudate, left medial temporal lobe, and right insula (Yu et al., 2010). Further, research suggests that white matter integrity deficits are consistent across the psychosis spectrum, with gray matter reductions appearing more widespread in schizophrenia than in bipolar disorder (Biur et al., 2017). Collectively, the evidence suggests that psychosis may be better represented as a spectrum rather than unique disorders. Further, this evidence lends support for the inclusion of patients experiencing FEP with and without a mood disturbance into a single group.

Although the neuroscience and epidemiological evidence is compelling, integrating psychotic disorders together may result in a loss of unique clinical differences among certain psychotic disorders. For example, though schizophrenia and bipolar disorder are part of the group of psychotic disorders, bipolar disorder largely manifests as a disturbance of mood, with mania or hypomania as a core feature. In contrast, schizophrenia is primarily a disorder of positive, cognitive, and negative symptoms, including affective and social deficits. Further, manic symptoms in bipolar disorder, including increased levels of activity, exaggerated self-esteem, racing thoughts, pressured speech, and a decreased need for sleep, are antithetical to the negative symptoms found in schizophrenia, characterized by social withdrawal, anhedonia, loss of motivation, and flattened affect. Research has also demonstrated differences in premorbid cognitive functioning, as well as the magnitude of subsequent impairment. For example, while both illnesses are characterized by deficits in premorbid intellectual functioning and lead to a further decline as the illness progresses, the magnitude of impairment in patients with schizophrenia remains greater than in bipolar disorder (Trotta et al., 2015). Deficits in cognitive

(Zanelli et al., 2010), as well as social functioning (Paya et al., 2013) tend to be more severe and more pervasive in patients with schizophrenia than in those with bipolar disorder.

Synthesizing the research, Murray et al. (2004) proposed a developmental model to explain the overlap and differences between schizophrenia and bipolar disorder. The authors propose that various susceptibility genes, common to both schizophrenia and bipolar disorder, can be characterized as predisposing factors to developing psychosis. Other factors, such as perinatal complications, may interact with the vulnerability causing further neurodevelopmental impairment, and leading an individual to develop schizophrenia. In the absence of subsequent neurodevelopmental impairment, a clinical profile more representative of bipolar disorder may manifest (Murray et al., 2004).

Clinical Profiles of Affective and Non-Affective Psychosis

Differences in the course of illness between affective and non-affective psychosis have been well documented, however, this dichotomy is mainly based on clinical observations. With the more classical concept of a categorical classification system being challenged and the idea of a continuum linking non-affective psychosis with affective psychosis, the need to further investigate the psychopathological differences between the two clinical presentations is of the utmost importance.

In one study, researchers examined whether there were clinical, neuropsychological, and functional differences between individuals with affective and nonaffective psychosis at baseline and two-year follow-up (Torrent et al., 2018). The sample consisted of 192 patients experiencing FEP. The affective group showed a better clinical profile at baseline compared to the non-affective group. At two-year follow-up, the non-affective group continued to demonstrate a more severe clinical picture than the affective group on several measures, including total score on the

Positive and Negative Syndrome Scale (PANSS) and depressive symptoms. The groups did not differ based on neuropsychological or functional outcomes. Similarly, Henry et al. (2010) found lower general psychopathology scores and fewer psychotic symptoms among individuals with affective psychosis after two-year follow-up. In another study, researchers sought to examine the differences between patients with non-affective psychosis and those with affective psychosis at baseline and at 3-month follow-up (Cerqueira et al., 2022). The sample consisted of 265 patients experiencing FEP, most of whom were male (70.9%), with a mean age of 21.36 years. Of the 265 patients, 53 patients (20%) were experiencing affective psychosis, and 212 patients (80%) were experiencing non-affective psychosis. Outcome measures of interest included sociodemographic data, duration of untreated psychosis (DUP) and psychotic/mood symptoms. Results suggested that groups were similar across most sociodemographic variables except for sex, as a higher proportion of females was documented in the affective psychosis group. Authors also observed that all domains of the PANSS improved for both groups. No differences for DUP or depression scores at baseline or follow-up were found. Regarding recovery specific outcomes, Banayan et al. (2007) reported better quality of life, symptomatic remission, and better overall functioning in patients with affective psychosis relative to those with non-affective.

In another study, advanced machine learning techniques were applied to a dataset of 202 patients with psychosis, of which, 120 patients had non-affective psychosis (i.e., schizophrenia) and 82 patients had affective psychosis. Patients were initially assessed with the Present State Examination (PSE), a test designed to assess the individual's present mental state, and followed up 2.5 years later, when *DSM III* diagnoses were applied. Based on the initial PSE data, machine learning classified patients with schizophrenia from patients with affective psychosis with 83.66% accuracy, suggesting validity to these diagnostic constructs (Jauhar et al., 2018). In an

additional study, researchers explored the clinical utility of this dichotomy based on clinical variables of interest in a sample of 330 patients with FEP (Ramain et al., 2020). Patients were recruited from an early intervention program and compared on premorbid history, baseline demographics, clinical outcomes, and development of symptoms over the course of three years. Results indicated that patients with affective psychosis were more likely to be female, a trend seen in other studies (Cerqueira et al., 2022). Results also indicated that positive symptoms remained higher over the follow-up period in the non-affective subgroup and at discharge (Ramain et al., 2020). Patients with affective psychosis had better quality of life. No differences were observed regarding depressive and negative symptoms. Differences in risk of relapse requiring hospitalization between patients with affective and non-affective psychosis have also been shown. More specifically, research has shown that individuals with non-affective psychosis have their highest risk of relapse requiring hospitalization in late adolescence, while patients suffering from affective psychosis have their highest risk in their early thirties (Lenzi et al., 2017). These results in combination, provide validity to the diagnostic constructs.

Research has also demonstrated that patients with affective psychosis may display a clinical presentation that differs from those with non-affective psychosis. Interestingly, differences in the subjective experience of positive symptoms between the two types of psychoses have been documented. For example, research has found group differences across diagnoses for certain characteristics of auditory verbal hallucinations, including frequency, number of voices, form of address (e.g., first versus third person), perceived voice location, level of conviction related to the veracity of the experience, and beliefs regarding origin (Toh et al., 2020). Research has also suggested there may be differences in delusional themes experienced by the two groups, with delusions of grandiosity being more prevalent among patients with

affective psychosis and persecutory delusions being more common in patients with non-affective psychosis (Picardi et al., 2018). Collectively, while research has demonstrated some similarities between the two groups, there are also specific clinical differences that suggest the two types of psychosis may have distinct histories and courses.

Substance Misuse and Psychosis

There are numerous studies suggesting that patients with psychosis and substance misuse have worse outcomes than those with no history of substance misuse (Sorbara et al., 2003; Wade et al., 2006). For example, in one systematic meta-analysis of 22 studies that included cross-sectional, longitudinal, and retrospective studies, Large et al. (2014) concluded that current substance users had significantly more positive symptoms than non-users, with a small to medium effect size. Additionally, Pencer and Addington (2003) demonstrated that substance use, as determined by *DSM-IV* criteria and the Case Manager Rating Scale (CMRS), was associated with higher levels of positive symptoms ($r = 0.18$, $p < 0.05$), as measured by the PANSS, at one year-follow-up in a population of 266 patients with FEP. Research has also demonstrated that patients with FEP who abused cannabis displayed significantly higher depressive symptoms, as measured by the Calgary Depression Scale for Schizophrenia (CDSS), than patients who did not use cannabis (Hadden et al., 2018). Turkington et al., (2009) provided further evidence for this relationship between substance use and depressive symptomatology, demonstrating that persistent substance users showed significantly more severe depressive symptoms ($M = 15.97$), as measured by the Beck Depression Inventory (BDI), than individuals who stopped using substances ($M = 10.46$) and those who reported no substance use history ($M = 11.13$) at one-year. Further, persistent users had a greater risk of relapse (56.3%) than individuals who ceased substance use (32.9%), and those with no reported history of substance use (35.6%) at one-year,

as well as poorer functional outcomes (M = 49.16) than either group, as assessed by the Global Assessment of Functioning (GAF; Turkington et al., 2009).

The most widely used substance within FEP populations is cannabis, with rates of use approximately three times higher than that of the general population (Hides et al., 2006; Myles et al., 2016). Further, approximately one half of patients with FEP report a history of cannabis abuse or dependence and approximately one third meet criteria for a current cannabis use disorder (CUD) (Wisdom et al., 2011). It is well established that cannabis misuse has deleterious effects on functional outcomes and symptomatic remission among individuals with FEP (Schubart et al., 2011). Research has shown that individuals that meet criteria for cannabis abuse or dependence are at increased risk of developing a psychotic episode if they have a vulnerability to psychotic disorders, such as a family history of psychosis in a first-degree relative or prodromal symptoms including social withdrawal and sub-threshold psychotic symptoms (Kraan et al., 2015). More specifically, evidence strongly suggests that misuse of cannabis at a young age is a risk factor for psychosis (i.e., approximately 2:1 for cannabis users and as high as 6:1 for heavier users) in vulnerable individuals (Ksir & Hart, 2016). In addition, cannabis misuse has been linked to increases in depressive and manic symptoms, as well as disengagement from treatment (Stone et al., 2014). Continued high-frequency use (i.e., daily use over 24-month period) following FEP has also been associated with an increased number of relapses (Incidence rate ratio 1.77; 95% CI 0.96 – 3.25), a shorter duration between psychotic episodes (b -0.22; 95% CI -0.40 to -0.04), and more intense psychiatric care (OR = 3.16; 95% CI 1.26 – 8.0.9; Schoeler et al., 2016b).

While cannabis use in FEP has received extensive attention, alcohol use has received less focus despite having rates of use similar to cannabis (Barnett et al., 2007). Alcohol has primarily

been included with other psychoactive drugs as a polysubstance composite variable, which limits our understanding of the unique contribution that alcohol may have on the illness. In one longitudinal study examining the relationship between alcohol consumption and clinical outcomes in psychosis over a 24-month period (sample size = 327; mean age = 37; 86.5% male), results indicated that alcohol misuse had no effect on severity of psychotic symptoms, as measured using the PANSS, or overall functioning, as assessed with the GAF (Barrowclough et al., 2013). Additionally, this study showed that change (i.e., increases and decreases) in total alcohol consumption significantly predicted change in depressive symptoms (Barrowclough et al., 2013). In another longitudinal study (sample size = 227; mean age = 23; 80.2% male) examining the specific impacts of different SUDs (i.e., alcohol, cannabis, cocaine, and amphetamines) on symptomatic and functional outcomes in a sample of patients experiencing FEP, results showed that misuse of each substance (including individuals with polysubstance use) was associated with lower functioning (social functioning assessed using the Social and Occupational Functioning Assessment Scale and overall functioning assessed using the GAF and Clinical Global Impression) at two-year follow-up. Results also suggested that cannabis, cocaine, and amphetamines had a greater negative impact on most measures than alcohol (Ouellet-Plamondon et al., 2017). Findings also indicated that only patients with a CUD had significantly worse longer-term symptom and functional ratings (i.e., between 12-months and 24-months) compared to other substance groups (i.e., alcohol, cocaine, and amphetamines). In another study examining the impact of cannabis and alcohol use on outcomes in an FEP population, alcohol use was associated with poorer adherence to antipsychotic medication (as measured by number of missed pills), while cannabis use was associated with greater illness severity and more

positive symptoms compared to non-users (Oluwoye et al., 2019). Thus, there is a great deal of variability in research examining alcohol misuse in patients with FEP.

The variability of findings in research examining the impact of substance misuse on psychosis may be partially accounted for by the fact that many of the studies include individuals with affective (bipolar disorder) and non-affective (schizophrenia) psychosis in a single cohort. The existence of a psychosis spectrum provides some support for this inclusion; however, this inclusion may negate various unique features of each disorder, as well as the unique effect that substance misuse may have on individuals who experience each disorder.

Cannabis Misuse and Schizophrenia

One of the most robust findings in the literature is that cannabis misuse has been associated with an earlier age of onset among individuals with schizophrenia (van Dijk et al., 2012; Veen et al., 2004). Although several studies have suggested a causal link between cannabis misuse and the onset of schizophrenia, cannabis misuse is a risk factor for schizophrenia among individuals who have an underlying predisposition for a psychotic illness (Arseneault et al., 2004). A recent systematic review and meta-analysis, in which 18 studies were included in the systematic review and 10 were inserted in the meta-analysis (enrolling a total of 66 816 individuals), also provides evidence for a dose-dependent relationship between level of cannabis misuse and the risk of psychosis, reporting an odds ratio of 3.90 (95% CI 2.84 – 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to non-users (Marconi et al., 2016). This suggests that substance misuse, specifically cannabis misuse, is further complicating an already complex disorder.

Positive Symptoms

Another robust finding that has been long recognized in the field is the relationship between cannabis use and the experience of psychotic symptoms among individuals with schizophrenia. More specifically, research has largely suggested that individuals with schizophrenia who consume cannabis show more prominent positive symptoms than those who abstain (Bersani et al., 2002; Henquet et al., 2010). There has also been research to suggest that premorbid cannabis use is significantly associated with more severe psychotic symptoms and impaired functioning in patients who developed schizophrenia (Ringen et al., 2016). Further, higher levels of premorbid cannabis use were associated with higher levels of psychotic symptoms and these associations were independent of current substance use and premorbid functioning (Ringen et al., 2016). The relationship between cannabis misuse and psychotic symptoms may also be bidirectional, whereby cannabis exposure predicts severity of psychosis, and individuals with more severe psychotic symptoms were more likely to use cannabis in the future (Foti et al., 2010). This link was found to remain after controlling for negative, disorganized, and depressive symptoms, as well as other substance use. Collectively this research demonstrates a well-established negative effect of cannabis use on psychotic symptoms among individuals diagnosed with schizophrenia.

Illness Severity

Cannabis abuse has also been linked to a more severe clinical profile for patients with schizophrenia. For example, patients with schizophrenia who use cannabis are at risk for more frequent hospitalizations than those use do not use cannabis (van Dijk et al., 2012). This relationship may be partially explained by the link between cannabis use and increased psychotic symptoms, which tend to be more severe and require more immediate medical attention. Other

research has also demonstrated that cannabis use in patients with schizophrenia was consistently associated with increased relapse and non-adherence (Zammit et al., 2008). In a longitudinal study, a dose-related increase in risk of relapse was observed among cannabis users with schizophrenia spectrum disorders, even when treated with long-acting injectable antipsychotics (Scheffler et al., 2021). Collectively, a more severe course of illness observed among individuals with schizophrenia and comorbid cannabis use may be related to a reduced threshold for psychotic breakthrough attributable to the effects of cannabis.

Overall Functioning

The research examining the relationship between cannabis misuse and overall functioning among patients with non-affective psychosis appears mixed, with research indicating decreased and increased overall levels of functioning among patients who use cannabis. For example, van der Meer et al. (2015) observed that patients who persistently used cannabis had worse global functioning as measured by the GAF compared to patients who never used cannabis and those who discontinued use in a sample of 678 patients with a non-affective psychotic disorder. Further, discontinuation of cannabis use was associated with greater improvement in global functioning compared with continued use at any stage of the illness. There is limited evidence to suggest increased overall functioning. For example, DeRosse et al. (2010) compared a large cohort of 455 patients with schizophrenia with or without a history of comorbid CUD on several measures, including the GAF. Results indicated that patients with a comorbid CUD had better GAF scores than the group with no CUD. The authors proposed that patients with schizophrenia and a comorbid CUD may represent a higher functioning subgroup of patients.

By and large, research has demonstrated that cannabis has a deleterious effect on individuals with schizophrenia, including increased positive symptoms and more severe course

of illness severity as demonstrated by increased risk of relapse, shorter time to relapse, and increased hospitalizations, though some exceptions exist. The relationship between cannabis misuse and overall functioning in patients with schizophrenia remains less clear, with research indicating increased and decreased overall levels of functioning among patients who use cannabis.

Alcohol Misuse and Schizophrenia

Studies have shown that the odds of having an alcohol use disorder (AUD) are three to four times higher for people diagnosed with schizophrenia (Barrowclough et al., 2014). The impact of a comorbid AUD among individuals with schizophrenia has shown similar negative functional and symptomatic outcomes found with cannabis misuse; however, its impact has been less well researched than cannabis. Additionally, most of this research has examined the impact of alcohol in combination with other substances, failing to consider the unique contribution that alcohol may play.

Positive Symptoms

Research investigating the relationship between alcohol use and positive symptoms among patients with non-affective psychosis has demonstrated more variable findings than those found in the literature on cannabis. For example, in a sample of 616 male inpatients diagnosed with schizophrenia, patients who drank alcohol were likely to experience more severe positive symptoms than individuals who abstained from drinking (Lv et al., 2023). This increase in risk occurred above and beyond depressive symptoms and negative symptoms. This is congruous with other research which demonstrated that alcohol use in the six months prior to hospitalization was associated with a higher frequency of positive psychotic symptoms among patients with

schizophrenia experiencing FEP (Compton et al., 2007). The association remained after controlling for relevant covariates, including cannabis use.

There have also been several studies that have failed to demonstrate a harmful effect of alcohol misuse on psychotic symptoms in patients with non-affective psychosis. For example, Barrowclough and colleagues (2014) found that alcohol consumption was not associated with subsequent severity of psychotic symptoms; however, alcohol consumption appeared to have a detrimental effect on mood. Several cross-sectional and short-term prospective studies have reported no differences in positive psychotic symptoms between patients who misuse alcohol and those who do not (Allen et al., 2000; Mohamed et al., 2006; Salyers & Mueser, 2001). Various longitudinal studies reporting on the association between alcohol use and psychotic symptomatology have also failed to report any significant relationship (Addington & Addington 2007; Sorbara et al., 2003; Xie et al., 2005).

Illness Severity

Research has more consistently demonstrated a significant harmful effect of alcohol use on the overall illness severity of patients with schizophrenia. For example, in a sample of 1338 patients, time to the first exacerbation of symptoms, first hospitalization, and recurrent hospitalization was shorter among patients with schizophrenia and a history of an AUD than for those with no history of AUD (Pathak et al., 2020). In a nationwide population study, all outcome variables, including rates of psychiatric admissions, emergency room (ER) visits, and medication possession ratio (MPR) (a measure of medication adherence) were worse in a group of individuals with first-episode schizophrenia and comorbid AUD than a matched control group composed of individuals with first-episode schizophrenia and no comorbid AUD (Ahn et al., 2021). It can therefore be suggested that overall, the presence of comorbid alcohol use in patients

with schizophrenia may lead to a more severe illness presentation by means of various clinical characteristics.

Overall Functioning

Patients with schizophrenia and active substance use (including alcohol), also report higher overall dysfunction and poorer functioning in three domains (i.e., interpersonal relations, role performance, social functioning) than patients with no reported history of substance misuse (Meydan et al., 2004). Carra et al. (2016) demonstrated that comorbid dependence on alcohol among people with schizophrenia was associated with impaired psychosocial adjustment, poorer quality of life, and poorer overall functioning as measured by the GAF. Other research has demonstrated that comorbid AUDs among patients with schizophrenia have also been associated with greater cognitive impairment (Thoma et al., 2006), poorer community functioning (Bowie, 2005), and medication non-compliance (Kamali et al., 2006) than that predicted by either diagnosis alone.

Cannabis Misuse and Bipolar Disorder

Like schizophrenia, research findings have indicated an association between the misuse of cannabis and an earlier age of onset among patients with bipolar disorder (Leite et al., 2015). Cannabis misuse in patients with bipolar disorder has also been associated with increased severity of manic symptoms, as well as an almost three-fold increase in the odds of experiencing symptoms of mania in non-clinical populations (Gibbs et al., 2015). There is also evidence to indicate that patients with bipolar disorder who ceased cannabis use during an acute manic or mixed episode had similar clinical and functional outcomes at two years as individuals who never used cannabis, while those who continuously misused cannabis had lower recovery and remission rates, higher recurrence of manic symptoms, and greater functional impairment at

work (Zorrilla et al., 2015). These results stress the importance of cannabis cessation as a goal for patients with bipolar disorder.

Positive Symptoms

Research has demonstrated a relatively consistent harmful effect of cannabis use on psychotic symptoms among patients with bipolar disorder. In a recent meta-analysis of 53 studies, the authors concluded that patients with bipolar disorder who use cannabis were more likely to present with lifetime psychotic symptoms than those without comorbid cannabis use (Pinto et al., 2019). Notably, Kvitland et al. (2015) failed to find a significant association between cannabis use and psychotic symptoms, though authors cited a potential type II error (i.e., false negative) due to the low number of patients who presented with continued cannabis use.

Illness Severity

On the overall impact of cannabis misuse on bipolar disorder, problematic cannabis use can worsen the occurrence of mood symptoms thereby increasing the risk of mania (Gibbs et al., 2015). Cannabis use is also associated with more rapid cycling, worsened affective episodes, increased suicide attempts, decreased long-term remission and increased disability among patients with bipolar disorder (Bally et al., 2014; Stoner, 2017). In a cross-sectional study, Patel et al. (2022) observed that a comorbid CUD was associated with increased odds of mania-related hospitalizations by 1.5-fold after statistically adjusting for potential risk factors including use of other substances when assessing 380,265 bipolar disorder-related hospitalizations. In a large sample of 3459 inpatients and outpatients with bipolar disorder, patients who used cannabis exhibited less treatment compliance and higher levels of overall illness severity, mania, and psychosis compared to patients who did not use cannabis over 12 months of treatment (van

Rossum et al., 2009). Finally, weekly to daily cannabis use has been shown to be associated with an increased incidence of mania or hypomania, suggesting a possible dose-response relationship between cannabis use and mood symptoms (Feingold et al., 2015).

Overall Functioning

Research has largely demonstrated a negative impact of cannabis on overall functioning among patients with bipolar disorder. After statistically adjusting for potential confounds, continued cannabis use was significantly associated with elevated mood and inferior global functioning as assessed using the GAF at one-year follow-up (Kvitland et al., 2015). Elevated mood also appeared to mediate the effect of cannabis use on global functioning. This is consistent with another study that showed that patients classified as "previous users" had similar outcomes to patients classified as "never users", while those classified as "current users" had lower recovery, greater work impairment, and were more likely to not be living with a partner (Zorrilla et al., 2015).

Alcohol Misuse and Bipolar Disorder

Patients with bipolar disorder are three times more likely to be diagnosed with an AUD than the general population (Hirschfield & Vornik, 2005). Research on the effects of alcohol on the course and progression of bipolar disorder is less clear, with substantial variability in findings across studies (Di Florio et al., 2013). In part, this might be explained by fewer research investigations in the area.

Positive Symptoms

Evidence regarding the effect of alcohol misuse on psychotic features is less clear than the evidence for mood-related symptoms in patients with affective psychosis (Barrowclough et al., 2013). In one cross-sectional survey of 186 outpatients with bipolar disorder, alcohol abuse

and dependence were associated with psychotic symptoms within the first episode of their illness (Cardoso et al., 2008). Interestingly, Pignon and colleagues (2020) compared the prevalence of psychotic symptoms among participants with different psychiatric disorders depending on whether there was an underlying AUD. They found that the co-occurrence of AUD in patients with bipolar disorder was associated with an increased risk of auditory hallucinations, but not with a generalized increase of psychotic symptoms. Overall, current evidence suggests a stronger association between alcohol misuse and a worsening of mood-related symptoms than between alcohol misuse and a worsening of psychotic symptoms in patients with bipolar disorder.

Illness Severity

Alcohol misuse has been consistently shown to have a significant and negative impact on overall illness course. In one systematic review of 23 studies (including 15 longitudinal studies and 8 retrospective studies), the authors concluded that alcohol use did not seem to affect time to mood episode remission, but alcohol misuse destabilized the course of the illness as evidenced by associations with increased rapid cycling and mood episode recurrence (Rakofsy & Dunlop, 2013). Further research has demonstrated an association between alcohol misuse and a worsening of symptoms, specifically increased affective instability (Lagerberg et al., 2017), and an increased risk of a depressive episode relapse (Simhandl et al., 2016).

Interestingly, in a prospective cohort study, no differences were reported between patients with no alcohol use, moderate use, and excessive use on several clinical outcome variables, including number of days ill, severity of depression, mania, and overall illness, global functioning as assessed by the GAF, or overall illness presentation either at baseline or at one-year follow-up (van Zaane et al., 2010). The authors proposed several explanations for their finding, including the potential for the patients in their study to have been less ill than patients in

previous studies, or to have had lower rates of abuse or dependence on other drugs. The authors also proposed that the negative effects of alcohol use on outcomes among patients with bipolar disorder may have an effect only in the early years of the disorder, whereas its effects may level out with longer illness duration. The mean illness duration in the reported sample was approximately 22 years. Lastly, the authors were able to measure medication adherence and participants reported taking their medication on more than 90% of the recorded days. It is possible that the high adherence rate could be an important protective factor against the effect of excessive alcohol use.

Overall Functioning

The detrimental effects of concurrent alcohol use among patients with bipolar disorder have been well documented in the literature. For example, moderate alcohol consumption in patients with bipolar disorder has been associated with poorer social and familial adjustment and increased healthcare use (Goldstein et al., 2006). Cardoso and colleagues (2008) also found that patients with bipolar disorder and comorbid alcohol abuse and dependence were associated with poorer functioning as assessed using the GAF in a sample of 186 patients. Patients with these co-occurring illnesses are also prone to more adverse consequences, including a variety of psychosocial difficulties such as unemployment, housing issues, and legal problems (Drake et al., 2004), which are all likely to affect overall functioning.

Limitations of the Current Literature

Many methodological limitations exist within the current literature examining comorbid substance misuse in people who experience FEP. To summarize there are three main limitations that the current study will address to better understand the impact of cannabis and alcohol among patients with FEP. First, most studies include patients with affective and non-affective psychosis

in a single cohort. Given the significant differences between schizophrenia and bipolar disorder symptom profiles, outside of psychosis, there would be a risk of missing unique trajectories associated with comorbid substance misuse. Second, previous studies vary widely in their methodology, with a majority using cross-sectional designs. Fewer studies have examined the impact of substance misuse in patients with FEP longitudinally, making it difficult to draw conclusions regarding the long-term effects of substance misuse on psychosis. Finally, many studies do not consider other substance use making it difficult to determine whether the substance of interest (i.e., cannabis and alcohol) is influenced by the misuse of other drugs (i.e., polysubstance misuse) or groups of substances other than cannabis and alcohol (e.g., hallucinogens, stimulants, or sedatives). The aim of the current study is to examine whether the affective differences between schizophrenia and bipolar disorder impact clinical outcomes among patients with FEP and comorbid cannabis and/or alcohol misuse over 24-months of treatment. Limitations in previous research will be addressed by using a longitudinal design and statistically adjusting for use of other substances.

Current Study

Despite research demonstrating relatively consistent harmful effects of cannabis and alcohol misuse on patients with FEP, less is known about how these outcomes may be affected depending on whether an individual has affective or non-affective psychosis. The current study is an examination of the impact of cannabis and alcohol use on clinical outcomes among people diagnosed with schizophrenia or bipolar disorder admitted to a FEP program in a naturalistic clinical setting. The primary objectives of this dissertation are as follows:

1) To explore whether patients with affective psychosis demonstrate different clinical trajectories than patients with non-affective psychosis on functional and symptomatic

measures, including positive symptoms, overall global functioning, illness severity, and overall improvement.

2) To examine the potential role of substance misuse (i.e., cannabis and alcohol) in the event of differing clinical trajectories between the two patient groups.

Ultimately, if patients with non-affective and affective psychosis demonstrate differing clinical characteristics, and more specifically, differing clinical trajectories, it can be argued that further attention and research is warranted into exploring this dichotomy and how their unique needs may be addressed. Additionally, findings related to the role that substance misuse may play in any differing clinical measures would highlight the continued need to determine the best treatment approach to reduce the impact of substance misuse on individuals, specifically those substances that may have historically received less attention.

Chapter 2:

A Comparison of the Impact of Cannabis and Alcohol Use on Clinical Outcomes in Patients Experiencing First Episode Psychosis and Diagnosed with Schizophrenia or Bipolar Disorder

Abstract

OBJECTIVE: This study assessed differences between patients with non-affective and affective psychosis across a 24-month period. This study also assessed how cannabis and alcohol misuse might affect clinical outcomes between the two patient groups.

METHOD: This study constituted a secondary analysis of data collected from patients admitted to an early psychosis intervention program in a naturalistic setting (N = 135). Patients completed assessments at three time periods: initial presentation, 12 and 24 months. Clinical characteristics (e.g., substance use, positive symptoms, global functioning, illness severity and overall improvement) were assessed at each time point.

RESULTS: Patients with schizophrenia who abused cannabis showed significantly greater levels of improvement across a 24-month period than patients with bipolar disorder who abused cannabis (b = -1.41, 95% C.I. [-2.71, -.11], p = .03). There were no significant associations between patient group and positive symptoms, global functioning, or illness severity over 24-months. Alcohol abuse was a significant predictor of global functioning (b = -5.36, 95% C.I. [-9.41, -1.31], p = .009) and illness severity (b = .39, 95% C.I. [.01, .77], p = .05) while cannabis abuse was not. Patients with schizophrenia were rated as having lower levels of global functioning (b = 6.85, 95% C.I. [2.96, 10.74], p = .001) and higher levels of illness severity (b = -.42, 95% C.I. [-.79, -.06], p = .02) than patients with bipolar disorder.

CONCLUSION: Despite some similarities, key differences emerged between patients with affective and non-affective psychosis, supporting their separation. More research into the clinical utility of this dichotomy and how substance use may differentially impact outcomes is needed.

Introduction

Substance use is common in patients experiencing FEP, with approximately half of individuals with psychosis meeting criteria for a substance use disorder, a rate approximately three times higher than that in the general population (Brunette et al., 2018; Sara et al., 2014). Of all types of substances, cannabis and alcohol are the most widely misused (Archie et al., 2007; Green et al., 2005; Margolese et al., 2004). The harmful impact of substance use on the course of psychosis has been well documented, with research demonstrating a consistent relationship between cannabis and psychosis, especially among younger populations (McHugh et al., 2017; Schubart et al., 2011) and those more vulnerable to developing psychosis due to a genetic predisposition (Ksir & Hart, 2016). Studies have also consistently linked cannabis misuse with poorer symptomatic and functional outcomes among patients experiencing psychosis. For example, research has shown that cannabis misuse was significantly associated with increased severity of psychotic, depressive, and manic symptoms, and poorer psychosocial functioning in a population of patients with FEP at 12-month follow-up (González-Pinto et al., 2011; Grech et al., 2005; Seddon et al., 2016). Studies have also demonstrated that continued cannabis use following FEP places individuals at a greater risk of experiencing a subsequent psychotic episode during periods of cannabis use relative to periods of no use (Schoeler et al., 2016a).

Alcohol misuse in patients with FEP occurs at similar rates as cannabis misuse; however less attention has been given to understanding the impact of alcohol on symptoms and functional outcomes (Green et al., 2005; Wisdom et al., 2011). Collectively, the literature on the impact of alcohol misuse on psychotic symptomatology has shown inconsistent findings, with most studies reporting no difference in psychotic symptoms between patients who misuse alcohol and those who do not (Barrowclough et al., 2013). Conversely, research has more consistently

demonstrated that alcohol tends to negatively impact functioning and other symptomatic outcomes such as depressive symptoms (Carra et al., 2016; Ouellet-Plamondon et al., 2017).

Variability in research findings examining the relationship between substance use and clinical outcomes among patients experiencing FEP may partially be explained by several limitations noted in the current literature (Gupta et al., 2013). For example, a large portion of studies have utilized cross-sectional methods, with only a small number reporting longitudinal data. Additionally, the type of substances examined tend to be broad (e.g., any form of psychoactive substance) and included in a single composite variable, which limits our understanding of the unique role that each substance may play in affecting symptomatic and functional outcomes. Gupta and colleagues (2013) further noted a lack of control for the effect of concomitant drug misuse, either through methodological or statistical means. While there have been some improvements in research addressing these concerns (e.g., an increase in longitudinal designs), there remains a paucity of research examining the potential differential impact of alcohol and cannabis on clinical outcomes among individual with affective versus non-affective psychosis independent of other substances within a longitudinal design.

Additionally, many studies that examine the role of substance use in individuals with psychosis integrate patients with non-affective (e.g., schizophrenia) and affective (e.g., bipolar disorder) psychosis. While the dichotomy of affective and non-affective psychosis is commonly used in clinical settings, the relevance of this dichotomy remains questioned on a scientific basis. Although limited, there is some data suggesting differing factors between affective and non-affective psychosis. For example, studies have reported differences in risk of hospital admission (Lenzi et al., 2017), improvement of positive and negative symptoms (Kapila et al., 2019; Torrent et al., 2018), gender and DUP (Conus et al., 2007). Currently there is not enough

evidence to suggest whether the two populations should be separated, and as such, little is known about whether misuse of cannabis and alcohol differentially affects those with non-affective psychosis versus those with affective psychosis. Although the impact of substance abuse in FEP populations has been well documented, combining individuals with both affective and non-affective psychosis into a single cohort may mask any unique impact that cannabis and alcohol may have on patients depending on the nature of their psychotic and affective symptoms.

Considering the paucity of data and the clinical relevance of the dichotomy between affective and non-affective psychosis, we examined the impact of substance use on patients admitted to a first episode psychosis program in a naturalistic clinical setting. The aim of this study was to examine whether cannabis and alcohol misuse differentially impacts psychotic symptoms, overall functioning, illness severity, and improvement over 24-months in patients with schizophrenia versus bipolar disorder. The current study will also seek to address the limitations surrounding study design and control of other substances reported by Gupta et al., (2013), by employing a longitudinal design in a naturalistic setting and statistically adjusting for multiple psychoactive substances. We hypothesized that 1) cannabis misuse would have a stronger association with increased positive symptoms than alcohol misuse for both patient groups. We hypothesized that 2) cannabis and alcohol misuse would also be associated with increased clinical global severity and lower overall functioning compared to those who did not misuse these substances for individuals with schizophrenia and bipolar disorder. Furthermore, we expected that these differences would be more pronounced among individuals with schizophrenia than those with bipolar disorder. We further hypothesized that 3) individuals diagnosed with bipolar disorder will have higher overall functioning and lower clinical global severity across 24-months compared to those with schizophrenia. Lastly, we hypothesized that 4)

cannabis would have a greater negative impact on symptoms and on functional outcome compared to alcohol among both patient groups.

Method

Setting

The current study was conducted at the Psychosis Intervention and Early Recovery Program (PIER), a specialized treatment program for patients with FEP located in St. John's, Newfoundland. The program consists of an interdisciplinary team that provides patients and their families with clinical care, education, and support. Depending on patient needs, an individual's team may consist of psychiatry, nursing (case management), social worker, occupational therapist, consulting psychologist, pharmacist. All patients are followed by a psychiatrist and case manager. Patients are eligible for treatment at PIER if they have been treated with antipsychotics for less than six months or if they are experiencing their first psychotic episode. There was no formal intervention provided for substance abuse, but a harm reduction model was used to educate patients about the harmful effects of substance use.

Sample

The sample consisted of 135 patients admitted to the PIER Program. Participants were between 15 and 58 years of age. Inclusionary criteria for the current study comprised patients diagnosed with schizophrenia or bipolar disorder (including type 1 and 2). Exclusionary criteria included patients diagnosed with a primary depressive disorder, substance induced psychosis, other psychotic disorders, and an underlying medical condition (e.g., traumatic brain injury). Patients were consecutively recruited at admission into the program from inpatient and outpatient healthcare environments. All patients provided consent to participate in the research study and were informed that declining participation would not impact their treatment in the program.

Procedures

The current study involved a secondary analysis of a previously collected dataset (Hadden et al., 2018). It is impotent to note that recruitment for this study took place prior to the legalization of cannabis in Canada. Ethical approval for the current study was obtained through the Health Research Ethics Board. Patients were assessed at three time points: admission, 12 months, and 24 months. At each time point, substance use was assessed by case managers using the Case Manager Rating Scale for Substance Use Disorders (CMRS; Drake et al., 1990). Patients were also administered the following symptomatic and functional measures at each time point: Positive and Negative Syndrome Scale (PANSS), Global Assessment Scale (GAS), and Clinical Global Impressions Scale (CGI). These assessments were completed by each patient's psychiatrist. All patients were seen by one of two experienced psychiatrists who diagnosed patients according to *DSM-IV* criteria at the one-year mark to increase diagnostic confidence.

Study Variables

Substance Use

Case managers utilized the CMRS to rate the level of substance use over the previous 3 months for each assessment period based on patient self-report. Level of use for each substance (i.e., cannabis, alcohol, cocaine, stimulants, narcotics, hallucinogens, sedative/hypnotics) was ranked as: zero (None), one (Mild), two (Moderate), three (Severe), or four (Extremely severe use). In the current study, level of substance use was determined using the CMRS according to the procedure identified by Addington and Addington (2007). A CMRS score of zero (None) or one (Mild) represents "No abuse", while CMRS scores ranging from two (Moderate) to four (Extremely severe use) were classified as abusing the substance.

Psychotic Symptoms

The PANSS is a 30-item scale used to measure positive symptoms (an excess or distortion of normal functions), negative symptoms (a loss of normal functions), and general psychopathology in patients with schizophrenia (Kay et al., 1987). Symptom severity is rated on a scale from 1 (*Absent*) to 7 (*Extreme*). The PANSS positive subscale was used in the current study to assess the presence of positive symptoms in patients with schizophrenia and bipolar disorder. The positive subscale assesses for delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, and hostility. Total scores for the PANSS positive subscale range from 7 to 49, with higher scores indicating greater symptom severity. The PANSS has shown good interrater reliability, normally distributed subscales, mutually exclusive constructs as measured by the negative and positive subscales, and evidence for criterion-related and predictive validity (Kay et al., 1987; Peralta & Cuesta, 1994).

Overall Functioning

The GAS was used to measure the patients' ability to function in day-to-day life. It is a single rating scale for evaluating the overall functioning of an individual during a specified period (Endicott et al., 1976). The scale values range from 1, representing the most severely impaired individual to 100, representing the hypothetically "healthiest" individual. The GAS was found to have good reliability validity, and sensitivity to change over time than did other ratings of overall severity, making it useful in a wide variety of clinical and research settings (Endicott et al., 1976).

Illness Severity and Improvement

The CGI is a summary measure that considers all available patient information, including patient's history, symptoms, behaviour, and ability to function (Guy, 1976). It is comprised of

two indices: the CGI-Severity and the CGI-Improvement. The CGI-Severity requires the clinician to answer the question, "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Ratings are made on a scale from one to seven with one being "Normal, not at all ill" and seven being "Among the most extremely ill patients." On the CGI-Improvement, the clinician is asked, "Compared to the patient's condition at admission to the project, this patient's condition is…" They are required to give an answer on a seven-point scale, with one being "Very much improved since the initiation of treatment" and seven being "Very much worse since the initiation of treatment." It is important to note that the CGI-I scores were reversed in all analyses in the current study. The CGI has been shown to correlate well with other standard scales such as Hamilton Rating Scale for Depression and the PANSS (Busner & Targum, 2007).

Statistical Analysis

Statistical analyses were conducted using Stata 13 (StataCorp, College Station, TX, USA). To determine if there were differences in clinical measures between patients with schizophrenia and patients with bipolar disorder at admission, analyses were conducted using ANOVA to assess differences in continuous variables (i.e., age, PANSS positive, GAS, CGI-S) and chi-square tests to assess differences in categorical variables (e.g., sex). Given the large number of comparisons, and to keep the Family-Wise Error Rate at 5%, a revised critical threshold was used ($p = .005$) for baseline comparisons. Column proportions were compared using z-tests in the event of significant differences for Chi-Square tests, using superscript letters to indicate differences between columns. Multiple z-tests utilized Bonferroni corrections to adjust for inflation in Family-Wise Error Rate. Fisher's exact test p-values were used in cases where Chi-Square cells had less than five respondents.

Associations of predictors (i.e., diagnostic group, alcohol abuse, and cannabis abuse) with outcome variables (i.e., PANSS Positive, GAS, CGI-S, CGI-I) were assessed in multilevel mixed-effects models to allow for relatedness of repeated measurements in individual patients. All test significance were determined using $p < .05$. For completeness, mixed models were examined with nested random effects (i.e., time of measurement nested within patient) and with crossed random effects (i.e., all levels of time of measurement repeated across patients). Full models were specified by including all variables of primary interest (i.e., diagnostic group, alcohol abuse, cannabis abuse, and time of measurement), while controlling for age, sex, and use of other substances (i.e., cocaine, stimulants, narcotics, hallucinogens, and sedatives/hypnotics). The following interaction terms of clinical interest were run for each outcome variable (i.e., PANSS positive symptoms, global functioning, illness severity, overall improvement) to test for relationships among variables: alcohol abuse by diagnostic group, cannabis abuse by diagnostic group, and diagnostic group by time. Additional interaction terms were run to examine the role of substance use in the event of a significant interaction between diagnostic group and time.

Results

Rate of Attrition

Prior to analyses, we compared the attrition rate of individuals with schizophrenia to those with bipolar disorder. Results indicated that the proportion of individuals with schizophrenia and bipolar disorder remained consistent across all three time periods ($\chi^2(2) = 2.56$, $p = 0.279$), suggesting that attrition did not disproportionately affect one group. The following *N* was retained for patients with schizophrenia across all three time points: Time 1 *N* (Baseline) = 84, Time 2 *N* (12-months) = 68, Time 3 (24-months) *N* = 61. The following *N* was

retained for patients with bipolar disorder across all three time points: Time 1 *N* (Baseline) = 51, Time 2 *N* (12-months) = 31, Time 3 (24-months) *N* = 25.

Participant Characteristics

As can be seen in Tables 1 and 2, demographic and assessment baseline scores were compared between diagnosis (i.e., schizophrenia and bipolar disorder) and substance (i.e., cannabis and alcohol). Results indicated that patients with schizophrenia who abused cannabis (*M* = 21.38, *SD* = 3.79) were significantly younger at admission than patients with schizophrenia who did not abuse cannabis (*M* = 26.90, *SD* = 9.06) and patients with bipolar disorder who did not abuse cannabis (*M* = 25.20, *SD* = 8.82). Patients with bipolar disorder who abused cannabis (*M* = 22.41, *SD* = 6.28) were also significantly younger at admission than patients with schizophrenia who did not abuse cannabis (*M* = 26.90, *SD* = 9.06) and significantly younger than patients with bipolar disorder who did not abuse cannabis (*M* = 25.20, *SD* = 8.82). There was also a greater proportion of males with schizophrenia who abused cannabis (20%) than either males (13%) or females (8%) with bipolar disorder who abused cannabis. In terms of alcohol, there was a greater proportion of males with schizophrenia who abused alcohol (17%) than males with bipolar disorder who abused alcohol (10%) or females with bipolar disorder who abused alcohol (7%). There were no differences in outcome variables at baseline for either cannabis or alcohol.

Table 1. Baseline demographic and clinical variables by diagnostic group and cannabis use

	Schizophrenia (N = 84)		Bipolar Disorder (N = 51)		Statistic & p-value
	No abuse	Abuse	No abuse	Abuse	
Age	26.90/9.06 [a]	21.38/3.79 [b]	25.20/8.82 [a b]	22.41/6.28 [b]	F=5.09, p=.002
Sex					χ^2=13.70, p=.003
Male	45 [a]	26 [a]	11 [b]	18 [a b]	
Female	9 [a]	4 [a]	11 [b]	11 [a b]	
Ethnicity					Fisher's, p=.129
Caucasian	50	29	19	26	
Asian	1	0	1	0	
Black	1	1	0	0	
Other	0	0	2	2	
Education					Fisher's, p=.625
Some High Sch.	31	23	13	17	
Some Post-Sec.	20	7	9	10	
Other	2	0	0	1	
Housing					Fisher's, p=.885
With Family	33	20	14	18	
With Spouse	5	1	3	2	
Ind. Housing	12	4	4	6	
Sup. Housing	1	1	0	0	
Other	2	4	1	2	
Marital Status					Fisher's, p=.467
Single	44	29	17	26	
Married	4	1	3	2	
Common-law	2	0	0	0	
Widowed	0	0	1	0	
Divorced/Sep.	3	0	1	0	
Employment					Fisher's, p=.034
Employed	13	2	5	9	
Unemployed	31	19	10	13	
School	6	1	5	4	
Other	3	8	2	2	
PANSS Positive	14.24/6.7	18.4/7.44	14.8/7.13	18.32/8.54	F=1.09, p=.355
GAS	53.71/15.8	47.71/18.51	59.51/18.88	52.32/19.07	F=1.06, p=.370
CGI-S	3.51/1.6	3.92/1.62	3.18/1.75	3.93/1.62	F=0.39, p=.758

Note. To keep the Family-Wise Error Rate at 5% a revised critical threshold was used (α = .005). In the event of significant differences for Chi-Square tests, column proportions were compared using z-tests, using superscript letters (i.e., [a b]) to indicate differences between columns. Multiple z-tests utilized Bonferroni corrections to control for Family-Wise Error Rate. If Chi-Square cells had cells with less than five respondents, Fisher's exact test p-values were presented.

Table 2. Baseline demographics and clinical variables by diagnostic group and alcohol use

	Schizophrenia (N = 84)		Bipolar Disorder (N = 51)		
	No abuse	Abuse	No abuse	Abuse	
Age	26.47/9.03	22.7/5.64	25.29/8.74	21.84/5.73	F=3.22, p=.025
Sex					χ^2=13.78, p=.003
Male	48 [a]	23 [a, b]	15 [b]	14 [b]	
Female	8 [a]	4 [a, b]	12 [b]	10 [b]	
Ethnicity					χ^2=13.64, p=.100
Caucasian	51	27	22	23	
Asian	1	0	1	0	
Black	2	0	0	0	
Other	0	0	3	1	
Education					χ^2=2.31, p=.975
Some High Sch.	35	18	15	15	
Some Post-Sec.	18	9	10	9	
Other	2	0	1	0	
Housing					χ^2=6.38, p=.889
With Family	34	18	15	17	
With Spouse	3	3	3	2	
Ind. Housing	13	3	7	3	
Sup. Housing	1	1	0	0	
Other	4	2	1	2	
Marital Status					χ^2=11.86, p=.579
Single	48	24	21	22	
Married	2	3	3	2	
Common-law	2	0	0	0	
Widowed	0	0	1	0	
Divorced/Sep.	3	0	1	0	
Employment					χ^2=20.06, p=.022
Employed	10	4	8	6	
Unemployed	35	15	10	13	
School	7	0	6	3	
Other	3	8	2	2	
PANSS Positive	14.28/6.91	18.14/7.02	15.02/6.72	18.55/9.22	F=2.78, p=.044
GAS	53.74/16.26	47.76/17.36	60.55/17.4	49.68/20.09	F=4.19, p=.007
CGI-S	3.50/1.60	3.92/1.64	3.18/1.63	4.05/1.74	F=1.14, p=.335

Note. To keep the Family-Wise Error Rate at 5% a revised critical threshold was used (α = .005). In the event of significant differences for Chi-Square tests, column proportions were compared using z-tests, using superscript letters (i.e., [a b]) to indicate differences between columns. Multiple z-tests utilized Bonferroni corrections to control for Family-Wise Error Rate. If Chi-Square cells had cells with less than five respondents, Fisher's exact test p-values were presented.

Positive symptoms

As can been seen in Table 3, mixed models of positive symptoms indicated that diagnostic group was not a significant predictor of PANSS positive scores (b = -.71, 95% C.I. [-2.29, .86], p = .38). Similarly, neither cannabis abuse (b = .74, 95% C.I. [-0.97, 2.45], p = .40) nor alcohol abuse (b = 1.59, 95% C.I. [-.05, 3.23], p = .06) were significant predictors of PANSS positive scores. There was a significant effect for time, indicating that PANSS positive scores decreased over 24-months (b = -4.71, 95% C.I. [-7.72, -1.71], p = .002) in the overall patient group. No significant interactions were observed between variables.

Table 3. Mixed model results for positive PANSS scores

	Coefficient	Standard Error	*z*	*p*	95% Confidence Interval	
Constant	22.57	3.69	6.11	.00	15.33	29.80
Age	-.02	.04	-.48	.63	-.11	.06
Sex	.83	.88	.94	.35	-.89	2.54
Cocaine	2.57	.95	2.71	.01	.71	4.42
Stimulants	2.38	1.33	1.79	.07	-.23	5.00
Narcotics	.62	.98	.64	.52	-1.29	2.54
Hallucinogens	-.06	1.08	-.06	.96	-2.18	2.06
Sedatives/Hypnotics	-3.36	1.55	-2.17	.03	-6.40	-1.71
Time	-4.71	1.53	-3.07	.00	-7.72	-1.71
Alcohol abuse	1.59	.84	1.90	.06	-.05	3.23
Cannabis abuse	.74	.87	.85	.40	-.97	2.45
Diagnostic group	-.71	.80	-.88	.38	-2.29	.87

Note: Model did not incorporate interaction terms because they were non-significant. Schizophrenia was used as reference group for diagnostic group variable.

Global Assessment Scale (GAS)

Mixed models of GAS indicated that alcohol abuse was a statistically significant predictor of GAS scores (b = -5.36, 95% C.I. [-9.41, -1.31], p = .009), while cannabis abuse was not (b = .11, 95% C.I. [-4.13, 4.35], p = .96) (See Table 4). More specifically, patients who abused alcohol had lower GAS scores, representing lower overall functioning, than patients who did not abuse alcohol. Diagnostic group was a significant predictor of GAS scores (b = 6.85, 95% C.I. [2.96, 10.74], p = .001) indicating that individuals with bipolar disorder were more likely to have higher GAS scores than those with schizophrenia. We then examined whether individuals with schizophrenia showed different trajectories than patients with bipolar disorder over the course of the 24-month period. Results indicated that the interaction was not significant (b = 2.47, 95% C.I. [-1.51, 16.45], p = .22), suggesting that while individuals with schizophrenia and bipolar disorder experienced significantly different overall levels of GAS, their GAS scores developed similarly over the 24-month period.

Table 4. Mixed model results for GAS scores

	Coefficient	Standard Error	*z*	*p*	95% Confidence Interval	
Constant	36.01	8.95	4.02	.00	18.47	53.56
Age	-.03	.11	-.29	.78	-.25	.18
Sex	.35	2.17	.16	.87	-3.91	4.61
Cocaine	-4.48	2.38	-1.88	.06	-9.15	.19
Stimulants	-5.26	3.37	-1.56	.12	-11.86	1.34
Narcotics	-.82	2.46	-.33	.74	-5.65	4.01
Hallucinogens	2.20	2.72	.81	.42	-3.14	7.53
Sedatives/Hypnotics	5.17	3.91	1.32	.19	-2.50	12.84
Time	10.07	3.68	2.74	.01	2.86	17.28
Alcohol abuse	-5.36	2.07	-2.60	.01	-9.41	-1.31
Cannabis abuse	.11	2.16	.05	.96	-4.13	4.35
Diagnostic group	6.85	1.98	3.45	.00	2.96	10.74

Note: Model did not incorporate interaction terms because they were non-significant. Schizophrenia was used as reference group for diagnostic group variable.

Clinical Global Impressions Scale – Severity (CGI-S)

Mixed models revealed that alcohol abuse was a statistically significant predictor of CGI-S scores (b = .39, 95% C.I. [.01, .77], p = .05), however, cannabis abuse was not (b = -.12, 95% C.I. [-.52, .28], p = .55) (See Table 5). More specifically, patients who abused alcohol had higher CGI-S scores, representing greater illness severity, than patients who did not abuse alcohol. Diagnostic group was a significant predictor of CGI-S scores (b = -.42, 95% C.I. [-.79, -.06], p = .02), indicating that individuals with schizophrenia were rated as having a higher overall level of CGI-S than individuals with bipolar disorder. No interactions were observed between variables.

Table 5. Mixed model results for CGI-Severity scores

	Coefficient	Standard Error	*z*	*p*	95% Confidence Interval	
Constant	5.13	.83	6.20	.00	3.51	6.75
Age	.01	.01	.50	.62	-.01	.03
Sex	.06	.20	.29	.77	-.34	.46
Cocaine	.39	.23	1.72	.09	-.05	.83
Stimulants	.53	.32	1.67	.10	-.09	1.15
Narcotics	.02	.23	.07	.94	-.44	.47
Hallucinogens	.13	.26	.50	.62	-.38	.63
Sedatives/Hypnotics	-.11	.37	-.30	.76	-.84	.61
Time	-1.00	.34	-2.96	.00	-1.67	-.34
Alcohol abuse	.39	.19	2.00	.04	.01	.77
Cannabis abuse	-.12	.20	-.60	.55	-.52	.28
Diagnostic group	-.42	.19	-2.28	.02	-.79	-.06

Note: Model did not incorporate interaction terms because they were non-significant. Schizophrenia was used as reference group for diagnostic group variable.

Clinical Global Impressions Scale – Improvement (CGI-I)

A final mixed model investigated CGI-I scores and its association with alcohol abuse, cannabis abuse, and diagnostic group (See Table 6). There was a significant time by diagnostic group interaction on CGI-I scores (b = -.69, 95% C.I. [-1.24, -.13], p = .02). These results indicated that individuals with bipolar disorder tended to worsen over the 24-month treatment period, while people with schizophrenia improved (see Figure 1). Additional analyses were conducted to test whether substance use influenced this significant interaction. Two three-way interaction terms for alcohol abuse and cannabis abuse were examined in separate models. Results indicated that the three-way interaction was not significant for alcohol abuse (b = -1.09, 95% C.I. [-2.37, .20], p = .19), however, was significant for cannabis abuse (b = -1.41, 95% C.I. [-2.71, -.11], p = .03) (See Table 7) (see Figure 2). This interaction indicated that individuals with schizophrenia who abused cannabis tended to show greater levels of improvement over 24-months than individuals with bipolar disorder who abused cannabis.

Table 6. Mixed model results for CGI-Improvement scores with two-way interaction term

	Coefficient	Standard Error	*z*	*p*	95% Confidence Interval	
Constant	4.89	.54	9.07	.00	3.83	5.94
Age	-.01	.01	-.99	.32	-.03	.01
Sex	-.19	.22	-.89	.38	-.63	.24
Cocaine	1.07	.96	1.11	.27	-.81	2.96
Stimulants	-.50	.28	-1.77	.08	-1.06	.05
Narcotics	.18	.29	.64	.52	-.38	.75
Hallucinogens	-.26	.40	-.64	.52	-1.04	.53
Sedatives/Hypnotics						Omitted
Time	.34	.14	2.39	.02	.06	.61
Alcohol abuse	-.30	.19	-1.60	.11	-.66	.07
Cannabis abuse	.06	.22	.27	.79	-.36	.48
Diagnostic group	1.76	.71	2.49	.01	.37	3.15
Diagnostic group * Time	-.69	.28	-2.43	.02	-1.24	-.13

Note: Sedative/hypnotics were omitted due to collinearity. Schizophrenia was used as reference group for the diagnostic group variable.

Table 7. Mixed model results for CGI-Improvement scores with three-way interaction term for cannabis abuse

	Coefficient	Standard Error	*z*	*p*	95% Confidence Interval	
Constant	5.24	.55	9.46	.00	4.15	6.32
Age	-.01	.01	-1.11	.27	-.03	.01
Sex	-.21	.23	-.91	.36	-.65	.24
Cocaine	.91	.97	.94	.35	-.98	2.81
Stimulants	-.59	.30	-1.99	.05	-1.17	-.01
Narcotics	.13	.29	.45	.65	-.44	.69
Hallucinogens	-.32	.42	-.75	.45	-1.15	.51
Sedatives/Hypnotics						Omitted
Time	.21	.15	1.41	.16	-.08	.50
Diagnostic Group	1.06	.81	1.31	.19	-.52	2.65
Diagnostic Group*Time	-.36	.33	-1.12	.27	-1.01	.28
Cannabis Abuse	-1.80	.97	-1.85	.06	-3.70	.10
Cannabis Abuse*Time	.82	.39	2.11	.04	.06	1.59
Diagnostic Group*Cannabis Abuse	3.20	1.70	1.88	.06	-.13	6.53
Diagnostic Group*Cannabis Abuse*Time	-1.41	.66	-2.13	.03	-2.71	-.11
Alcohol Abuse	-.35	.19	-1.87	.06	-.71	.02

Note: Sedatives/hypnotics were omitted due to collinearity. Schizophrenia was used as reference group for the diagnostic group variable.

Figure 1

Trajectories for CGI Improvement Scores for Patients with Schizophrenia or Bipolar Disorder Across Time

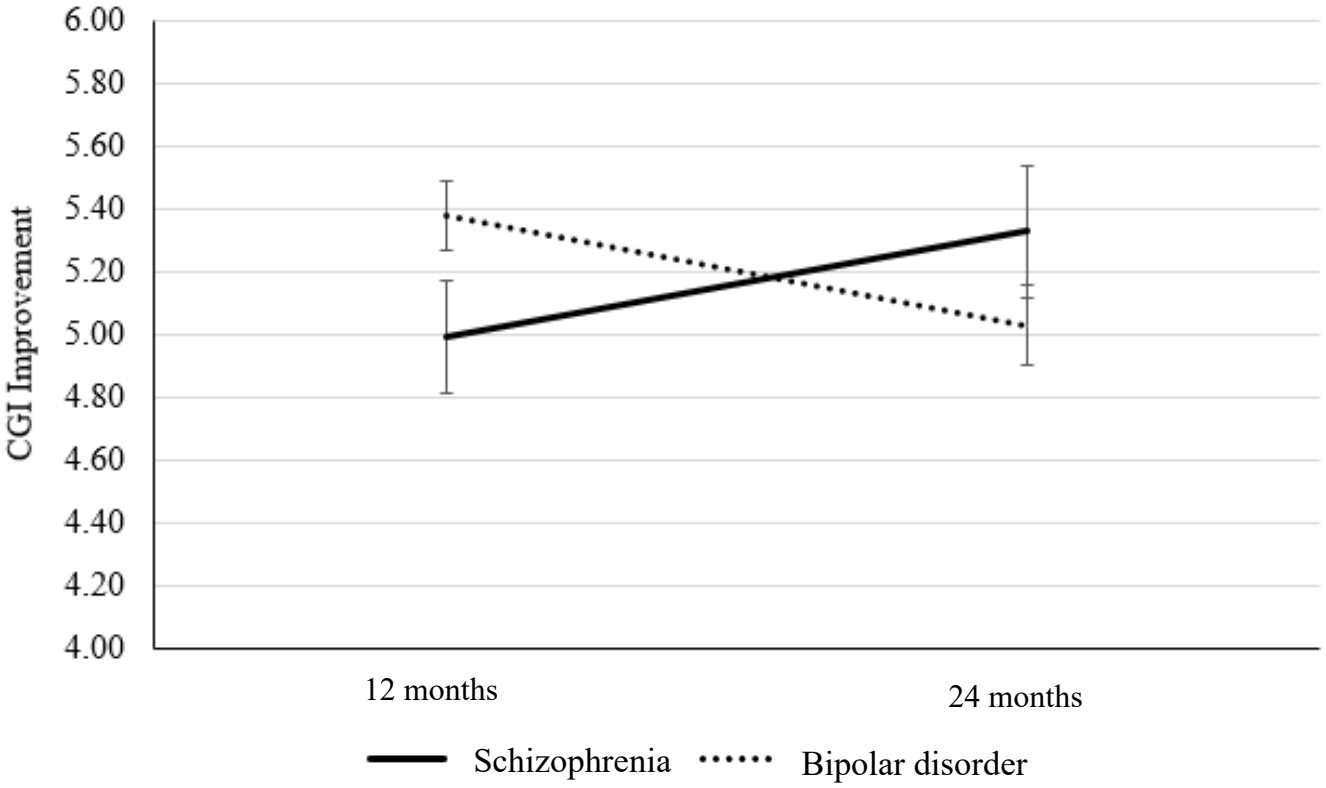
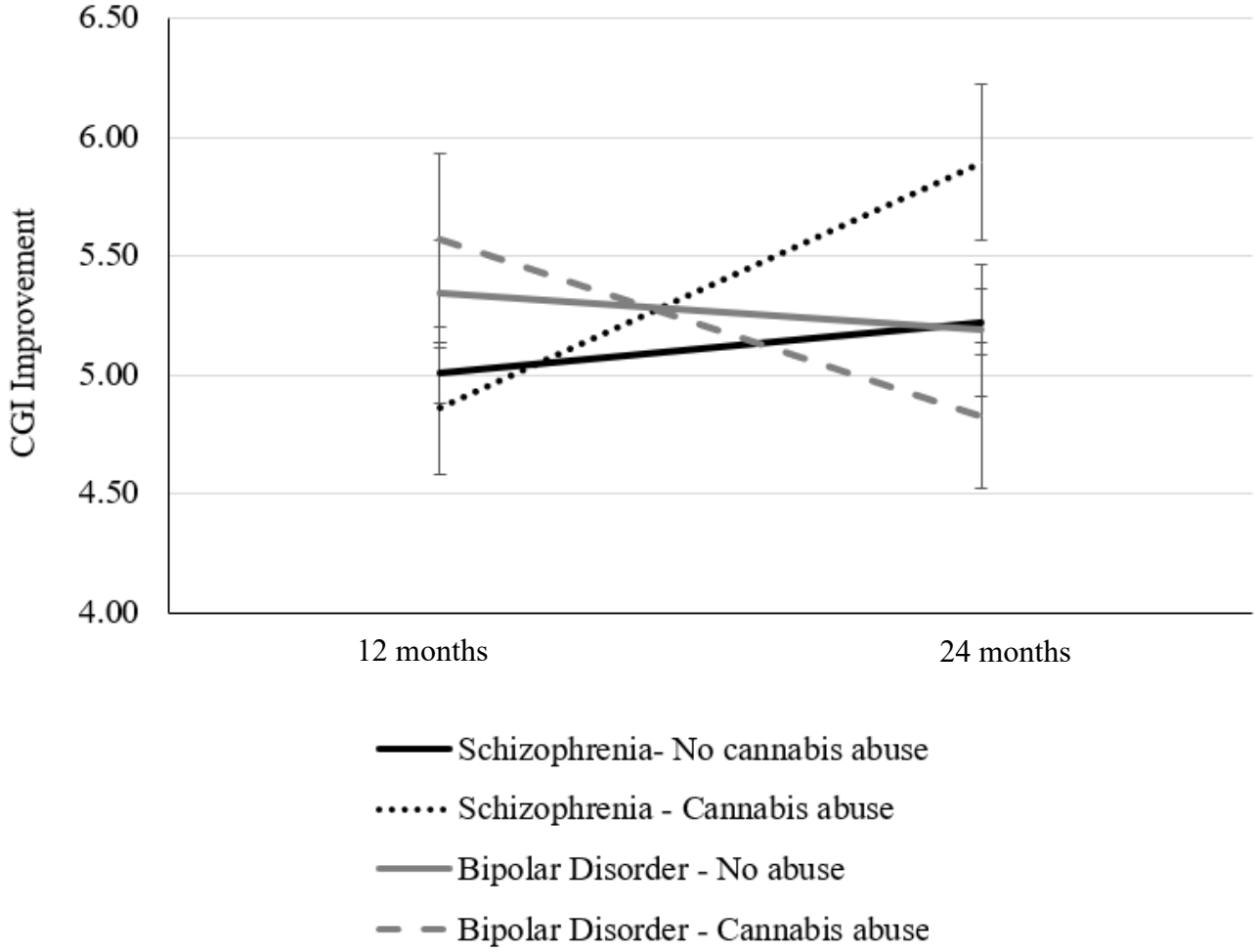


Figure 2

Trajectories for CGI Improvement Scores for Patients with Schizophrenia or Bipolar Disorder and Cannabis Use Status Across Time



Discussion

The purpose of the present study was to investigate whether patients with affective psychosis demonstrated different clinical features than patients with non-affective psychosis on several outcomes in a naturalistic setting, as well as how substance use might differentially impact patients with either form of psychosis. In this study, cannabis abuse (44%) and alcohol abuse (38%) were the most prevalent drugs used by patients in the program. Use of other types of drugs was relatively rare, a common pattern reported in the literature. Like previous studies, we found that patients who used cannabis experienced their first psychotic episode at a younger age compared to those who abstained (Addington & Addington, 2007; Clausen et al., 2014). Male patients with schizophrenia were also more likely to misuse cannabis and alcohol compared to male or female patients with bipolar disorder. Gender differences in substance abuse, in general, and cannabis abuse, specifically, have been a robust finding in previous research (Grech et al., 2005; Veen et al., 2004). Overall, while there were many similarities between the patients with FEP diagnosed with schizophrenia and bipolar disorder, there were distinctions that were unique to each patient group.

Substance Use and Overall Levels of Improvement

The primary finding of this study revealed that patients with schizophrenia who abused cannabis showed significantly greater levels of improvement than patients with bipolar disorder who abused cannabis over the course of 24 months. There are several possible explanations for this finding. Firstly, the current study measured frequency of cannabis use rather than dosage of substance use. Previous research has shown that the deleterious effects of cannabis may be dose dependent (Henquet et al., 2005; Moore et al., 2007; van Os et al., 2002). Given that the current study did not measure dosage, it is not clear whether patients with schizophrenia were using the

same quantity of cannabis as patients with bipolar disorder. Thus, patients with schizophrenia may have been using cannabis at a level that did not interfere with their treatment and allowed for improvements to occur. Previous research has also found that patients with schizophrenia who have higher cognitive functioning tend to use more cannabis (Rodríguez-Sánchez et al., 2010; Yucel et al., 2012). Therefore, our finding may reflect a group of patients with schizophrenia who possess levels of cognitive and social resources needed to access illicit drugs. It is important to note that recruitment for this study was completed before the legalization of cannabis in Canada. Higher levels of cognitive and social resources may by extension lead to improved outcomes. Third, patients with schizophrenia and bipolar disorder may engage in varying levels of treatment adherence. For example, previous research has shown that patients with schizophrenia who have more severe symptom profiles tend to adhere to medical treatment better than those with mild symptoms (Rettenbacher et al., 2004). Given that patients with schizophrenia had higher symptom severity scores than patients with bipolar disorder in the current study, it is possible that patients with schizophrenia may have been more consistent with their treatment, such as taking their antipsychotic medications. Further, research has demonstrated high rates of treatment non-adherence in patients with bipolar disorder, particularly during manic episodes (Colom et al., 2005). This could be due to a lack of insight or cognitive impairment during such episodes (Chakrabarti, 2016), or patients missing the pleasure experienced during manic episodes (Greenhouse et al., 2000; Sajatovic et al., 2011), all of which might increase the risk of treatment non-adherence. Given that we did not measure treatment adherence in the current study, no definitive associations can be determined at this time, however, future research may wish to pursue this endeavor.

Patients with bipolar disorder and schizophrenia also experience unique clinical features that may have contributed to the discrepancy in outcomes. For example, patients with bipolar disorder may have experienced manic episodes during the second year of the illness which could have contributed to lower overall levels of improvement at 24-months. It is therefore possible that they experienced a deterioration due to symptoms of mania rather than psychosis. This potential explanation is supported by our finding that both patient groups experienced a decrease in positive symptoms over time, thus, the overall decreased levels of improvement observed in patients with bipolar disorder is likely due to some other factor. Previous research has also shown that relapse rates for patients with bipolar disorder significantly increased following the first year of illness, which could serve as another potential explanation for the current study's finding (Hett et al., 2023). In summary, the current study demonstrated that patients who were abusing cannabis showed a different trajectory in terms of overall clinical improvement depending on whether they were presenting with affective versus non-affective psychosis. This provides evidence to support the separation of affective and non-affective psychosis when examining drug misuse.

Substance Use and Positive Symptoms

Contrary to our hypothesis, we did not find a significant association between cannabis misuse and positive symptoms. While previous research has demonstrated that cannabis use can lead to an increase in positive symptoms (Quattrone et al., 2021; Schoeler et al., 2016), it is possible that patients were using cannabis at a dose that did not produce negative effects (Zammit et al., 2008). Our findings also revealed a trend toward increased positive symptoms for patients who abused alcohol, however the association was not significant, which is consistent with some previous studies in the field (Sorbara et al., 2003). Our findings also suggested that

the course of positive symptoms developed similarly for patients with affective psychosis and non-affective psychosis. Consistent with the efficacy of early intervention, specifically antipsychotic medications (Crossley et al., 2010; Harrow et al., 2022) and previous research (Barrowclough et al., 2013; Cerqueira et al., 2022; Hadden et al., 2018), patients' positive symptoms decreased from admission to 24 months, regardless of diagnosis or drug status.

Substance Use and Global Functioning

Consistent with our hypothesis, we found that patients with bipolar disorder tended to enter treatment with higher global functioning compared to patients with schizophrenia, which was maintained across the 24-month treatment period. This is consistent with previous research demonstrating that individuals with schizophrenia tend to have lower levels of functioning compared to patients with bipolar disorder (Martin et al., 2015). It is also possible that a difference in cognitive abilities may partially explain this finding. For example, research has shown that patients with schizophrenia consistently show more severe and pervasive cognitive deficits than healthy controls and patients with bipolar disorder (Green, 2006). While the current study did not measure cognitive abilities, it is possible that patients with non-affective and affective psychosis demonstrated variable cognitive abilities that would affect their overall level of functioning, a measure of overall psychological, social, and occupation functioning.

We also found alcohol abuse had a negative impact on global functioning for patients with FEP regardless of whether there were affective symptoms associated with their illness. This is consistent with previous research which has shown that comorbid AUDs in patients with schizophrenia have been associated with poorer community functioning (Bowie et al., 2005) and lower GAS scores than those reported by patients with schizophrenia and no alcohol dependence

(Carra et al., 2016). Similar findings have also been found for patients with bipolar disorder (O'Connell et al., 1991; Weiss et al., 2005).

Substance Use and Illness Severity

Consistent with our hypothesis, we found that patients with schizophrenia were rated as significantly more severe than patients with bipolar disorder and the clinical trajectories between the two diagnostic groups did not differ over time, which is consistent with previous literature (Bowie et al., 2010). We also hypothesized that patients who abused cannabis and alcohol would demonstrate higher levels of illness severity, which was partially supported. Specifically, individuals who abused alcohol tended to show higher levels of illness severity, which is consistent with several lines of research. Comorbid AUDs have been shown to be associated with increased morbidity, more inpatient treatment, and overall poorer quality of life (Drake & Mueser, 2022; Roland et al., 2011) in patients with schizophrenia, as well as significant increased risk of associated psychopathology and an overall decreased degree of function (Farren et al., 2012) in patients with bipolar disorder.

Strengths and Clinical Implications

Our study holds several important strengths and clinical implications. First and foremost, our collective findings have provided evidence that patients experiencing affective psychosis display clinical characteristics that differ from patients experiencing non-affective psychosis, despite sharing some similarities. Second, our findings can more readily translate to clinical practice given that our methods reflect a naturalistic setting which used measures routinely employed in research and psychiatric practice, as well as a real-world community sample. Our findings have also highlighted the importance of examining the unique impact of individual substances on clinical outcomes, particularly those that have historically received less attention,

such as alcohol. This also highlights the importance of interventions which account for comorbid substance use.

Limitations and Future Research

There are important limitations to note within our current study. The first is that assessment of substance use relied on case manager ratings based on retrospective self-reports. While this method of assessment has potential for bias, including patient underreporting, the FEP program in the current study took a risk reduction stance where patients were not discharged if they misused psychoactive substances, therefore reducing the potential for self-report bias. There is also some evidence to suggest that self-report has high concordance to biological assays of substance use (Wolford et al., 1999). While quantifying substance use is difficult in clinical populations, it would be beneficial to determine if naturalistic samples have similar dose-dependent effects observed in large-scale control cohorts when examining estimations of substance dose in future work.

Evaluations of substance use were dichotomized into two categories for statistical purposes. Doing so may mask the potential nuances of substance use that could be observed when evaluated in a continuous manner, and how such fine degradation in use might impact clinical outcomes. A potential direction for future research may be to include a qualitative component to gather more detailed information regarding substance use. Additionally, the PANSS has become widely used to measure symptoms in other mental illnesses (e.g., bipolar disorder) despite being originally developed for use with people with schizophrenia. There is research to suggest that the positive factor of the PANSS was the least consistent across three diagnoses, including schizophrenia, schizoaffective disorder, and bipolar disorder (Anderson et al., 2017). Though this does not imply that the instrument cannot be used to measure symptoms

in disorders other than schizophrenia, it may be important to consider the instrument measures constructs differently within each disorder.

In conclusion, while our study found that patients with affective and non-affective psychosis demonstrated similar trajectories for most clinical outcomes we examined, we also found significant and key differences between the two groups. Further, cannabis use differentially impacted the trajectories of patients with schizophrenia relative to patients with bipolar disorder in terms of overall improvement, suggesting that psychotic symptoms alone are not a sufficient feature to merit integration of patients with affective and non-affective psychosis into a single cohort. The study of this dichotomy may provide key elements to improve management that might otherwise be lost.

Chapter 3: Final Discussion

Summary of Main Findings

While the negative impact of substance misuse on clinical outcomes in FEP has been well documented, less is known about how specific substances may uniquely affect the trajectories for patients with affective psychosis versus non-affective psychosis. As such, the aim of the current study was to examine whether alcohol and cannabis misuse differentially impacted symptomatic and functional outcomes in patients diagnosed with a primary diagnosis of bipolar disorder versus schizophrenia. Given the high prevalence of use of both substances among FEP populations, gaining a better understanding of their effects is of high clinical utility. Further, shedding light on the unique relationships between use of these substances and the clinical trajectories of patients with non-affective psychosis and psychosis may help to tailor early intervention efforts based on an individual's presentation.

Substance Use and Overall Levels of Improvement

The main finding of the current study demonstrated that patients with schizophrenia who abused cannabis tended to improve over 24 months while patients with bipolar disorder who abused cannabis tended to decline. At first glance, this result may appear to suggest that cannabis abuse had a positive influence on patients with schizophrenia, however, there are several possible explanations for this finding. First, similar findings have been reported for patients with FEP who misuse cannabis. Specifically, previous research has found that patients with schizophrenia who use cannabis tend to have a higher level of cognitive functioning compared to patients with schizophrenia who do not use cannabis (Rodríguez-Sánchez et al., 2010). Conversely, research has demonstrated that neurocognitive functioning at baseline predicts community functioning at follow-up, but not diagnosis or clinical baseline scores (Lewandowski et al., 2013). It is possible that this relationship reflects the social skills and cognitive functioning

required to facilitate accessing illegal drugs (i.e., cannabis prior to its legalization), rather than cannabis use leading to improvements in patients with schizophrenia. Our finding should also be considered in the context of how level of substance use was quantified in this study. That is, we measured frequency of cannabis use rather than dose of cannabis consumed. Research has demonstrated a dose-dependent relationship between self-reported cannabis use and the risk of subsequently developing psychotic symptoms (Henquet et al., 2005; Moore et al., 2007; van Os et al., 2002). It is possible that patients with schizophrenia were using cannabis at a dose that did not interfere with their antipsychotic medications, allowing for improvements to occur. Relatedly, research has shown that cannabis use significantly decreases among patients with schizophrenia in the early phases of treatment (i.e., 6 to 12 months) (Foti et al., 2010; Harrison et al., 2008; Wisdom et al., 2011). A decrease in the frequency of use is likely associated with a decrease in dose; however, further research would be needed to explore this relationship. Interestingly, positive symptoms were also observed to decrease in both diagnostic groups over time in our study. Given this, it is possible that patients with bipolar disorder experienced other symptoms unique to their mental illness, such as mania, that contributed to an overall deterioration in functioning. Cannabis use has been associated with an exacerbation of manic symptoms in individuals diagnosed with bipolar disorder (Gibbs et al., 2015).

There are also unique clinical features of each illness that may account for the discrepancy in treatment trajectories. For example, research has demonstrated high rates of treatment non-adherence in patients with bipolar disorder, particularly during manic episodes (Colom et al., 2005). This could be due to a lack of insight or cognitive impairment during such episodes (Chakrabarti, 2016). Patients with bipolar disorder have also reported missing the pleasure experienced during manic episodes (Greenhouse et al., 2000; Sajatovic et al., 2011),

which might increase the risk of treatment non-adherence. Additionally, some research has shown that individuals with schizophrenia who have more severe symptoms tend to show better adherence to medication, which may positively contribute to their improvement (Rettenbacher et al., 2004). This potential explanation is supported by the illness severity scores (CGI-S) found in our study, which indicated that patients with schizophrenia were rated as demonstrating more severe illness presentations than patients with bipolar disorder. In summary, our study found that patients who were abusing cannabis showed different clinical trajectories in terms of improvement depending on whether they were presenting with affective versus non-affective psychosis. This finding provides evidence to support the separation of affective and non-affective psychosis when examining drug misuse.

Substance Use and Positive Symptoms

We hypothesized that patients who misused cannabis would demonstrate higher levels of positive symptoms, regardless of diagnostic group. Contrary to our hypothesis, we did not find a significant association between cannabis abuse and positive symptoms which is inconsistent with previous literature demonstrating that cannabis use can lead to an increase in positive symptoms (Schoeler et al., 2016; Quattrone et al., 2021). One possible explanation may be related to how cannabis was measured (i.e., frequency of use instead of biological verification). Some research has suggested that changes in positive symptoms may be dependent on cannabis dose (Zammit et al., 2008). There was a trend toward increased positive symptoms for patients who abused alcohol, however the association was not significant. The fact that alcohol misuse had no significant impact on positive symptoms is consistent with some previous studies in the field (Sorbara et al., 2003). Our findings also suggested that the course of positive symptoms developed similarly for patients with affective psychosis (i.e., bipolar disorder) and non-affective

psychosis. More specifically, our results suggested that the level of positive symptoms significantly decreased over time for patients with schizophrenia and bipolar disorder, regardless of substance use status. This is consistent with previous research demonstrating a decline in positive symptoms (Addington & Addington, 2007; Barrowclough et al., 2013; Hadden et al., 2018) and is likely a by-product of early intervention. For example, most antipsychotic medications are effective at reducing positive symptoms in patients experiencing psychosis (Crossley et al., 2010; Harrow et al., 2022).

Substance Use and Global Functioning

We predicted that patients with bipolar disorder, who did not abuse alcohol or cannabis, would have significantly better global functioning than patients with schizophrenia abstaining from alcohol and cannabis. This hypothesis was supported in that patients with bipolar disorder had higher global functioning scores compared to those with schizophrenia. Thus, patients with bipolar disorder tended to enter treatment with higher global functioning compared to patients with schizophrenia, which was maintained across the 24-month treatment period. This is consistent with previous research that demonstrated that individuals with schizophrenia tend to show the poorest levels of functioning, whereas individuals with bipolar disorder tend to show the highest levels of functioning, while individuals with schizoaffective disorder fell between the two groups (Martin et al., 2015). It must also be recognized that clinicians were asked to consider the patient's overall psychological, social, and occupational functioning when assessing overall global function. Each of these domains may be affected by an individuals' cognitive abilities, and research has shown that patients with schizophrenia consistently show more severe and pervasive cognitive deficits than healthy controls and patients with bipolar disorder (Green, 2006). More specifically, patients with bipolar disorder have been shown to suffer from

cognitive deficits (e.g., psychomotor speed, attention, executive functioning, fluency, and verbal and visual memory) that are qualitatively similar to those of patients with schizophrenia, however, are milder in terms of severity (Schretlen et al., 2007). It is possible that a difference in cognitive abilities may partially explain the differences observed for overall levels of functioning.

We also found that alcohol abuse negatively impacted global functioning for both diagnostic groups, however, no such association was found for cannabis abuse. While alcohol abuse has less consistently been linked to changes in positive symptoms, there is more research to support that alcohol use has deleterious effects on overall functioning in patients with schizophrenia and bipolar disorder. For example, comorbid AUDs in patients with schizophrenia have been associated with poorer community functioning (Bowie et al., 2005) and lower GAS scores than those reported by patients with schizophrenia and no alcohol dependence (Carra et al., 2016). Similar findings have also been found for patients with bipolar disorder (O'Connell et al., 1991; Weiss et al., 2005). Interestingly, some research has found that the presence of a comorbid SUD in patients with bipolar disorder worsens their social functioning to the level observed in patients with schizophrenia, suggesting that the presence of an SUD may hold greater weight than the main diagnosis (e.g., schizophrenia versus bipolar disorder) to predict worse social adjustment and poorer outcome (Jaworski et al., 2010).

Substance Use and Illness Severity

In terms of overall illness severity, we hypothesized that patients with bipolar disorder would have lower levels of illness severity than patients with schizophrenia and that this would be maintained across a 24-month period. This hypothesis was supported in that illness severity was rated significantly higher among patients with schizophrenia relative to those with bipolar

disorder, and the clinical trajectories between the two diagnostic groups did not differ over time This is consistent with previous literature that demonstrates greater levels of disability and severity among individuals with schizophrenia versus bipolar disorder (Bowie et al., 2010). We also hypothesized that patients who abused cannabis and alcohol would demonstrate higher levels of illness severity. This was partially supported in that alcohol misuse predicted illness severity, where cannabis use did not. More specifically, individuals who abused alcohol tended to show higher levels of illness severity regardless of diagnosis, which is consistent with several lines of research demonstrating the adverse effects of alcohol use. For example, comorbid AUDs in people with schizophrenia are associated with increased morbidity, higher levels of inpatient treatment, and overall poorer quality of life (Drake & Mueser, 2022; Roland et al., 2011). Similarly, research on the comorbidity of bipolar disorder and AUD indicates that the combination leads to a significant increased risk of associated psychopathology and an overall decreased degree of function (Farren et al., 2012). Taken collectively, our findings suggest that alcohol abuse was found to have a negative impact on illness severity, further emphasizing the importance of studying its unique contribution to the clinical trajectories of patients with a comorbid AUD.

Clinical Implications

The findings of the current study suggest several clinical implications worthy of consideration. In our study, alcohol was observed to negatively impact clinical features for patients experiencing FEP. The clinical implications of this are twofold. First, this finding further highlights the necessity to treat comorbid SUDs as a primary clinical focus of intervention, especially in the early stages of the disease. More specifically, our research highlights that treatment planning should give equal consideration to the impact of other substances, such as

alcohol, in addition to cannabis. This holds clinical implications that are of particular importance since alcohol use has been shown to reduce the effectiveness of antipsychotic medication (Negrete, 2004). Second, the results have provided support for furthering this line of research in a controlled and structured way which allows for examining of the unique impact that alcohol use may have on clinical outcomes in patients with psychosis. Given that alcohol is as prevalent as cannabis, more research is needed to examine the relationship between cannabis and alcohol use for patients in the early stages of their illness.

Additionally, and perhaps most importantly, our study demonstrated key differences between the clinical characteristics of patients with affective and non-affective psychosis. For example, patients with bipolar disorder were rated as having higher levels of overall functioning than patients with schizophrenia, while patients with schizophrenia were rated as displaying overall higher levels of illness severity. Regarding substance use, patients with schizophrenia who misused cannabis tended to improve over the course of 24-months, while patients with bipolar disorder who misused cannabis showed a different clinical trajectory resulting in significantly lower levels of improvement at 24-months. With a current debate in the literature regarding the diagnostic classification of patients experiencing psychosis, our study provided evidence to support the clinical observations highlighting the utility of the dichotomy demarcating patients with affective psychosis from those with non-affective psychosis. While defining a diagnosis in the early phase of psychosis may be complex, consideration of the affective and non-affective dichotomy may help facilitate the introduction of appropriate treatment at a critical stage of the illness. For example, this dichotomy has been incorporated in treatment guidelines (Lambert et al., 2003) to provide early intervention adjusted to the specificities of psychotic disorders. While treatment would likely still involve the use of

antipsychotics for both patient groups, the co-occurrence of mood episodes in affective psychosis may require pharmacotherapy that considers the mood symptoms in addition to the psychotic symptoms. Interestingly, a previous study on first episode bipolar disorder reported that patients might receive more benefit from a mood stabilizer as maintenance treatment rather than an antipsychotic such as quetiapine (Berk et al., 2017). Additionally, Kessing et al. (2003) reported that patients in the early course of an affective psychotic disorder such as bipolar disorder may benefit more from a specialized outpatient mood disorder clinic rather than standard care. Further studies are needed to determine what each patient group might benefit from the most.

Strengths, Limitations, and Future Research

There are several strengths of the current study. First, the current study's methods reflect a naturalistic setting with measures routinely used in psychiatric practice and research. By utilizing tools that are already part of practice in many clinical settings, this research can more readily translate its findings for clinical utility. In addition, by using a community sample of patients with FEP, we were able to provide information on how substance misuse impacts clinical outcomes in a "real world" population. This is of particular importance and further highlights the need for more naturalistic treatment research as participants with comorbid SUDs have typically been excluded from clinical trials (Preuss et al., 2021). Second, the current study utilized a longitudinal design allowing for comparisons over time. Additionally, we used mixed model analyses that controlled for within-patient correlations and allowed all data points to be included, reducing the impact of attrition. Third, the current study statistically adjusted for covariates that commonly influence outcomes of patients experiencing FEP, such as age of onset, gender, and use of drugs other than cannabis and alcohol.

There are limitations to note within our current study. The first is that our assessment of substance use relied on retrospective estimations. In the current design, case managers rated the level of substance use over the previous 3 months. It is possible that there were natural variations regarding the case manager's ratings. Additionally, our substance use assessment was also based on patient self-report since biochemical verification was unavailable. While this method of assessment has potential for bias, including patient underreporting, the FEP program in the current study, took a risk reduction stance where patients were not discharged if they misused psychoactive substances, which possibly reduced self-report bias. It is also relevant to note that cannabis was classified as an illegal drug during this study's recruitment and data collection, which may hold implications for how willing a participant may have been to disclose cannabis use. While quantifying substance use is extremely difficult in clinical populations, examining estimations of substance dose in future work would be beneficial to determine if naturalistic FEP intervention samples have similar dose-dependent effects found in large-scale control cohorts. Additionally, future research may consider examining THC concentration, which has been shown to be a relevant contributor to increased risk for addiction and mental health disorders (Freeman et al., 2021).

The current study also utilized a rating scale to measure substance use, which was dichotomized into two categories, no abuse and abuse for statistical purposes. Doing so may mask the potential nuances of substance use and how this might impact various clinical outcomes. A potential direction for future research may be to include a qualitative component to allow for more detailed information gathering regarding the substances used by patients, including frequency, consumption methods, and duration of use. It would also be of great clinical utility to have a deeper understanding of patient beliefs regarding any perceived benefits of using

substances, particularly cannabis, despite its known adverse effects on the illness. Instruments such as the Marijuana Motives Questionnaire (MMQ) could assist with this endeavor. Interestingly, Costain (2008) sampled 30 patients with schizophrenia and reported various reasons for continued cannabis use, including enhancing auditory hallucinations (e.g., cannabis helped make voices louder and clearer), which was associated with enhanced clarity of thought and spiritual awareness. Several patients elaborated that adhering to antipsychotic medication adversely affected their spirituality for that reason. Other reasons included control of symptoms, to feel normal, perceived improvement in cognitive function, reduced psychological pain, and increased energy. It could also hold clinical relevance for research to examine whether motivations for substance differs between patients with affective or non-affective psychosis. Since these beliefs may influence a person's adherence to treatment and their future cannabis use, this line of future research has implications for improving clinician insight, with a goal of developing stronger therapeutic alliances in the service of improved patient care.

Additionally, while the current study examined the differential impact of substance use on various clinical features of patients with affective psychosis versus patients with non-affective psychosis, there is research to suggest that cognitive functioning also differs between the two patient groups (Amoretti et al., 2018; Li et al., 2020). For example, a recent meta-analysis demonstrated that patients with schizophrenia performed significantly worse than patients with bipolar disorder on several cognitive measures, including attention and social cognition (with large effect sizes), as well as processing speed, working memory, verbal and visual learning, reasoning, and problem solving (with medium effect sizes) (Li et al., 2020). Given the prevalence of substance use in both populations, it would be important to see how substance use,

particularly cannabis and alcohol, may affect cognitive performance in patients with FEP, and if this might differ depending on whether there is an affective component.

It is also important to consider the measures used to assess clinical outcomes, specifically, the use of the PANSS for patients with bipolar disorder. While the PANSS was originally developed for use with people with schizophrenia, it has become widely used to measure symptoms in other mental illnesses, including bipolar disorder, extending beyond its original use. There is some research to suggest that the positive symptom factor of the PANSS was the least consistent across three diagnoses, including schizophrenia, schizoaffective disorder, and bipolar disorder (Anderson et al., 2017). Though this does not imply that the instrument cannot be used to measure symptoms in disorders other than schizophrenia, it may be important to consider that the instrument measures constructs differently within each disorder. More research on the use of the PANSS in other psychotic disorders would be important to evaluate the psychometric properties for each disorder to determine the specific reliability and validity.

Lastly, while the current study provided evidence regarding differences in clinical features between patients with affective and non-affective psychosis, it would be important for future research to continue this line of work by exploring other potential differences and similarities between the two that may affect treatment outcomes. For example, measurements of relapse rates and adherence to medications are two potential components which could assist with this goal. In a recent study, Amoretti and colleagues (2018) demonstrated that cognitive reserve (CR) (i.e., the brain's capacity to cope with pathology to minimize symptoms) played a differential role in the outcome of psychoses according to a non-affective versus affective diagnosis. Based on their results, the authors concluded that patients with non-affective psychosis and low CR may require enriched cognitive rehabilitation via pro-cognitive

pharmacological agents, while functional remediation therapy may be more appropriate for patients with low CR and affective psychosis. With a better understanding of the unique clinical profiles, research can more appropriately and accurately identify treatment targets. Doing so could hold important implications for individualized treatment that is responsive and adapted for the patient's specific presentation.

Conclusion

Substance misuse is common among individuals experiencing FEP, with alcohol and cannabis being the most widely used substances. There are also distinct clinical differences between individuals experiencing non-affective psychosis (e.g., schizophrenia) and affective psychosis (e.g., bipolar disorder). This study sought to examine whether the clinical trajectories of patients with bipolar disorder versus schizophrenia differed over time, and if so, how substance misuse may have affected the differing trajectories. This study identified that while there were some similarities between patients with affective and nonaffective psychosis, there were distinct differences that suggest that psychotic symptoms are not a sufficient factor to warrant integration into a single group. More specifically, this study identified that patients with schizophrenia who abused cannabis tended to show greater levels of improvement over 24-months compared to patients with bipolar disorder who abused cannabis. Overall, the findings of the current study contribute to the literature exploring the relevance of dichotomizing individuals with affective versus nonaffective psychosis, specifically as it relates to substance misuse. The findings presented here also support the value of further exploration into this dichotomy and contribute to the growing evidence supporting the separation of the two patient groups. Clinical relevance of this dichotomy can apply directly to treatment, especially as early interventions and accurate diagnoses prove critical for individuals experiencing psychosis.

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