# THE EFFECT OF ALCOHOL AND CANNABIS ON QUALITY OF LIFE AND FUNCTIONING IN FIRST EPISODE PSYCHOSIS PATIENTS

BY

KRYSTAL K. BURSEY

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## Abstract

Schizophrenia is one of the leading causes of disability worldwide. New early intervention programs have shown some success in managing initial symptoms and improving the course of illness by beginning treatment during the first psychotic episode. Although these programs are a step forward towards recovery for people with schizophrenia and other psychotic disorders, in order for patients to attain a good quality of life, research needs to identify barriers that negatively interfere with symptom remission and illness management. Substance misuse has been identified in the literature as a prevalent issue within first episode psychosis patients and has been shown to negatively affect clinical outcomes; however, little is known about its impact on quality of life and functioning. This study aimed to address this gap in knowledge by examining the impact of course of substance misuse on quality of life, symptomatology, and global functioning over a 24-month period. A hundred and eighty-nine participants were categorized into one of three course of substance misuse groups: continued misuse, discontinued misuse and no misuse. No significant differences were observed between course of cannabis misuse groups (continued misuse, discontinued misuse or no misuse) over 24-months on any outcome variable; however, there was a significant course of alcohol misuse group difference on the positive symptoms outcome. It was found that those who continued misuse of alcohol had more positive symptoms than those who never misused alcohol or those who discontinued misuse of alcohol. These results indicate that alcohol misuse does impact clinical outcomes among first episode psychosis patients and that more research is needed to understand the full impact of substance misuse on this population.

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# The Effect of Alcohol and Cannabis on Quality of Life and Functioning in First Episode Psychosis Patients

Schizophrenia has been ranked as one of the top 25 leading causes of disability worldwide in 2010 (Whiteford et al., 2015). Schizophrenia can be a devastating illness due to its early onset (typically from adolescence to young adulthood), its considerable disability from illness onset, and its disruption or prevention of meaningful educational, occupational, and social experiences or achievements. New early intervention programs have shown some success in managing initial symptoms and improving the course of illness by beginning treatment during the first psychotic episode. However, there is still great variability in remission rates (i.e., level of symptoms that does not interfere with an individual's behaviour for at least six months) that have been shown to vary from 17% to 78% (AlAqeel et al., 2011; Lally et al., 2018). Considering the substantial disability associated with schizophrenia and related disorders, it is essential to identify barriers that negatively interfere with symptom remission and illness management, which are necessary factors for attaining a good quality of life (QOL) for those who have schizophrenia.

Researchers have begun to examine factors that negatively influence outcomes experienced by individuals in the early stages of schizophrenia onset, with the first psychotic episode being the initial treatment target. A noteworthy discovery that may account for some of the variance in successful clinical outcomes has been the high prevalence of substance misuse among patients with first episode psychosis (FEP) and its associated adverse effects (such as more severe psychopathology and higher relapse rates; Radhakrishnan et al., 2014; Wade et al., 2007). Much of the recent literature on this topic has focused on the impact of substance misuse on symptom reduction, with fewer studies examining the social and functional implications,

particularly quality of life (QOL). The present study aimed to fill this gap in the literature by evaluating the impact of substance misuse on QOL, symptomatology (positive and negative symptoms), and overall functioning over a 24-month early intervention program. In the remainder of my introduction, I present a review of the topics that relate to my thesis, including information on (i) the condition of schizophrenia and psychosis, (ii) what intervention(s) are recommended in clinical guidelines, (iii) important patient outcomes, (iv) the effectiveness of first-episode psychosis interventions on patient outcomes, and (v) factors that may influence treatment effectiveness; including substance misuse, which is the focus of my thesis. Lastly, I will highlight the gaps in the literature around the assessment of substance misuse and treatment outcomes, followed by a description of my thesis aims and hypotheses.

**Understanding the Condition of Schizophrenia and Psychosis**

Schizophrenia is a severe long-term mental health disorder. According to the *DSM-V* (American Psychiatric Association, 2013) definition, schizophrenia is defined by having two or more characteristic symptoms for at least one month (including delusions, hallucinations, disorganized speech, disorganized behaviour or negative symptoms) and social and/or occupational dysfunction in one or more areas of functioning including work, self-care or interpersonal relationships. To be diagnosed with schizophrenia, you must have continuous signs of disturbance for six months (American Psychiatric Association, 2013). There is no known cause; however, it is believed that a combination of genetic and environmental factors may be involved.

A key symptom of schizophrenia is episodes of psychosis. Psychosis can be described as an episode where one loses touch with reality. Symptoms of psychosis are divided into two categories: positive symptoms and negative symptoms. Positive symptoms are symptoms that

add or distort functioning like delusions, hallucinations, and disorganized speech. Negative symptoms reduce functioning like lack of affect, restricted speech, or difficulty generating thoughts or ideas (American Psychiatric Association, 2013). People who suffer from psychotic episodes, especially those with schizophrenia**,** also have poor social and occupational functioning and report lower levels of quality of life (specifically related to psychosocial, material, spare time, affective, occupational, activities, and cognition; Bechdolf et al., 2005; Song et al., 2011).

Researchers and clinicians often refer to two different types of psychosis: affective and non-affective. Affective psychosis refers to affective or mood disorders with psychotic features like major depressive disorder and bipolar disorder or schizoaffective disorder. Non-affective psychosis refers to schizophrenia and other related psychotic disorders, including schizophreniform disorder, brief psychotic disorder, psychosis not otherwise specified, and delusional disorder (Gafoor et al., 2018). My thesis is concerned primarily with the treatment of those with schizophrenia and other related psychotic disorders; thus, the remainder of my introduction will mainly focus on this group of conditions referred to as non-affective psychosis**.**

**Current Treatment of Non-Affective Psychosis**

Best practice for treating any type of psychosis focuses on providing evidence-based pharmacological and non-pharmacological interventions, which typically consist of the prescription of antipsychotics and the delivery of psychosocial interventions, including cognitive behavior therapy, family interventions, and social supports (Bird et al., 2010). The intervention is intended to be both comprehensive (e.g., providing emotional support, education, and practical assistance with day-to-day living) and patient-centered (e.g., encouraging patient engagement and choosing specific treatment strategies that are tailored to the patient's individual needs and goals; Nolin et al., 2016; Peterson et al., 2008). Clinical guidelines also recommend starting

treatment as soon as possible, preferably with the patients being referred for treatment when they experience their first episode of psychosis (FEP). These interventions are referred to as FEP programs (Bird et al., 2010). Typically, the overall aim of the intervention is to control/manage symptoms of psychosis and improve daily function and quality of life. Therefore, there is often intensive follow-up through case management (i.e., collaborative process for the provision of health care and services) and continuity of care (i.e., ongoing management of illness). Before the implementation of FEP programs, typical or usual care of individuals experiencing psychosis was hard to define due to its heterogeneity but typically consisted of the prescription of an antipsychotic and monitoring (in-patient or outpatient).

## Important Outcomes Related to FEP Treatment and Research

Several important outcomes should be considered when conducting research on patients attending FEP programs. Some of these include positive and negative symptoms, global functioning, and quality of life (QOL). These outcomes are important clinical and social outcomes for patients with FEP as they indicate how well patients are managing their illness and how they are functioning in their everyday lives. A growing number of other outcomes are being measured because they have been identified as indicators of improved illness management (e.g., relapse, hospitalizations). The following section will describe how these outcomes are measured and what we know about the effectiveness of specialized FEP treatment on them.

### *Positive and Negative Symptoms*

As mentioned previously, positive symptoms add or distort functioning (e.g., delusions, hallucinations, disorganized speech). In contrast, negative symptoms reduce functioning (e.g.,, lack of affect, restricted speech, or difficulty generating thoughts or ideas). These symptoms are typically measured together using the Positive and Negative Syndrome Scale or PANSS. The

PANSS consists of a clinical interview that uses three scales: the positive scale (7 items), the negative scale (7 items), and the general psychopathology scale (16 items). The positive scale consists of items on delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, and hostility. The negative scale consists of items on blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general psychopathology scale includes items on somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement or insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance. These symptoms are considered the hallmark symptoms of psychosis and are the most critical clinical measurement of psychopathology for individuals experiencing these conditions. Even though there is an overall score, the positive symptoms scale and the negative symptoms scale score are commonly reported separately. This is because these symptoms are very different, and a total score does not always reflect the actual status of a patient (Kay, 1990).

*Global Functioning*

The scale used in this paper is the Global Assessment Scale (GAS) which rates patients on a continuum from 1 (needing constant supervision, no attempts to maintain minimal personal hygiene) to 100 (no symptoms, superior functioning in a wide range of activities; Endicott et al., 1976). A more common scale used in the literature is the Global Assessment of Functioning Scale (GAF), an updated version of the GAS. When the GAF was updated from GAS, subjective criteria such as “most untrained people would not consider him sick” were removed.

Additionally, the GAF emphasizes the experience of suicidal thoughts and serious suicidal acts, making their presence indicate a lower score than the GAS (Hu, 2003).

Overall functioning and illness severity are used interchangeably in the literature to describe and interpret the results of the GAS or GAF. However, there has been some skepticism around using one single scale to assess both the psychological symptoms and social and occupational functioning of an individual since it is possible that these three dimensions do not always vary together (Goldman et al., 1992; Pedersen et al., 2020). As a potential solution to these criticisms, the Social and Occupational Functioning Assessment Scale (SOFAS) was created. The SOFAS differs from the GAF by solely focusing on patients' social and occupational functioning independent of the overall severity of the individual's psychological symptoms. Some researchers have also taken the GAF scale and split the scale into a functional impairment component and a symptoms component, essentially making two separate scales (Jones et al., 1995). It is also possible to see the Clinical Global Impression (CGI; Guy, 1976) scale used to describe illness severity or functioning in FEP research. The CGI is a brief tool comprised of two one-item measures that evaluate the severity of psychopathology and the change from the initiation of treatment. Thus, several prominent scales are used to assess overall functioning for individuals with psychosis. It is possible to see any of these scales used in research today on illness severity or functioning in FEP.

*Quality of Life*

An essential consideration in the treatment and management of early psychosis is examining the patient's well-being beyond simply assessing clinical symptom outcomes. It is not enough to solely strive for the remission of symptoms if these improvements do not translate into a better QOL for patients struggling with these complex clinical disorders. QOL can be defined

as a multifaceted construct encompassing one's psychological well-being, social well-being, functional (i.e.,, ability to look after oneself)/occupational well-being, and integration into society (Song et al., 2011). There are a few measures of QOL used in FEP research, but the measure used in this paper is the Quality-of-Life Scale (QLS) which has been developed for populations with schizophrenia. The QLS measures four domains of quality of life: intrapsychic foundations (measures patient's sense of purpose, motivation, curiosity, anhedonia, aimless inactivity, empathy, and emotional interaction), interpersonal relations (related to patient's household, friends, acquaintances, social activity, social network, social initiative, withdrawal, and sociosexual behaviour), instrumental role (measures occupational role, work functioning, work level, and work satisfaction), and common objects activities (measures patient's level of participation in the community, time utilization, essential things they have and do).

*Relapse*

Relapse can be important to measure because relapses within the first few years of treatment are an important determinant of long-term clinical and functional outcomes (e.g., recovery can be slow and more psychotic symptoms are possible; Brown et al., 2020). Relapse has been measured in several different ways. According to a systematic review on relapse measurement in randomized controlled trials of relapse prevention in patients with FEP, the most common measurement of relapse is readmission to a psychiatric hospital (Gleeson et al., 2010). However, a recent by Taylor and Jauhar (2019) pointed out that equating hospital readmissions with relapse can be misleading. For example, not everyone experiencing a relapse (i.e., deterioration in symptoms and functioning) is hospitalized. Similarly, other factors such as a suicide attempt or violence could lead to hospitalization, and it can be unclear if they individual

had relapsed in terms of symptoms or functioning. Thus, while hospitalizations are often used as a marker for relapse, it is important to understand the limitations of this type of measure.

**Effectiveness of Specialized FEP Treatment on Patient Outcomes**

FEP programs represent the best care for individuals in their first episode of psychosis. Before its recommendations for widespread use, the effectiveness of FEP programs was studied in several randomized controlled trials (RCTs), which have been analyzed together in several systematic reviews (Bird 2010, Bond 2015, Chan 2019, Correll 2018). A review by Bird et al. in 2010 included four trials ($n$ =800) of early intervention services from the United Kingdom, Denmark, and Norway. They found that those who were offered early intervention (consisting of medication management and a range of psychosocial interventions) were less likely to relapse (typically defined as either hospital readmission or clinical judgement based on case notes; RR = 0.66, 95% CI [0.47, 0.94]), less likely to be admitted to hospital (RR = 0.67, 95% CI [0.54, 0.83]), and had a greater reduction in positive (SMD = -0.21, 95% CI [-0.42 , -0.01]) and negative symptoms (SMD = -0.39, 95% CI [-0.57, - 0.20]) compared to those who had standard care (Bird, 2010). A more recent review by Correll et al. (2018) identified 10 RCTs of early intervention compared to usual care and found similar results to those reported by Bird et al. in 2010. They also found that quality of life was significantly higher in the early intervention group among four of the ten studies (SMD = 0.23, 95% CI [0.00, 0.46], $p$ =.046). In seven of the ten studies, global functioning was also significantly higher for the early intervention group (SMD = 0.21, 95% CI [0.09, 0.34], p= .001). In both of these reviews, the samples were primarily individuals with schizophrenia with a duration of follow-up varying between 6 months to 2 years. Similarly, Cassidy et al. (2010) have shown a better prognosis and management of illness for those who receive FEP interventions. To try and adopt recommendations for early

intervention, most hospitals and mental health facilities have implemented programs to identify and treat individuals in their first episode of psychosis.

*What is the effectiveness of FEP interventions on QoL?*

Over the last fifteen years, research has shown that functional recovery and QOL has not improved as much as symptom remission, as patients with FEP seem to remain relatively socially isolated, limited in their ability to perform moderate to vigorous activities, have low satisfaction with financial or living situation, high rates of unemployment and limited interest in hobbies at home or outdoors (Bechdolf et al., 2005; Song et al., 2011). Moreover, unsurprisingly, patients with FEP have been observed to place great value in functional recovery (i.e.,, the ability to participate in society, function independently and attain meaningful relationships; Ramsay et al., 2011). Individuals who achieved remission of positive symptoms were more likely to have higher levels of QOL; although, still significantly poorer functioning than non-psychiatric controls (Addington et al., 2003; Nuttall et al., 2019; Phahladira et al., 2020). In a longitudinal study conducted by Henry and colleagues (2010) on individuals with FEP, those individuals with schizophrenia had significantly lower scores than those experiencing affective psychosis (i.e., those experiencing psychosis with mood episodes such as individuals with bipolar disorder or major depressive disorder), on QOL at seven-year follow-up. In fact, of the 424 patients in the study, 59% met the criteria for psychiatric symptom remission, but nearly 77% of those individuals were in the affective psychosis group. Of those in the schizophrenia and related disorders group, only 30% achieved symptomatic remission, only 24% achieved social/vocational recovery, and only 17% achieved both (Henry et al., 2010). Thus, while FEP treatment programs have shown to be effective on these outcomes, the degree to which patients improve on some of these outcomes can be variable. A growing body of research aims to

understand what factors may be influencing the variation in effectiveness, and this will be discussed next.

## Factors that Influence the Treatment Outcomes of Patients with FEP

Previous research has identified several factors that influence the treatment outcomes of psychosis in patients with FEP (de Castro-Manglano et al., 2011; Grossman et al., 2008; Thorup et al., 2012; Veldhuizen et al., 2007). For example, premorbid functioning (i.e., the individual's functioning prior to the onset of illness) and duration of untreated psychosis serve as consistent predictors of clinical outcomes, with poorer premorbid functioning and a longer period of untreated psychosis being associated with a poorer course of illness (i.e., clinically significant levels of positive and negative symptoms, poorer functioning; Addington et al., 2003, Drake et al., 2018). The following section will discuss some of the most prominent factors identified in the literature, including gender, age of onset, and substance misuse. The research in this area is mainly regarding positive and negative symptoms and functioning with less research on the outcome of quality of life, possibly because quality of life is not as routinely measured in FEP programs as the other clinical outcomes of symptoms and functioning. I will discuss what is known about each of these factors related to the treatment outcomes described above.

### *Gender*

Perhaps one of the most notable and well-studied non-modifiable factors is gender (Grossman et al., 2008; Thorup et al., 2007; Thorup et al., 2012). A five-year longitudinal study by Thorup and colleagues (2012) identified several significant differences between FEP males and FEP females who had attended an FEP program. They followed 578 patients with FEP in the schizophrenia spectrum and found that males had significantly higher symptoms and lower functioning levels than females. Grossman and colleagues (2008) followed 97 patients with

psychosis (43 females and 54 males) for six follow-up periods over 20 years in the United States. They found that females demonstrated a lower percentage of psychotic activity (i.e., the presence of positive symptoms) over the course of illness at 7.5 years and 20 years follow-up and more significant improvement in psychotic activity when compared to males. Additionally, they found that females showed significantly better global functioning at half of the follow-ups (2 years, 7.5 years and 10 years) and that 61% of females with schizophrenia showed a period of symptom remission during the 20 years compared to only 41% of the males. Furthermore, these gender differences were similar between all types of psychotic disorders.

It is possible that these findings may not be related to a gender issue but rather differences in other factors related to social support and living arrangements between the two groups. For example, in Thorup and colleagues (2012) study, males were more likely to live alone and suffer from a substance use disorder than females. Moreover, females were more likely to reach higher levels of social functioning, live with children, and more likely to be employed or in education than their male counterparts. Females were also more likely than males to comply with medication and enter remission. In a follow-up study, Thorup and colleagues (2014) found no significant differences in QOL between males and females. Overall, it appears males tend to have more negative outcomes throughout the course of illness compared to females (Grossman et al., 2008; Thorup et al., 2007; Thorup et al., 2012).

*Age of Onset*

Age of onset of psychosis is another factor that has been widely studied and influences the course and treatment of psychosis. A study by Compton et al. (2014) demonstrated that in non-affective patients with FEP, a poor premorbid/early onset of illness was associated with greater negative symptoms, preoccupation symptoms, and greater psychosocial problems.

Furthermore, a study by Legge and colleagues (2020) demonstrated that in patients with schizophrenia and other related psychotic disorders, individuals with an earlier age of onset of psychosis not only had poorer premorbid functioning but were also more likely to be treatment-resistant (i.e., remains symptomatic despite antipsychotic treatment or given clozapine (an antipsychotic that is provided if inadequate response to other antipsychotics)). Moreover, illness onset before the age of 19 is associated with a longer duration of untreated psychosis in schizophrenia patients (Fond et al., 2018). In a study with 322 individuals with FEP (with a schizophrenia spectrum diagnosis), found that a later age of onset predicted impaired cognitive functioning after ten years along with male gender, unemployment, and poor premorbid achievement (Bergh et al., 2016). However, while there is limited research on how the age of onset impacts QOL, one study by Dominguez-Martinez and colleagues (2015) found that age of onset of prodromal symptoms (i.e., symptoms individuals experience before entering a psychotic episode) was not related to subjective QOL. Another study by Malla and colleagues (2004) found that QOL pertaining to social relations was positively correlated to later onset. Thus, while an earlier age of onset seems to be related to poorer outcomes and a worse course of illness for FEP individuals, less is known on how it impacts QOL.

*Substance Misuse*

Substance misuse is a prevalent issue among individuals with psychosis and has been shown to have a significant impact on treatment outcomes. For example, a recent Canadian study found high substance misuse rates among patients with FEP, with 42.9% of participants misusing cannabis, 19.3% misusing alcohol and 20% of participants reporting polysubstance misuse (Abdel-Baki et al., 2017). The research on substance misuse as a factor that may influence treatment outcomes has focused on assessing misuse of multiple substances in a single composite

variable or each substance separately. The composite measure approach can help look at additive effects but can also be problematic because it is unclear the degree to which individual substances on their own are detrimental to treatment effects. Thus, other research has focused on separately assessing the influence of misusing individual substances such as cannabis and alcohol. I will describe what is known about the effect of each of these substance misuse variables separately (see Appendix Table 1 for details about the studies presented below).

**Composite Variable Substance Misuse.** Composite variables of substance misuse tend to be defined as a substance use disorder diagnosis or as self-reported misuse of a substance. For example, a longitudinal study on 212 patients with FEP by Abdel-Baki et al. (2017) found that persistent substance misuse (measured by a diagnosis of any substance use disorder) was associated with impairments in QOL and functioning, more symptoms and increased service use (e.g.,, emergency services and hospitalizations). Research using composite substance misuse variables has also shown differences in the severity of substance misuse. In a study with 92 patients with FEP ($n$ = 50 non-affective psychosis diagnosis), researchers found that those with heavy or more severe substance misuse were associated with poorer social functioning and more positive symptoms but not associated with negative symptoms or QOL after controlling for gender, duration of untreated psychosis, medication adherence, and positive symptoms (Wade et al., 2007). However, as mentioned above, since these studies used a composite variable of substance misuse, we cannot determine the specific impacts of each substance, which impacts the study's generalizability. Thus, the evidence on the effect of substance misuse on QOL and functional outcomes has been limited and inconclusive. More research is needed to determine the specific impacts of substances on QOL and overall functioning.

**Polysubstance Misuse.** While polysubstance misuse also involves the misuse of more than one substance, the substances are identified. There is some evidence to suggest that polysubstance misuse may have an additive negative effect on outcomes. For example, a recent retrospective, cross-sectional study by Cookey et al. (2020) on 264 non-affective early psychosis patients examined clinical characteristics (positive and negative symptoms, overall functioning, state-trait anxiety, and depression) associated with alcohol and cannabis use. They divided their sample into four groups: no-to-low cannabis and alcohol misuse ($n$ = 44), moderate to high alcohol misuse only ($n$ =33), moderate to high cannabis misuse only ($n$ = 55), and moderate to high alcohol and cannabis misuse ($n$ = 132). They found that the polysubstance misuse group was the youngest group and that trait anxiety was the highest in this group. There were no differences between the low misuse group and the polysubstance misuse group on positive and negative symptoms or functioning. In a separate study by Ouellet-Plamondon and colleagues (2017), they found that those who misused at least two substances had higher positive and negative symptoms, lower GAF scores, lower QOL scores, and more hospitalizations compared to those who misused to those who did not misuse at two years follow-up. While there is some support for polysubstance misuse having an additive negative effect, the area is understudied and examining polysubstance misuse does not allow us to understand the specific impacts of individual substances.

**Cannabis Misuse.** Cannabis has numerous negative implications for symptom remission and treatment outcomes in patients with FEP. For example, cannabis misuse in patients with schizophrenia has been associated with higher relapse rates, more extended hospitalizations, increased positive symptoms, non-adherence to medication, cognitive deficits, and reduced glutamate levels in the prefrontal cortex (Ouellet-Plamondon et al., 2017; Radhakrishnan et al.,

2014; Schoeler et al., 2017). Research findings have also indicated that those patients with FEP who consistently misuse cannabis have higher levels of illness severity, poorer psychosocial functioning, increased negative and depressive symptoms (Hadden, 2018; Oluwoye et al., 2019; Ouellet-Plamondon et al., 2017; Seddon et al., 2016). For example, a national longitudinal study by Seddon et al. (2016) followed 1027 patients with FEP (schizophrenia $n = 227$, other non-affective psychosis $n = 468$, affective psychosis $n = 117$, unknown diagnosis $n = 215$) in an early intervention program in the UK. Their results demonstrated that cannabis misuse was associated with increased severity of psychotic symptoms, mania, depression, and poorer psychosocial functioning. Furthermore, continued cannabis misuse was associated with poorer total PANSS scores, negative symptoms, depression, and psychosocial functioning that could not be explained by age, gender, duration of untreated psychosis, age of psychosis onset, ethnicity or other substance misuse.

There is also some support that cannabis misuse impacts QOL. A study by Addington and Addington (2007) on 203 FEP (diagnosed mainly with schizophrenia (69.9%), total $n = 203$) patients found that cannabis misuse was associated with a significantly poorer QOL at two years follow-up but not at 1- or 3-years follow-up. However, the number of users of cannabis for these follow-up periods were low, which could have impacted the results (baseline $n = 71$, 1 year $n = 31$, 2 years $n = 12$, 3 years $n = 10$) reducing the power to detect a significant difference. A longitudinal study by Ouellet-Plamondon et al. (2017) on 284 patients with FEP found similar results. Those diagnosed with a cannabis use disorder had poorer QOL and functioning at two years follow-up compared to those who did not have a substance use disorder.

Similar to Addington and Addington (2007), Ouellet-Plamondon and colleagues (2017) had low numbers of patients in the substance misuse groups for alcohol (1 year $n = 12$, 2 year $n$

= 16) and cannabis (1 year $n$ = 28, 2 years $n$ = 24) which could have impacted their results and thus, limits the generalizability of their findings. Unlike the studies by Abdel-Baki et al. (2017), Addington and Addington (2007) and Ouellet-Plamondon et al. (2017), Oluwoye and colleagues (2019) did not find any significant difference between those who did not misuse cannabis or alcohol and those who misused cannabis or alcohol on QOL in their longitudinal study of 404 patients with FEP with a schizophrenia spectrum diagnosis. However, they found that those who misused cannabis were associated with more significant impairment in overall functioning at the two-year follow-up.

While several negative implications of cannabis misuse in FEP populations have been discovered, we are still unsure of the mechanism behind this effect. The recent literature on cannabis misuse and psychosis has supported the notion that there may be a dose-response relationship between positive symptoms and the THC content in cannabis. In an extensive, multinational case-control study by Quattrone et al. (2021) of 901 patients with FEP (47% had non-affective psychosis) and 1,235 controls, it was demonstrated that individuals with FEP with daily use of high potency cannabis presented with more positive symptoms and less negative symptoms than those who never misused cannabis or only used low potency types. Potency was measured by the different varieties of cannabis in each catchment area, based on their government and national data, collected by the European Monitoring Centre for Drugs and Drug Addiction. For example, low potency was defined as THC< 10% and it included products that were likely to have <10% THC, which included the following: hash/resin from UK and Italy, imported herbal cannabis from the UK, Italy, Spain and France, Brazilian marijuana and hash and the Dutch Geimporteerde Wiet. High potency was defined as THC>10%, which included: UK home-grown skunk/sensimilla UK Super Skunk, Italian home-grown skunk/sensimilla,

Italian Super Skunk, the Dutch Nederwiet, Nederhasj and geimporteerde hasj, the Spanish and French Hashish (from Morocco), Spanish home-grown sensimilla, French home-grown skunk/sensimilla/super-skunk and Brazilian skunk. Although this study lends support for the relationship between THC dosage in cannabis and increased positive and negative symptoms, the dose of THC is only an estimation. The difference in potency presents a significant measurement issue when examining the impact of cannabis misuse within FEP populations. Many studies rely on the patients' self-reported use of cannabis where THC potency cannot be accurately assessed. It is not always feasible to measure the THC concentration of the cannabis they are using. To date, we could not find a study that controlled for specific dosage.

**Alcohol Misuse.** Despite the prevalence of alcohol misuse in patients with FEP, research on its impact is limited with cannabis being the primary substance studied in this population. Like cannabis misuse in patients with FEP, alcohol misuse has been associated with poor medication adherence (higher numbers of missed pills), male gender, and younger age of onset (Addington & Addington, 2007; Oluwoye et al., 2019). Additionally, research has found links to alcohol misuse with increased depressive symptoms and suicidal ideation (Abdel-Baki et al., 2017; Leeson et al., 2012; Radhakrishnan et al., 2014). Some research has also indicated that alcohol misuse is associated with lower negative symptom scores (Cetty et al., 2019), whereas other research has shown that alcohol misuse has no impact on negative or positive symptoms (Ouellet-Plamondon et al., 2017).

Additionally, Addington and Addington did not find any significant differences between users and non-users of alcohol on QOL at any follow-up (1, 2 or 3 years). Ouellet-Plamondon and colleagues (2017) found that those with an alcohol use disorder had a significantly poorer QOL at one-year follow-up than those who did not misuse alcohol. Still, the difference

disappeared at the two-year follow-up. Those with an alcohol use disorder were also found to have significantly poorer functioning at both the 1-year follow-up and the two-year follow-up compared to those who did not misuse alcohol. Ouellet-Plamondon and colleagues (2017) had low numbers of patients in the substance misuse groups for alcohol (1 year $n$ = 12, 2 years $n$ = 16), which could have impacted their results and, thus, limited their findings' generalizability. Oluwoye and colleagues (2019) did not find any significant difference between those who did not misuse alcohol and those who misused alcohol on QOL in their longitudinal study of 404 Patients with FEP with a schizophrenia spectrum diagnosis.

It is unclear how alcohol misuse affects these symptoms, but a possible explanation is lack of patient adherence to their antipsychotic medication treatment while misusing alcohol. Given the interaction between antipsychotic medication and alcohol, patients are often told to not drink alcohol due to the possibility of adverse events. Antipsychotics have some depressive effects on our central nervous system and can enhance the side effects of one or both of the medications and/or alcohol and drugs. Additionally, patients who have pre-existing liver disease may not even be eligible to use some antipsychotics. Thus, when examining outcomes like positive symptoms in FEP individuals, it is essential to be cautious in the interpretation of findings. While it is possible there is a valid link between alcohol and positive symptoms, it is also possible that patients are discontinuing their medication to drink.

*Impact of Course of Substance Misuse*

Another important consideration when examining the impact of substance misuse that is often not addressed is the pattern or course of substance misuse. Many studies utilize baseline measures of substance misuse to classify their participants, but this method does not allow for analysis of the variation in the pattern of substance misuse. For example, some research has

highlighted that those who discontinue substance misuse within the first two years after diagnosis have outcomes comparable to those participants who never misused substances (Abdel-Baki et al., 2017; Gonzalez-Pinto et al., 2011; Weibell et al., 2017). Specifically, research has shown better long-term functional outcomes for those who discontinue the misuse of cannabis and alcohol than those who either continued to misuse during follow-up or never misused this substance. Additionally, those who discontinued cannabis misuse also exhibited fewer negative symptoms than those who continued cannabis misuse, whereas discontinuing alcohol misuse did not significantly impact positive or negative symptoms (Gonzalez-Pinto et al., 2011). Research has shown that participants achieved lower symptom remission rates for episodic and continuous cannabis misuse than those who did not misuse this drug. Continuous misuse of cannabis was also associated with a more significant number of hospital days (Abdel-Baki et al., 2017; Weibell et al., 2017). Thus, research has highlighted some crucial distinctions between patterns of substance misuse that are clinically relevant to the treatment and illness management of individuals with FEP and should be considered when researching this area.

**The Present Study**

Current research on patients with FEP has started to move from simply targeting symptom improvement to improving all outcomes that affect a patient's well-being; however, more research is still needed to identify factors associated with functional outcomes. Few studies have examined the impact of substance misuse on QOL and overall functioning in FEP populations, and the present study aims to address this gap in the literature. Given the variability in study results examining cannabis and alcohol misuse and outcomes, exploring these questions with a more homogenous group (schizophrenia vs. mood disorders) within longitudinal methodology is essential. Furthermore, many studies are limited by using composite substance

misuse variables where the separate effects of each substance cannot be determined. Additionally, not enough longitudinal studies examine the impact of substance misuse on QOL or patients' ability to live their lives (i.e., overall functioning). Few studies look at the potential impact of substance misuse on specific aspects or domains of QOL. The quality of an individual's life should be a critical factor in determining treatment success. In past research, there is an assumption that symptom reduction leads to a more fulfilling life; however, the limited research on patients with FEP and comorbid substance misuse has suggested the relationship is much more complicated.

The present study seeks to address the above limitations by examining the impact of course of substance misuse on QOL (including the four domain scores: interpersonal relationships, instrumental role functioning, intrapsychic foundations and common objects, and activities) among individuals with schizophrenia that are participating in an FEP program. The present study will also examine symptoms (positive and negative symptoms) and global functioning over a 24-month treatment period. Patients will be separated into three groups based on substance misuse patterns to examine the impact of the course of misuse. These groups are as follows: continued misuse, discontinued misuse and no misuse. These groups will be described further in the following methodology section. The following hypotheses are based on the limited research available:

1. Patients who discontinue cannabis, or alcohol misuse, in the first year of treatment will report a significantly better overall QOL (including the domains: interpersonal relations, instrumental role, intrapsychic foundations, and common objects and activities) than those who continue to misuse this substance across the 24-month period.

2. Patients who discontinue cannabis, or alcohol misuse in the first year of treatment, will report a significantly better overall functioning (GAS) than those who continue to misuse this substance.
3. Continued cannabis, or alcohol misuse, will lead to increased positive symptoms from treatment admission (Baseline) to 24-month follow up. In contrast, those participants who discontinued cannabis or alcohol misuse will have a significant decrease in positive symptoms at the 24-month follow up. Similarly, participants who never misused cannabis or alcohol will show a significant decrease in positive symptoms from admission to 24-month follow up. Given the research indicating that negative symptoms improve over the course of treatment, it is expected that negative symptoms will improve over time.

*Clinical Implications of this Study*

Healthcare professionals are now recognizing the importance of the social consequences of illness and that treatment should be aimed at remission or management of an illness and improving one's quality of life. Newer definitions of recovery or remission from an illness involve a multidimensional concept focusing on clinical remission and social functioning (Vita & Barlati, 2018). In the medical field, a patient's quality of life is frequently a barometer for the quality, effectiveness, and efficiency of health care service/treatment. Mental healthcare should not be exempt from this quality-of-care assurance. Functional outcomes and a good QOL should be made a priority target for early psychosis intervention programs. Research such as the current study is necessary to identify factors and understand their impacts on function and QOL outcomes to be addressed in therapeutic interventions. Only multifaceted treatment approaches that involve pharmacotherapy, psychosocial interventions, and attention to environmental

circumstances will be sufficient to treat complex illnesses. Therefore, it is essential that research target the concepts necessary to understand how to develop and facilitate these multifaceted treatment approaches. The results of this study could help facilitate that and further this goal towards improved treatment and intervention programs.

## Methods

### Participants

The database consists of 192 early psychosis patients ranging from 15 to 58 years old. Participants were recruited at admission to the Psychosis Intervention and Early Recovery (PIER) Program in Newfoundland, Canada, which is the only specialized assessment and treatment service for early psychosis in the province. All patients were seen by one of two psychiatrists who diagnosed patients according to *DSM-IV* criteria (American Psychiatric Association, 2000).

Inclusion criteria included meeting the DSM-IV criteria for schizophrenia or a schizophrenia spectrum disorder. Additionally, to be eligible for the PIER program, patients had to be treated with antipsychotics for less than six months or were experiencing their first psychotic episode. Exclusion criteria for the study included patients diagnosed with a mood disorder or substance-induced psychosis according to DSM-IV criteria, or an underlying medical condition (e.g., traumatic brain injury) to minimize potential confounds. Additionally, we excluded those who started misuse at the 24 month follow up ($n$ =9) as we did not have enough data to analyze the impact of substance misuse on their outcomes.

## Procedure

This study used a pre-existing database created for a 2-year study on the impact of cannabis use on outcomes in a first episode psychosis population (Hadden et al., 2018). The database consists of multiple variables, including marital status, age at entry, education level, employment, living circumstances, ethnic background, positive and negative symptoms, substance misuse, quality of life, global functioning, diagnosis (both affective and non-affective psychosis), premorbid functioning, and depression (using the Calgary Depression Scale). Demographic variables included in the present study were age at admission, gender, education level, employment, and living circumstances. Patients were assessed on all measures at admission to the program (baseline), after 12-months, and again at 24-months for a total of three assessments periods. The Case Manager Rating Scale (CMRS) was administered by the case manager for each participant, and all other measures were administered by one of the two psychiatrists who diagnosed the patients. Ethics approval was obtained from the Health Research Ethics Authority of Newfoundland and Labrador.

## Measures

### *Positive and Negative Syndrome Scale*

To assess positive and negative symptoms, the Positive and Negative Syndrome Scale (PANSS) was used. The PANSS is a semi structured interview that rates patients from 1 to 7 on 30 different symptoms categorized into three symptom groups: the positive scale, the negative scale, and the general psychopathology scale. Since 3 is the lowest score given per item, scores can range from 3 to 210 (Kay, 1991). This scale has been shown to have strong interrater reliability ($r$ = .83 – $r$ = .87), criterion-related validity and construct validity (Kay, 1990).

### *Global Assessment Scale*

The Global Assessment Scale (GAS) is a measure of overall functioning of a subject during a period of psychological illness. The scores range from 1 (*severely ill*) to 100 (*healthiest*). The scale is divided into ten equal intervals (i.e., 1-10, 11-20 and so on up to 100). The two highest intervals (81-90 and 90-100) indicate a lack of significant psychopathology and the possibility of traits indicating superior functioning (e.g., effective social skills, variety of interests, integrity, etc.). The interval from 71-80 indicates minimal psychopathology and possession of some of the traits of superior functioning. The majority of individuals in treatment are rated from 1-70 (Endicott et al., 1976). This scale has been shown to be reliable (interrater reliability $r$ =.85) and have moderate construct and predictive validity (Endicott et al., 1976; Kuhlman et al., 1991).

*Quality of Life Scale*

Finally, the Quality of Life Scale (QLS) was used to assess the quality of life. The QLS is a 21-item scale that measures four domains of quality of life: intrapsychic foundations, interpersonal relations, instrumental role, and common objects activities. The QLS has a 7-point response scale with higher scores indicating a better quality of life. This scale has been designed for schizophrenia populations and has shown good reliability (interrater reliability $r$= .97 – $r$ = .91) and convergent and divergent validity (Gupta et al., 2000; Heinrichs et al., 1984; Simon-Abbadi et al., 1999).

*Case Manager Rating Scale*

The CMRS was used to assess substance misuse. The CMRS is a short checklist used to determine the level of an individual's substance misuse at each follow-up period using the healthcare providers knowledge from the following evidence: patient's self-reported misuse,

information from clinical interviews, behavioural observations, and collateral reports (such as reports from family, friends etc.). The level of misuse is ranked as none (0 – i.e., no misuse during time interval), mild (1 – i.e., patient has misused substance during time interval but showed no signs of persistent or recurrent social, occupational, psychological or physical problems related to use), moderate (2 – i.e., patient has used substance during time interval and has showed signs of persistent or recurrent social, occupational, psychological or physical problems related to use. Problems has persisted for at least one month), severe (3 – i.e., meets criteria for moderate misuse and at least three of the following criteria: greater amounts or intervals of use than intended, much time spent obtaining or using substance, frequent intoxication or withdrawal interferes with other activities, activities given up for misuse, continued misuse despite knowledge of problem, marked tolerance, characteristic withdrawal symptoms) or extremely severe (4 – i.e., meets criteria for severe plus related problems are so severe it makes noninstitutional living difficult; Drake et al., 1990). This scale has been used in several previous studies (e.g.,, (Drake et al., 1990; Hadden et al., 2018)). For classification purposes, all ratings of 0 or 1 were classified as no substance misuse, while ratings from 2-4 were classified as substance misuse. This classification was used to stay consistent with previous research (Addington & Addington, 2007; Coldham et al., 2002; Hadden et al., 2018). While this scale does not provide a diagnosis, it has been shown to have strong correlations with DSM-III diagnoses of alcohol misuse disorders for both current (0.41, $p<.001$) and lifetime diagnoses (0.61, $p<.001$;Drake et al., 1990).

*Substance Misuse Course Classification*

Patient substance misuse course classification followed the previous work of Gonzalez-Pinto et al. (2011) and Hadden et al. (2018). Course of substance misuse was classified

separately for cannabis and alcohol. Course of misuse was categorized into Never Misused, Discontinued Misuse, and Continued Misuse. The Never Misused group consisted on patients that never misused either cannabis or alcohol at admission to the program and across the 24-month treatment intervention. Those in the Discontinued Misuse group consisted of patients that ceased misuse of cannabis or alcohol between program admission and 12-month follow up. This cut-off was used as previous research has shown that discontinuing misuse by 12-months was associated with outcomes comparable to those who never misused (Gonzalez-Pinto et al., 2011). Patients who continued cannabis or alcohol misuse across all three time periods were classified as Continued Misuse group. The Continued Misuse group also consisted of patients who misused cannabis or alcohol between 12-month to 24-month follow up. Patients who started misuse at 24-months were excluded ($n$ =9).

**Statistical Analysis**

Statistical Package for the Social Sciences (SPSS) v. 20 was used to perform the statistical analyses. Data for 192 patients were assessed for univariate and multivariate outliers on the following variables: quality of life (including the subscales of: intrapsychic foundations, interpersonal relations, instrumental role, and common objects activities), positive and negative symptoms, and global functioning. Mahalanobis distances were used to examine multivariate outliers and missing values were imputed using multiple imputation in the missing values package for SPSS. A total of ten imputations were run. Analyses were run on each imputation, with the median F-values and p-values being reported for each interaction or main effect.

Four separate 3(time: baseline, 12-months, and 24-months) x 3(course of use: never used, discontinued misuse, continued misuse) repeated measures analysis of covariances (ANCOVA) were run for each substance type to determine the effect of substance misuse (cannabis only and

alcohol only) on participants QOL (including the subscales of: intrapsychic foundations, interpersonal relations, instrumental role, and common objects activities), global functioning, positive and negative symptoms after controlling for covariates age, gender and alcohol misuse or cannabis misuse. Tukey's post hoc analyses were used to assess any significant main effects or interactions.

We did not create covariates to control for the other drugs that were misused (cocaine, stimulants, narcotics, hallucinogens, sedatives, and other drugs). There were several reasons for this decision; firstly, the prevalence of misuse was simply too low to analyze (misuse ranged from 4.2% - 0%). Additionally, not including those covariates prevented us from reducing our degrees of freedom unnecessarily and reducing statistical power.

## Results

Data for 192 patients were assessed for univariate and multivariate outliers on the following variables: quality of life (including the subscales of: intrapsychic foundations, interpersonal relations, instrumental role, and common objects activities), positive and negative symptoms, and global functioning. There were no univariate outliers with a z-score greater than 3.29 found for all three time points ($p<.001$; see Tabachnick & Fidell, 2013). Mahalanobis distances were used to examine multivariate outliers. Three cases were found to exceed the $\chi^2$critical= 26.125, and thus, were removed from the dataset. Therefore, 189 participants data were used for the imputation. The data was found to not be missing at random, $\chi^2$ (18, $N$ = 189) = 2.906, $p$ = 0.99. The percentage of missing values for each outcome for all time points can be seen in Table 1.

**Sociodemographic and Clinical Characteristics**

Sociodemographic data (see Tables 2 - 3) show that most of the participants in the study were male (*n* = 141, 74.6%), Caucasian (*n* = 176, 93.1%), and single (*n* = 167, 88.4%). Additionally, most participants lived with family (*n* = 133, 70.3%) and had an education level ranging from high school to postsecondary (*n* = 183, 96.8%). As seen in Table 4, the highest rates of substances that were misused in the sample were cannabis (baseline: 36%) and alcohol (baseline: 31.7% - 32.8%).

We compared age, gender and outcome variables (PANSS positive and negative symptoms, GAS, total QOL) at baseline by alcohol course misuse status (no misuse, discontinued misuse and continued misuse) and cannabis course misuse status (no misuse, discontinued misuse and continued misuse). Results demonstrated that those who continued to misuse cannabis (M= 21.71, $M_{diff}$ = 6.092, p=.001) and those who discontinued misuse of cannabis (M = 22.22, $M_{diff}$ = 5.582, p=.002,) were significantly younger at baseline than those who did not misuse (M= 27.72, See Table 2). Similarly, those who continued to misuse alcohol (M= 22.22, $M_{diff}$ = 4.873, *p* = .006) were significantly younger at baseline than those who did not misuse alcohol (M= 27.09, See Table 3). At baseline, there was a greater proportion of males than females in the sample across all course of substance misuse groups for cannabis (75.6% vs 24.4%, $\chi 2$ (2, *N* = 180) = 13.279, p=.001) and alcohol (74.4% vs. 25.6%, $\chi 2$ (2, *N* = 172) = 7.338, p=.026). Participants who continued misuse of cannabis (M= 22.81) had higher positive symptoms at baseline than those who did not misuse (M= 19.78, $M_{diff}$ = 3.026, p=.029). At baseline, participants who discontinued cannabis misuse (M=38.83) had lower global functioning scores than those who never misused (M= 46.52, $M_{diff}$ = -7.692, p=.014). No other significant differences were found for either course of substance misuse groups.

**Quality of Life**

Separate 3 (Course) x 3 (Time: Baseline, 12-months, 24-months) repeated measures ANCOVAs were conducted to determine the effect of cannabis misuse course (continued misuse, discontinued misuse and no misuse) on overall QOL and the four QLS subscales after controlling for age, gender and course of alcohol misuse. Results indicated that there were no significant differences between groups for total QOL or QLS subscales (See Table 5). However, results did indicate that there was a significant effect of Time for total QOL, F (2, 147) = 3.712, $p$ = .027, partial $\eta^2$ = 0.048, demonstrating that participants increased their overall quality of life from baseline (M = 67.673) to 12-months (M = 81.173), $M_{diff}$= -13.500, $p$ <.001), and maintained these gains at 24-months (24-months M = 80.905; $M_{diff}$= -13.232, $p$ <.001). There was also an effect for Time for the QOL subscales interpersonal relations QOL, $F$(2, 146)= 5.309, $p$ = .006, partial $\eta^2$ = .068, indicating that participants significantly increased their social relationships over the first 12-months (baseline (M = 6.984), 12-months (M = 10.932), Mdiff = -3.949, $p$ <.001), and maintained these gains at 24-months (24-months (M= 11.100), $M_{diff}$= -4.116, $p$ <.001). There was a main effect for Time for instrumental role QOL, $F$(2, 158)= 5.665, $p$ = .004, partial $\eta^2$ = .067, indicating that participants significantly increased their functioning in their role of worker, student, or parent over the first 12-months (baseline (M = 24.899), 12-months (M = 30.753), $M_{diff}$ = -5.855, $p$ <.001), and maintained these gains at 24-months (24-months (M= 31.159), $M_{diff}$= -6.260, $p$ <.001). There was a significant covariate effect for gender, showing that males reported lower overall QOL (M = 74.15 vs M =79.70) and the subscales intrapsychic foundations (M = 26.93 vs. M = 28.26), interpersonal relations (M = 9.34 vs M = 10.91), instrumental role (M = 28.30 vs. M = 30.27) and common objects and activities (M = 8.97 vs. M = 9.45) when compared to female participants.

Separate 3 (Course) x 3 (Time) repeated measures ANCOVAs were conducted to determine the effect course of alcohol misuse on QOL of participants after controlling for age, gender and course of cannabis misuse. As can be seen in Table 6, there were no significant effects for course of alcohol misuse on overall QOL or QLS subscales. However, results indicated that there was a significant effect of Time for total QOL, F (2, 160) = 5.127, $p$ = .007, partial $\eta^2$ = 0.060, showing that participants increased their overall QOL over the first 12 months (baseline (M = 63.604) to 12-months (M = 80.756), $M_{diff}$= -17.152, $p$ <.001), and maintained these improvements at 24-months (24-months M = 81.166; $M_{diff}$= -17.562, $p$ <.001). Additionally, results indicated that there was a significant effect of Time for interpersonal relations, F(2, 160) = 6.430, $p$ = .002, partial $\eta^2$ = 0.074, indicating that participants increased aspects of their social experience from baseline (M = 7.287) to 12-months (M = 10.862), $M_{diff}$= -3.576, $p$ <.001, and maintained these gains at 24-months (M = 10.782; $M_{diff}$= -3.495, $p$ <.001). Results showed that there was a significant effect of Time for instrumental role, F(2, 160) = 7.214, $p$ = .001, partial $\eta^2$ = 0.083, indicating that participants increased their functioning in their role of worker, student, housekeeper or parent over the first 12 months (baseline (M = 25.067), 12-months (M = 30.643), $M_{diff}$= -5.577, $p$ <.001), and maintained these at 24-months (24-months M = 30.927; $M_{diff}$= -5.861, $p$ <.001). Results indicated that there was a significant effect of Time for common objects and activities, F(2, 158) = 4.750, $p$ = .01, partial $\eta^2$ = 0.057, indicating that participants increased their use common objects or increased their participation in common activities over the first 12 months (baseline (M = 7.921), 12-months (M = 9.833), $M_{diff}$= -1.911, $p$ <.001), and maintained these at 24-months (24-months M = 9.509; $M_{diff}$= -1.588, $p$ <.001). There was a significant covariate effect of gender indicating that males scored significantly

lower than females on overall QOL (M = 74.15 vs. M = 79.70), intrapsychic functioning QOL (M = 27.23 vs. M = 28.30), and interpersonal relations QOL (M = 9.24 vs. M= 10.91).

**Global Functioning**

Separate 3 (Course) x 3 (Time: Baseline, 12-months, 24-months) repeated measures ANCOVAs were conducted to determine the effect of course of cannabis misuse on overall functioning of participants after controlling for age, gender and course of alcohol misuse. Results showed that course of cannabis misuse did not significantly impact participants overall functioning across the treatment period $F(2, 167) = 0.529$, $p = .590$, partial $\eta^2 = .006$ (See Table 5).

Similar analyses were conducted for course of alcohol misuse, which indicated that there were no significant effects for course of alcohol misuse on participants overall functioning, $F(2, 155) = 0.550$, $p = .578$, partial $\eta^2 = .007$ (See Table 6). However, there was a significant effect for Time indicating that participants overall functioning increased across the 24-month treatment period ($F(2,166) = 12.727$, $p < .001$, partial $\eta^2 = .133$), with significant changes occurring from baseline (M = 43.948) to 12-months (M = 62.928), $M_{diff} = -18.980$, $p < .001$, with additional improvement between 12-to-24 months ($M_{diff} = -8.956$, $p < .001$) and significant improvement overall from baseline to 24-months (M = 71.884), $M_{diff} = -27.936$, $p < .001$.

**Positive and Negative Symptoms**

Separate 3(Time) x 3(course group) repeated measures ANCOVAs were conducted to determine the impact of course of cannabis misuse on positive symptoms after controlling for age, gender and course of alcohol misuse. Results indicated that there were no group differences for course of cannabis misuse on positive symptoms, $F(2,167) = 0.564$, $p = .570$, partial $\eta^2 = .007$. However, there was a main effect of Time, $F(2,166) = 6.593$, $p = .002$, partial $\eta^2 = .074$, with

significant changes occurring from baseline (M = 19.969) to 12-months (M = 10.707), $M_{diff}$ = 9.263, $p < .001$ and were maintained at 24-months (M = 11.217), $M_{diff}$ = -8.752, $p < .001$.

Separate 3(Time) x 3(course group) repeated measures ANCOVAs were conducted to determine the impact of course of alcohol misuse on positive symptoms after controlling for age, gender and course of cannabis misuse. Results showed that there were group differences for course of alcohol misuse on positive symptoms, $F(2,152) = 3.107$, $p = .048$, partial $\eta^2 = .039$, indicating that those who continued misuse (M= 15.664) had higher PANSS positive symptom scores than those who discontinued misuse (M = 13.743; $M_{diff}$= -1.921, p <.001) and those who never misused (M = 13.475; $M_{diff}$= -2.189, p <.001). Additionally, there was a main effect of Time, $F(2,154) = 12.478$, $p < .001$, partial $\eta^2 = .139$, with significant changes occurring from baseline(M = 21.268) to 12-months (M = 10.486), $M_{diff}$ = 10.782, $p < .001$, from 12-months to 24 months (M = 11.601), $M_{diff}$ = -1.115, $p = .029$, and from baseline to 24-months, $M_{diff}$ = 9.668, $p < .001$.

In terms of negative symptoms, there were no significant effects for course of cannabis misuse, F(2, 148) = 1.187, $p = .313$, partial $\eta^2 = .044$, but there was a main effect of Time for course of alcohol misuse, F(2, 146) = 3.327, $p = .039$, partial $\eta^2 = .044$. This indicated that there were significant changes from baseline (M= 18.350) to 12 months (M= 15.994; $M_{diff}$= 2.356, p <.001), and that these changes were maintained at 24 months (M= 15.690; $M_{diff}$= 2.661, p <.001).

## Discussion

The current study examined the impact of substance misuse (cannabis and alcohol misuse) on QOL, functional and symptom outcomes among individuals with FEP over 24-

months. The main findings of the current study were that QOL was not associated with the course of substance misuse. However, there was evidence that positive symptom outcomes at 24-months were associated with alcohol misuse. Specifically, results indicated that those who continued to misuse alcohol maintained higher positive symptoms than those who discontinued or never misused alcohol. This result is inconsistent with the previous research on the impact of alcohol misuse for positive symptoms as increased positive symptoms is not typically associated with alcohol misuse (Addington & Addington, 2007; Cetty et al., 2019; Oluwoye et al., 2019; Ouellet-Plamondon et al., 2017). This finding builds on the limited research that examines the impact of alcohol misuse on first-episode psychosis.

**Clinical Characteristics of Participants at Admission to the FEP Program**

Similar to previous research, cannabis and alcohol misuse rates were 36% and 32%, respectively (Addington & Addington, 2007). At admission into the program, those who continued to misuse cannabis or alcohol were significantly younger and more likely to be male than those who never misused these substances. These characteristics are consistent with previous research findings in FEP populations with those that misuse cannabis (Gonzalez-Pinto et al., 2011; Van Mastrigt et al., 2004). In addition, we found that those who continued to misuse cannabis had significantly higher positive symptoms at admission to the program than those who never misused this substance. This finding is consistent with previous research indicating that cannabis misuse is associated with more severe psychotic symptoms (Abdel-Baki et al., 2017; Addington & Addington, 2007; Seddon et al., 2016).

In terms of overall functioning at admission, those who discontinued cannabis misuse before completing their first year of treatment (i.e., the discontinued misuse group) were functioning at a significantly higher level than those who never misused cannabis. Previous

longitudinal research has found conflicting results regarding overall functioning (i.e., ability to participate in society and complete day-to-day activities) in patients with FEP at admission. For example, Gonzalez-Pinto and colleagues (2011) found no differences between cannabis misuse groups on global functioning scores at admission. Other research has demonstrated significant differences in functioning at admission between those who did not misuse cannabis and those who continued misuse of cannabis (Weibell et al., 2017). Several reasons could explain these differences. One potential explanation is that Gonzalez-Pinto (2011) and Weibell (2017) included participants with mood disorders (i.e.,, Major Depressive Disorder and Bipolar Disorder) in their study populations. In contrast, our study only looked at FEP in patients with nonaffective schizophrenia spectrum disorders. Research has demonstrated several key differences between these two populations that could lead to differences in results. In most cases, those with a nonaffective schizophrenia spectrum disorder experience more unfavourable outcomes such as higher levels of disturbance in the basic sense of self, poorer functional outcomes, more persistent psychotic symptoms, poorer cognitive functioning and greater likelihood of relapse (Nelson et al., 2012; Velthorst et al., 2017). Thus, the differences in results could be affected by the differences between the two populations.

In another 10-year longitudinal study examining the course of substance misuse, Weibell and colleagues (2017) used similar categories as the current sample for classifying course of substance misuse (continued misuse, discontinued misuse, and no misuse) and found that patients who discontinued misuse within the first two years had similar outcomes to those who never misused. Additionally, they found that those who were episodic misusers and those who continued to misuse had more symptoms than those who did not. However, they did include a fourth group labelled "episodic" misuse, whereas the present study included these patients in the

continued misuse category. This addition of a fourth group could lead to different findings due to differences in the categorization of individuals. Moreover, Weibell and colleagues used a composite variable to measure substance misuse rather than examining each substance separately. A composite variable does not allow for the examination of individual impacts of substances. Therefore, it could lead to differences in findings because you cannot determine which substance or combination of substances led to the result. Therefore, the differences between the current study results and those of previous work could be explained by variations in the classification of course of substance misuse and differences in the measurement of substance misuse (i.e., combining all substances versus examining specific impacts).

## Quality of Life

### *Cannabis Misuse*

It was hypothesized that those participants who discontinued cannabis misuse in the first year of treatment would report a significantly better QOL than those who continue to misuse this substance. The present study's findings indicated that there were no significant differences between cannabis course groups and QOL. Oluwoye and colleagues (2019) similarly found no significant differences in cannabis misuse and QOL; however, these authors did not account for substance misuse course in their analysis but instead grouped participants by whether or not they misused the substance at admission. Their grouping variable is a significant methodological difference because substance misuse is not always a static phenomenon. Furthermore, the course of misuse has been shown to impact outcomes in Patients with FEP in the literature (Gonzalez-Pinto et al., 2011, Weibell et al., 2017). Therefore, it is unclear if our results are truly comparable or similar due to these significant methodological differences.

Other research that has examined overall QOL (total score) among individuals with FEP has found that those who misused cannabis demonstrated poorer QOL at the 24-month follow-up (Addington & Addington, 2007; Ouellet-Plamondon et al., 2017). A possible explanation for the difference in results between the present study (i.e., no significant differences in cannabis misuse course groups on QOL) and previous research may be related to statistical methods for dealing with missing data. Specifically, the current study used multiple imputations to manage missing data and median F-values to interpret results, which are conservative statistical methods that reduce the chance of a Type 1 error. Both Addington and Addington (2007) and Ouellet-Plamondon and colleagues (2017) did not use statistical methods to include data from their dropouts; therefore, their results may not accurately reflect their population as their data is subject to attrition bias. It is more advantageous to impute missing data because it allows you to use all of your collected data and improves the generalizability and validity of your results (Kang, 2013).

While no group differences were found between the course of cannabis misuse groups, there was a main effect of Time and Gender. We found that cannabis misuse group participants showed improvements on their overall QOL, QOL relating to interpersonal relations and QOL relating to instrumental role. Previous research on QOL in this population has demonstrated that improvements in overall QOL are often seen during FEP treatment, particularly in the first six months to one year (Addington et al., 2003; Caton et al., 2014; Nuttall et al., 2019; Phahladira et al., 2020; Setién-Suero et al., 2017). To our knowledge, no previous research has documented specific improvements over time within each QOL domain.

We found that for cannabis misuse groups, there were significant differences between males and females for total QOL and on each domain (intrapsychic, interpersonal, instrumental

role, common objects and activities), indicating that males scored lower on all aspects of QOL compared to females. Research has shown that males tend to have poorer outcomes and a worse illness course than females (Thorup et al., 2012). While, to our knowledge, no study has examined the gender differences in each domain of the QLS, some research has documented differences that may explain these results. For example, research has shown that females are more likely to be employed, have better social functioning and are more likely to reach a state of recovery than men (Setién-Suero et al., 2017; Thorup et al., 2012). These factors are associated with better functioning and quality of life, which may explain the differences found between males and females.

*Alcohol Misuse*

Similar to cannabis misuse, it was hypothesized that those participants who discontinued alcohol misuse in the first year of treatment would report a significantly better QOL than those who continue to misuse this substance. Our hypothesis was not supported; no significant alcohol group differences or interactions were found on any domain of QOL. Previous research has shown inconsistent findings in terms of alcohol misuse and quality of life. Some studies have found that alcohol misuse had no impact on participants quality of life (Addington & Addington, 2007; Oluwoye et al., 2019), while other studies have found alcohol misuse disorders were associated with poor overall quality of life at 12-month follow-up (Ouellet-Plamondon et al., 2017). One explanation for the difference in results could be the different methods of categorizing substance misuse. Ouellet-Plamondon and colleagues (2017) grouped their participants by substance use disorder status but did not account for the course of misuse. This grouping method does not account for the pattern of misuse as some patients may discontinue misuse while others may continue misuse. Additionally, the FEP sample from Ouellet-

Plamondon and colleagues (2017) contained a high number of stimulant misuse, whereas our sample had relatively low numbers of stimulant misuse. These differences introduce variance into their grouping variable and could have resulted in different findings.

Similar to cannabis misuse, we found that alcohol misuse group participants showed improvements on overall QOL, interpersonal relations, instrumental role and common objects and activities over the 24-month follow-up. Again, previous research on QOL in this population has demonstrated that improvements in overall QOL are often seen during FEP treatment, particularly in the first six months to a year (Addington et al., 2003; Nuttall et al., 2019; Phahladira et al., 2020). For example, Addington and colleagues (2003) found that all 177 Patients with FEP at 1-year follow-up had significant improvements in QOL. However, even those in remission from positive symptoms had poorer QOL compared to non-psychiatric controls. Furthermore, Phahladira and colleagues (2020) found similar results but also noted that improvement in QOL was slower to improve than other outcome variables (e.g., psychopathology (PANSS core item-total score) and functioning) and only reached statistical significance at the one-year follow-up mark. To our knowledge, no previous research has documented specific improvements over time within separate domains of QOL.

There was also a main effect of Gender for alcohol misuse groups. Similarly, males scored lower on overall QOL, instrumental role QOL, intrapsychic foundations QOL, and common objects and activities QOL. As mentioned previously, a common finding in this area of research is that males have poorer outcomes than females (Thorup et al., 2012). However, unlike the cannabis misuse groups, there was no significant difference between males and females in the interpersonal relations domain. This finding differs from previous research on individuals with FEP, which has shown that females tend to have better social functioning than males

(Thorup et al., 2012). It is possible that our low number of female participants in the sample may have limited the power to find significant differences.

## Global Functioning

### *Cannabis Misuse*

It was hypothesized that those who discontinued cannabis misuse in the first year of treatment would report significantly better global functioning than those who continue to misuse this substance. Our results showed no significant group differences or interactions between any cannabis misuse group on global functioning (GAS); therefore, our hypothesis was not supported. These results are in contrast to previous research that has used a similar classification of course of misuse, and those that did not, as both groups of studies have found significant differences in global functioning scores (Gonzalez-Pinto et al., 2011; Oluwoye et al., 2019; Ouellet-Plamondon et al., 2017; Seddon et al., 2016; Weibell et al., 2017). Possible explanations for the difference in results include that the impact of cannabis misuse has been shown to be dose-dependent, with the concentration of THC being the critical factor in this substance's impact on FEP patient outcome (Ramesh et al., 2013; Zammit et al., 2008). A recent study has shown that the mean THC concentration levels in cannabis and related products have increased significantly over the past ten years in the USA and Europe (Chandra et al., 2019). This increase is likely to be similar in Canada and may also contribute to variations in results. In the current study, cannabis misuse was defined by the frequency of use rather than biological compound, making it difficult to compare study findings without specific information about how much THC was in the cannabis used by our study participants. Although this is a limitation of the current study, it is also a reality of cannabis misuse in the community where THC concentration varies and is not controlled in a laboratory setting.

Other possible explanations for why there were no course of cannabis misuse group differences include the classification of substance misuse course since most studies do not account for the course of substance misuse in their analysis. This method could be argued as a less rigorous classification method since the course of misuse has been shown to impact outcomes (Abdel-Baki et al., 2017; Gonzalez-Pinto et al., 2011; Weibell et al., 2017). Furthermore, previous research has also shown that there are often delays in the appearance of impairment due to the nature of cannabis misuse, as there is often more negative consequences the longer the misuse (Addington & Addington, 2007; Gonzalez-Pinto et al., 2011). Therefore, it is possible that we may have not yet captured the negative impact of cannabis misuse within our follow-up period.

While we did not find any significant group differences between the course of cannabis misuse groups, we did find a significant main effect of Time for overall functioning, indicating that participants improved their functioning over the 24 months. Previous research on patients with FEP in early intervention programs has found similar improvements over time in this area (Caton et al., 2014; Phahladira et al., 2020; Setién-Suero et al., 2017). A likely explanation for some of these improvements is reductions in positive symptoms (i.e., fewer hallucinations, delusions, etc.) due to antipsychotic medication treatment, as assessments of functioning measure illness severity. Previous research has shown that positive symptoms can impact functioning in those with schizophrenia. For example, Racenstein and colleagues (2002) demonstrated that there was a significant relationship between psychotic symptoms and increased impairment in work functioning over ten years in patients with early schizophrenia (follow-up 2 year $r= 0.33$, follow-up 4.5 years $r= 0.39$, follow-up 7.5 years $r= 0.43$, follow-up ten years $r=.43$, all $p<.01$). This means that the more severe psychosis, the less likely for the patient to be functioning

effectively. Therefore, the decrease in positive symptoms experienced by patients in the current study may be related to the increase in global functioning.

*Alcohol Misuse*

It was hypothesized that those participants who discontinued alcohol misuse in the first year of treatment would report significantly better overall functioning (GAS) than those who continue to misuse this substance. Our results showed no significant group differences or interactions between alcohol misuse groups; therefore, our hypothesis was not supported. These results differ from previous research demonstrating that alcohol misuse was associated with poorer functioning at 12 months and 24 months follow-up (Ouellet-Plamondon et al., 2017). Similar to the cannabis misuse results, these differences could be explained by the lack of inclusion of the course of substance misuse. Furthermore, some research has shown that alcohol misuse in patients with psychosis is associated with functional difficulties such as unemployment, housing instability, and family problems (Drake et al., 1996; Koskinen et al., 2010); however, we did not find any significant differences between alcohol misuse groups on employment, housing or marital status. Problems in areas like employment, housing and relationship status are typically indicative of impaired functioning (i.e., inability or difficulty completing everyday activities and integrating themselves into society; Drake et al., 1996; Koskinen et al., 2010); therefore, the lack of any significant differences between alcohol misuse groups in the present study could be the reason why we did not see any differences in functioning between groups.

Similar to cannabis misuse, we did find a significant main effect of Time for overall functioning, indicating that participants improved their functioning over the 24 months. As mentioned above, research on patients with FEP in early intervention programs have found

similar results and demonstrated that the treatment is working (Caton et al., 2014; Phahladira et al., 2020; Setién-Suero et al., 2017).

**Positive and Negative Symptoms**

*Cannabis Misuse*

For symptomatology, it was hypothesized that those participants who discontinued cannabis misuse in the first year of treatment would report significantly lower positive symptoms than those who continue to misuse this substance. It was also hypothesized that there would be no significant changes in negative symptoms for either group. Overall, we found that there were no significant group differences for either positive or negative symptoms. The lack of group differences on positive symptoms with those who misuse cannabis differs from previous research, which has indicated that cannabis misuse is associated with higher positive symptoms over time (Addington & Addington, 2007; Brunette et al., 2018; Oluwoye et al., 2019; Ouellet-Plamondon et al., 2017; Van Mastrigt et al., 2004). Additionally, previous research has shown that continuous cannabis misuse is associated with higher psychotic symptoms than discontinued misuse and those who never misused (Clausen et al., 2014). A possible explanation for these differences is high quantities of other substance misuse confounding the results. For example, the FEP sample from Ouellet-Plamondon and colleagues (2017) contained a high level of stimulant misuse (2% of total sample psychostimulant only, 14% of total sample polysubstance misuse with psychostimulant at baseline). In contrast, our sample had low levels of stimulant misuse (2% of total sample psychostimulant misuse at baseline). While our data was collected over similar periods, our sample may be more reflective of the Canadian trends in drug misuse as cocaine, hallucinogens, and amphetamine substances were less prevalent in Canada (*Canadian Tobacco Alcohol and Drugs (CTADS): 2015 summary*, 2017). Thus, these differences in

substances misused could help explain some of the variations between the current study's findings and other research in this area.

Furthermore, Clausen et al. (2014) found that continued cannabis misuse was associated with more positive symptoms. The differences between the results of the current study (i.e., no association of cannabis misuse with increased positive symptoms) and the study by Clausen et al. (2014) maybe because they have seen significant differences due to the longer follow-up period of five years compared to our two-year follow-up. Research has shown that the negative consequences of cannabis misuse are often seen over more extended periods (Addington & Addington, 2007). It is possible that while we did have an extensive follow-up period, that a longer follow-up period may have captured a significant difference between the course of cannabis misuse groups. Additionally, we found improvements in positive symptoms across all cannabis misuse groups over time. Improvements in positive symptoms are expected because research on antipsychotics has shown that symptoms are often significantly reduced after one year with antipsychotic treatment (Haddad & Correll, 2018; Nuttall et al., 2019).

However, our study results showed no significant differences between groups of course of cannabis misuse on negative symptoms, which was consistent with our hypothesis. These results are consistent with the literature in that it appears that cannabis misuse does not have any effect on negative symptoms in FEP populations (Addington & Addington, 2007; Brunette et al., 2018; Clausen et al., 2014; Oluwoye et al., 2019; Van Mastrigt et al., 2004).

*Alcohol Misuse*

It was hypothesized that those who discontinued alcohol misuse in the first year of treatment would have significantly lower positive symptoms than those who continue to misuse

this substance. We also hypothesized that there would be no significant changes in negative symptoms for either group. Interestingly, we found an impact of alcohol misuse course on positive symptoms with those who continued to misuse alcohol, demonstrating higher levels of positive symptoms than those who discontinued alcohol misuse and those who never misused alcohol. This finding is surprising as most recent research has found that alcohol misuse does not impact positive symptoms (Abdel-Baki et al., 2017; Addington & Addington, 2007; Cetty et al., 2019; Oluwoye et al., 2019; Ouellet-Plamondon et al., 2017). A possible explanation for this result is that it is discouraged to drink alcohol while taking antipsychotics. Patients frequently discontinue antipsychotic medication to drink alcohol, explaining the increase in positive symptoms (Drake & Mueser, 2002).

As was hypothesized, we found no impact of the course of alcohol misuse on negative symptoms. While some research has found no association between negative symptoms and alcohol misuse, others have indicated that alcohol misuse is associated with lower negative symptoms. While this may seem surprising, some have suggested that it could be explained by the social nature of drinking, where alcohol misuse may be higher in those with less social withdrawal (Cetty et al., 2019). Since there is limited research on alcohol misuse in this population, more longitudinal research needs to be conducted before definitive conclusions can be established.

We found a main effect for Time for both positive and negative symptoms across all alcohol misuse groups (i.e., continued alcohol misuse, discontinued alcohol misuse, and no alcohol misuse groups). It is expected that improvements in positive symptoms with appropriate treatment would be found because, as mentioned previously, research on antipsychotics has shown that symptoms are often significantly reduced after one year with antipsychotic treatment

(Haddad & Correll, 2018; Nuttall et al., 2019). Conversely, significant improvements in negative symptoms are not typically seen in those with FEP. A study by Austin and colleagues (2015) has shown that over ten years, negative symptoms remain relatively consistent with poorer negative symptom trajectories associated with schizophrenia; however, there is a portion of individuals with FEP who do see significant reductions in negative symptoms between two to ten years after diagnosis. For example, they reported that poorer social functioning was associated with poorer negative symptom trajectories (OR 1.34-5.55, $p<0.05$). In our sample, alcohol misuse groups reported significant improvements over time in functioning and the interpersonal relations domain on the QLS, which relates to one's ability to socialize and relate to others. Thus, it is possible that the improvements in negative symptoms over time we see in this group are related to the improvements in these areas.

**Strengths and Limitations**

One strength of our study was that it was longitudinal, which allowed us to suggest causal mechanisms within our data. This is an essential feature of our study as there are not enough longitudinal studies in FEP research. Additionally, we examined the effects of the two most misused drugs in this population, as well as their course of misuse. The course of misuse is often not considered in the literature as most previous research has looked at drug misuse as a composite variable or did not account for changes in misuse patterns over time. The course of misuse also allows for the examination of the impact of discontinuing misuse on outcomes. Specifically, whether or not the discontinuation of a substance improves long term outcomes (e.g., QOL, functioning, positive symptoms) or outcomes that are comparable to those who never misused the substance. Furthermore, the utilization of multiple imputations for the missing cases in our sample was another strength of our study. This method allowed us to use a more practical

and conservative assessment of our data because it includes data from all the participants. Finally, our study examined the effect of alcohol misuse, which is rarely explored in the literature. Given the accessibility of alcohol, and the high rate of misuse in the FEP population, more attention to the negative impact of this drug should be addressed in future research.

While our study addressed some significant limitations of previous work, some improvements could be made in future work. First, while our study did utilize multiple imputations to manage missing data, we did use the median imputation for our statistical values. This method is less rigorous than calculating the pooled values across all ten imputations; however, it closely approximates the pooled effect. Second, our study was limited by the low sample sizes within the substance misuse groups and the high number of uncorrected statistical tests conducted. These limitations reduced our power and increased our probability of making at least one type 1 error. Third, dichotomizing substance misuse to categorize participants by substance misuse pattern and not including patients with episodic misuse (e.g., only misusing at one time point) could have also made it less likely to pick up on nuanced results.

Additionally, our study relied on self-report of drug misuse, which may have been affected by social desirability; however, the PIER program does not refuse treatment to patients with comorbid substance misuse issues, and there was no adverse consequence for patients who misused any substance (i.e., a harm reduction approach to treatment), which could increase the likelihood of valid self-reports. Also, our study did not include data on medication adherence or patient engagement in the program which presents another possible limitation given the consequences of medication non-adherence and its association with substance misuse. Furthermore, like other longitudinal studies with FEP populations, the current study had some attrition; however, imputing the values for missing cases using multiple imputations is an

effective method for dealing with dropouts while maintaining power. Moreover, our study did not address those who misused both alcohol and cannabis (i.e.,, polysubstance misuse), and it is possible for different combinations of substances to cause different impacts on outcomes. Finally, the current study measures the frequency of use rather than a biological measurement that would have provided insight into whether the dosage of substances impacted the findings. Previous research has shown a dose-dependent relationship for cannabis misuse as the concentration of THC is a critical factor in determining its impact on patient outcomes (e.g., positive symptoms; Ramesh et al., 2013; Zammit et al., 2008).

## Conclusions

This study contributes to understanding the variation in clinical and functional outcomes in individuals with FEP who misuse cannabis and alcohol. This study highlights the importance of considering the clinical implications of alcohol misuse as we found that continued alcohol misuse was associated with more positive symptoms. Most of the research on substance misuse in patients with FEP has focused on cannabis with limited information on the impact of alcohol misuse. Furthermore, this study demonstrates the importance of examining the course of substance misuse on FEP outcomes. This study has shown differences between those individuals who continue to misuse alcohol, who discontinue misuse of alcohol during treatment and those who never misused alcohol. The current findings suggest support for the prevalence of alcohol misuse in this population and the potential barrier to positive symptom remission. However, the effect sizes for this evidence are small, thus further research is needed to test the replicability of these results.

**Clinical Implications**

This study supports substance misuse treatment to be added as a component of FEP programs and treatment. Our findings show that alcohol misuse does impact outcomes in this population. Moreover, if the patient discontinues alcohol misuse, their outcomes are similar to their peers who never misused. Thus, targeting these behaviours should be a priority to help give the best possible outcomes to patients with FEP. Additionally, these findings of this study show that it is possible that the impact of cannabis misuse on symptomatology, QOL and functioning is not as prominent as the literature has suggested. Alternatively, it is also possible that the impact of cannabis misuse on these outcomes isn't apparent until after the 2-year mark of misuse. Furthermore, this study highlighted that this FEP program did improve functional and QOL outcomes over time. While this study did not find any group differences of course of misuse on these outcomes, it is still essential for first episode intervention programs to ensure improvements in QOL and functioning are targeted treatment goals.

**Future Research**

Future research should also include qualitative methodology to inform how patients with FEP manage their alcohol usage with the negative interaction with antipsychotic medications. Using a harm reduction model, the psychiatrists in the early intervention program warn patients with FEP that they should not drink alcohol with the antipsychotic. A possible avenue of research in the future will be to examine if the individual prioritizes alcohol over their antipsychotic medication by ceasing the antipsychotic when they plan to consume alcohol. This line of research would clarify whether the significant relationship between alcohol misuse and increased positive symptoms was associated with the subgroup of patients that misused alcohol or if these patients stopped taking their antipsychotic medication to consume alcohol leading to

relapse in positive symptoms. Future research should include qualitative interviews with patients better to understand their perspectives on their quality of life.

Additionally, future research should include the measurement of tobacco misuse as some new research by Oluwoye and colleagues (2019) has shown that it has been associated with greater illness severity, more missed pills, more psychiatric symptoms and lower QOL compared to patients with FEP who do not smoke. Future research should also consider using other measures of substance misuse (such as biological measures) to corroborate self-report measures of substance misuse. This would help ensure the accuracy of reported misuse and help with the classification of course of misuse. Finally, future research should consider using larger sample sizes to ensure a more diverse sample (particularly to ensure female representation) and assessing the potential impacts of polysubstance misuse in longitudinal study design.

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**Figure 1**

*Scores on Positive Symptoms by Alcohol Course over Time*

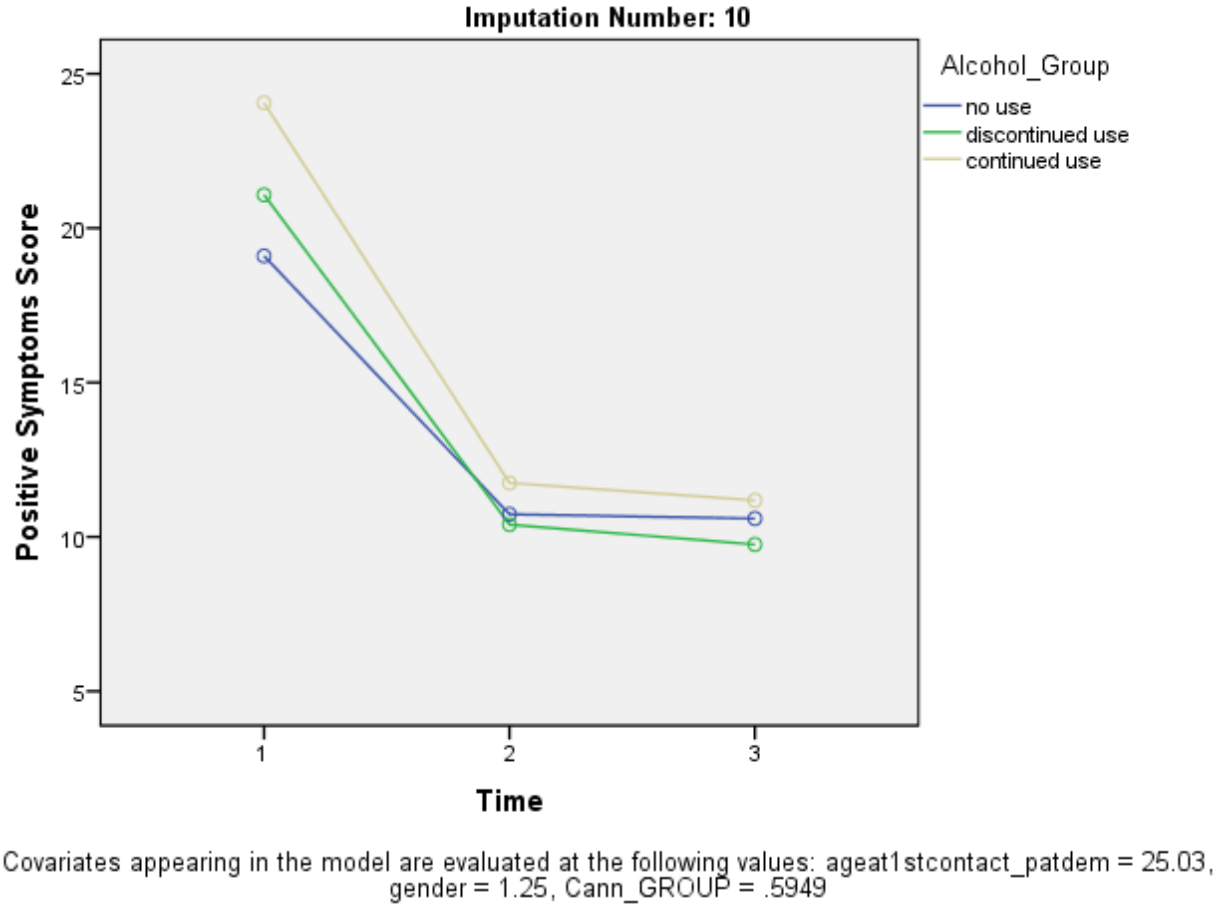

**Table 1**

*Missing Data for Outcome Variables at Each Time Point*

| Outcome | Baseline (%) | 12 Months (%) | 24 Months (%) |
|---|---|---|---|
| TQOL | 1.1 | 44 | 56 |
| Intrapsychic Foundations | 1.1 | 44 | 56 |
| Interpersonal Relations | 1.1 | 44 | 56 |
| Instrumental Role | 1.1 | 44 | 56 |
| Common Objectives and Activities | 1.1 | 44 | 56 |
| GAS | 0.5 | 43 | 53 |
| Positive Symptoms | 0.5 | 45 | 56 |
| Negative Symptoms | 2.1 | 46 | 57 |

* $n$ = 189

**Table 2**

*Demographic and Outcome Variables by Cannabis Misuse at Baseline*

| | No misuse | Discontinued Misuse | Continued Misuse | Statistic & p-value |
|---|---|---|---|---|
| Age (*N* =170) | 27.72 (10.03) | 22.22 (4.91) | 21.71 (4.23) | $F(2,169) = 10.395$, $p < .001$ |
| Gender | | | | $\chi^2(2, N = 180) = 13.279$, $p = .001$ |
| Male | 69 | 46 | 21 | |
| Female | 36 | 5 | 3 | |
| Ethnicity | | | | $\chi^2(6, N = 176) = 5.046$, $p = .538$ |
| Caucasian | 96 | 38 | 32 | |
| Asian | 2 | 0 | 1 | |
| Black | 3 | 1 | 0 | |
| Other | 2 | 2 | 1 | |
| Education | | | | $\chi^2(4, N = 176) = 7.818$, $p = .098$ |
| Some High Sch. | 66 | 32 | 24 | |
| Some Post-Sec. | 33 | 7 | 8 | |
| Other | 3 | 0 | 3 | |
| Housing | | | | $\chi^2(8, N = 92) = 14.445$, $p = .071$ |
| With Family | 35 | 19 | 9 | |
| With Spouse | 6 | 1 | 0 | |
| Ind. Housing | 15 | 1 | 3 | |
| Sup. Housing | 2 | 0 | 0 | |
| Other | 0 | 0 | 1 | |

| | No Misuse | Discontinued Misuse | Continued Misuse | Statistic & p-value |
|---|---|---|---|---|
| Marital Status | | | | $\chi^2(6, N = 177) = 5.748, p = .452$ |
| Single | 90 | 36 | 32 | |
| Married | 11 | 1 | 1 | |
| Common-law | 2 | 0 | 1 | |
| Widowed | 0 | 0 | 0 | |
| Divorced/Sep. | 2 | 0 | 1 | |
| Employment | | | | $\chi^2(6, N = 175) = 8.082, p = .232$ |
| Employed | 24 | 5 | 6 | |
| Unemployed | 55 | 24 | 20 | |
| School | 11 | 3 | 0 | |
| Other | 12 | 9 | 6 | |
| Diagnosis | | | | $\chi^2(6, N = 92) = 1.264, p = .974$ |
| Schizoaffective Disorder | 16 | 6 | 4 | |
| Schizophrenia | 41 | 15 | 10 | |
| PANSS Positive ($N$ =173) | 19.78 (6.56) | 21.45 (5.67) | 22.81 (4.74) | $F(2,172) = 3.621, p = .029$ |
| PANSS Negative ($N$ =174) | 18.30 (5.74) | 17.22 (5.69) | 19.94 (6.98) | $F(2, 173) = 1.995, p = .139$ |
| GAS ($N$ =170) | 46.52 (14.08) | 38.83 (14.55) | 43.68 (12.09) | $F(2, 169) = 4.086, p = .019$ |
| TQOL ($N$ =173) | 64.51 (21.22) | 65.06 (21.22) | 62.28 (21.90) | $F(2, 172) = 0.183, p = .833$ |

**Table 3**

*Demographic and Outcome Variables by Alcohol Misuse at Baseline*

| | No misuse | Discontinued Misuse | Continued Misuse | Statistic & p-value |
|---|---|---|---|---|
| Age ($N$ =180) | 27.09 (9.50) | 24.81 (7.08) | 22.22 (6.03) | $F$ (2,179) = 5.056, $p$ =.007 |
| Gender | | | | $\chi^2$ (2, $N$ = 172) = 7.338, $p$ =.026 |
| Male | 64 | 35 | 29 | |
| Female | 32 | 5 | 7 | |
| Ethnicity | | | | $\chi^2$(6, $N$ = 172) = 5.680, $p$ = .460 |
| Caucasian | 95 | 32 | 35 | |
| Asian | 3 | 0 | 0 | |
| Black | 4 | 0 | 0 | |
| Other | 1 | 1 | 1 | |
| Education | | | | $\chi^2$(4, $N$ = 180) = 4.339, $p$ = .362 |
| Some High Sch. | 72 | 27 | 24 | |
| Some Post-Sec. | 34 | 8 | 9 | |
| Other | 2 | 3 | 1 | |
| Housing | | | | $\chi^2$(8, $N$ = 179) = 8.211, $p$ = .325 |
| With Family | 63 | 22 | 30 | |
| With Spouse | 10 | 4 | 1 | |
| Ind. Housing | 29 | 3 | 9 | |
| Sup. Housing | 3 | 1 | 1 | |
| Other | 2 | 1 | 0 | |

| | No Misuse | Discontinued Misuse | Continued Misuse | Statistic & p-value |
|---|---|---|---|---|
| Marital Status | | | | $\chi^2(6, N = 180) = 5.113, p = .529$ |
| Single | 94 | 26 | 39 | |
| Married | 9 | 4 | 1 | |
| Common-law | 3 | 0 | 0 | |
| Widowed | 0 | 0 | 0 | |
| Divorced/Sep. | 2 | 1 | 1 | |
| Employment | | | | $\chi^2(6, N = 165) = 8.878, p = .181$ |
| Employed | 19 | 10 | 5 | |
| Unemployed | 55 | 22 | 18 | |
| School | 12 | 1 | 2 | |
| Other | 12 | 6 | 7 | |
| Diagnosis | | | | $\chi^2(4, N = 89) = 1.717, p = .788$ |
| Psychotic Disorder NOS | 11 | 3 | 6 | |
| Schizoaffective Disorder | 12 | 5 | 4 | |
| Schizophrenia | 31 | 8 | 9 | |
| PANSS Positive ($N$ =179) | 20.14 (6.36) | 21.63 (6.10) | 19.58 (5.17) | $F(2,179) = 1.303, p = .274$ |
| PANSS Negative ($N$ =175) | 19.01 (5.58) | 16.30 (6.10) | 18.44 (7.13) | $F(2, 174) = 3.101, p = .067$ |
| GAS ($N$ =170) | 47.39(13.54) | 41.93 (16.88) | 44.54 (12.28) | $F(2, 169) = 2.324, p = .101$ |
| TQOL ($N$ =177) | 63.10(21.23) | 65.72 (18.56) | 63.11 (26.55) | $F(2, 176) = 0.217, p = .805$ |

**Table 4**

*Substance Misuse at Baseline and Follow-Ups*

| | Baseline | 12-months | 24-months |
|---|---|---|---|
| Alcohol | 31.7 (60) – 32.8 (62) | 18.0 (34) – 30.7 (58) | 14.3 (27) – 34.4 (65) |
| Cannabis | 36.0 (68) | 10.6 (20) – 19.6 (37) | 11.6 (22) – 28.0 (53) |
| Cocaine | 4 (2.1) | 0 (0) | 1.1 (2) – 3.2 (6) |
| Stimulants | 1.1 (2) | 0 (0) | 0.5(1) |
| Narcotics | 0.5 (1) | 0.5 (1) | 0 (0) |
| Hallucinogens | 3.7 (7) – 4.2 (8) | 0 (0) | 0 (0) |
| Sedatives | 1.1 (2) | 0 (0) | 0.5 (1) |
| Other Drugs | 1.1 (2) | 0.5 (1) | 0.5 (1) – 1.1 (2) |

Presented in ranges from least to greatest across imputations - %(N)

**Table 5**

*ANCOVA Table for Cannabis Misuse*

| | TQOL | Intrapsychic Foundations | Interpersonal Relations | Instrumental Role | Common Objects & Activities | GAS | Positive Symptoms | Negative Symptoms |
|---|---|---|---|---|---|---|---|---|
| Time | 3.712 (.027*) | 1.262 (.286) | 5.309 (.006*) | 5.665 (.004*) | 2.670 (.072) | 10.327 (<.001**) | 6.593 (.002*) | 1.187 (.313) |
| Time x Group | 0.562 (.690) | 1.181 (.319) | 1.287 (.275) | 0.845 (.495) | 0.542 (.705) | 0.773 (.545) | 1.439 (.226) | 2.334 (.055) |
| Group | 0.800 (.451) | 2.001 (.139) | 1.287 (.275) | 0.258 (.773) | 1.058 (.350) | 0.529 (.590) | 0.564 (.570) | 2.861 (.060) |

*Note.* F(p), * <.05, **<.001
Covariates of age at entry, gender, and course of alcohol misuse.

**Table 6**

*ANCOVA Table for Alcohol Misuse*

| | TQOL | Intrapsychic Foundations | Interpersonal Relations | Instrumental Role | Common Objects & Activities | GAS | Positive Symptoms | Negative Symptoms |
|---|---|---|---|---|---|---|---|---|
| Time | 5.127 (.007)* | 1.827 (.164) | 6.430 (.002)* | 7.214 (.001)* | 4.750 (.010)* | 12.727 (<.001)** | 12.478 (<.001)** | 3.327 (.039)* |
| Time x Group | 0.864 (.486) | 2.178 (.071) | 0.656 (.623) | 1.146 (.335) | 1.000 (.377) | 1.321 (.262) | 1.418 (.228) | 1.677 (.161) |
| Group | 0.150 (.869) | 1.043 (.355) | 0.399 (.672) | 0.480 (.619) | 0.253 (.777) | 0.550 (.578) | 3.107 (.048)* | 1.466 (.052) |

*Note.* F(p), * <.05, **<.001
Covariates of age at entry, gender, and course of cannabis misuse

## Appendix 1

**Table 1**

*Studies that Examine Substance Misuse on Outcome Variables of Psychotic Symptoms, Functioning, QOL, and Relapse*

| Study | Population % non-affective (N) | factor | Treatment outcomes | | | | |
|---|---|---|---|---|---|---|---|
| | | | Positive | Negative | Function | QoL | Relapse |
| Abdel-Baki et al., 2017 | 77.3 (212) | PS: N/A | | | | | |
| | | CV: Grouped patients into one of 3 groups: persistent substance use disorder, stopped substance use, and no substance use. | Persistent substance use disorder at 1- and 2-years follow-up had more positive symptoms compared to those without a substance use disorder on the PANSS scale. | Persistent substance misuse disorder at 1- and 2-years follow-up had more negative symptoms compared to those without a substance use disorder on the PANSS scale. | Persistent substance misuse disorder at 1- and 2-years follow-up had worse functioning compared to those without a substance use disorder on the Social and Occupational Functioning Assessment scale. | Persistent substance misuse disorder at 1- and 2-years follow-up had worse QOL compared to those without a substance use disorder on the QLS scale. | The number of hospitalization days over 2 years was significantly more in those with persistent substance use disorders. |
| | | Alc: N/A | | | | | |
| | | Can: N/A | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Addington and Addington, 2007 | 91.7 (203) | PS: N/A | | | | | |
| | | CV: N/A | | | | | |
| | | Alc: Used the Case Manager Rating Scale to dichotomize misuse: none or mild use was no misuse and moderate to extremely severe was coded as misuse. | No difference between those who misused and those who did not misuse. | No difference between those who misused and those who did not misuse. | N/A | No difference between those who misused and those who did not misuse. | N/A |
| | | Can: Used the Case Manager Rating Scale to dichotomize misuse: none or mild use was no misuse and moderate to extremely severe was coded as misuse. | Significantly higher positive symptoms for those who misused compared to those who did not misuse at 1 year, 2 years and 3 years follow-up on PANSS. | No difference between those who misused and those who did not misuse on PANSS. | N/A | Significantly lower scores on QOL for those who misused compared to those who did not misuse on the QLS scale. | N/A |
| Cetty et al., 2019 | 75.6 *(280) | PS: N/A | | | | | |
| | | CV: N/A | | | | | |
| | | Alc: Hazardous alcohol use was | No difference between those who misused | Hazardous alcohol use was associated with | No difference between those who misused | Hazardous alcohol misuse was found to | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | measured using the 10-item brief screening instrument: the Alcohol Use Disorders Identification Test (AUDIT). A total score of 8 and above was used in the present paper to ascertain hazardous alcohol use. | and those who did not. | lower negative symptoms compared to those who did not misuse alcohol. | and those who did not. | predict three out of four domains of QOL on the World Health Organization Quality of Life -BREF scale (physical health, social relationships, and environment domains). The physical health domain relates to pain, energy levels, mobility, sleep and capacity for daily living activities. The social relationship domain has to relate to satisfaction with personal relationships and social support. The environment domain relates | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | to the home environment, access to transport, opportunity for leisure activities, satisfaction with finances, and access to health services. | |
| | | Can: N/A | | | | | |
| Clausen et al., 2014 | 100* (314) | PS: N/A | | | | | |
| | | CV: N/A | | | | | |
| | | Alc:N/A | | | | | |
| | | Can: Use of cannabis was assessed using Schedule for Clinical Assessment in Neuropsychiatry (SCAN) interviews. patients were divided into four groups: (1) abstainers – no use of cannabis at baseline and at 5-year follow-up; (2) stoppers | Those who continued cannabis misuse scored higher on the Scale for the Assessment of Positive Symptoms (SAPS), meaning they experienced more positive symptoms. | There was no difference between groups on the Scale for the Assessment of Negative Symptoms (SANS). | Those who continued cannabis misuse had lower scores on the Global Assessment of Functioning (GAF). | N/A | No difference between groups in the number of hospital days during the first 5 years. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | – stopped cannabis use within the last 5 years; (3) starters – started cannabis use within the last 5 years; and (4) continuers – continued use of cannabis throughout the 5 years | | | | | |
| Cookey et al., 2020 | 100* (264) | PS: The World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) was Used to determine misuse. A score 4 or more for alcohol and 2 or more for cannabis was used to code as polysubstance misuse. | No significant difference (measured by PANSS). | No significant difference between groups (measured by PANSS). | Significant difference between groups. Those who misused alcohol and cannabis has the second highest scores on social functioning on the Social and Occupational Functioning scale. | N/A | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | CV: N/A | | | | | |
| | | Alc: The World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) was Used to determine misuse. A total specific substance score cutoff of greater than or equal to 11 is used to code those as misusing the substance. | The lowest positive symptom scores on PANSS compared to those with low to no misuse, those who misused cannabis, and those who misused cannabis and alcohol. | No significant difference between groups (measured by PANSS). | Significant between group difference on social functioning with those who misused alcohol having the highest scores on the Social and Occupational Functioning scale. | N/A | N/A |
| | | Can: The World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test | Significantly higher positive symptoms than the alcohol misuse group on PANSS scale. | No significant difference between groups (measured by PANSS). | Significant between group difference on social functioning with those who misused cannabis having the | N/A | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | (WHO-ASSIST) was Used to determine misuse. A total specific substance score cutoff of greater than or equal to 4 is used to code those as misusing the substance. | | | lowest scores on the Social and Occupational Functioning scale. | | |
| Gonzalez-Pinto et al., 2011 | Unknown (92) | PS: N/A | | | | | |
| | | CV: Grouped all other drugs misused together except for alcohol and cannabis. | Stopping other drug use did not have a significant effect on positive symptoms (as measured by PANSS). | Stopping other drug use did not have a significant effect on negative symptoms (as measured by PANSS). | Other drug use had a significant effect on GAF score (as measured by the Global Assessment of Functioning Scale). This indicated that stopping other drug use improved functioning. | N/A | N/A |
| | | Alc: Misuse was measured by the Addiction Severity Inde.g., | Alcohol misuse did not affect positive symptoms | Alcohol misuse did not affect negative symptoms | Showed that alcohol misuse had a significant | N/A | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | (measured by PANSS). | (measured by PANSS). | effect on GAF score (as measured by the Global Assessment of Functioning Scale), indicating that ceasing alcohol misuse improved functioning. | | |
| | | Can: Created 3 groups based on course of misuse – continued misuse of cannabis, discontinued misuse of cannabis (those who discontinued during follow-up) and those who never misused cannabis. Misuse was measured by the Addiction Severity Inde.g., | All three groups showed significant improvements (reductions) in PANSS positive symptoms scores. | Significant improvement (reduction) in PANSS negative scores in the discontinued misuse group only. | The discontinued misuse group showed significant improvement (increase) in GAF score (as measured by the Global Assessment of Functioning Scale. This improvement was more than that of the no misuse group. | N/A | The mean number of hospitalizations did not differ between groups. |

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| Leeson et al., 2012 | 89 (99) | PS: | | | | | |
| | | CV: | | | | | |
| | | Alc: | | | | | |
| | | Can: Information on substance use was obtained using the semi structured interview within the Diagnostic Interview for Psychosis-Diagnostic Module. Cannabis use was classified as nonusers, high-frequency user (defined as daily or almost daily use) and low-frequency users (habitual use). | Symptoms improved over time and did not differ between groups over the two years (measured by PANSS). | Symptoms improved over time and did not differ between groups over the two years (measured by PANSS). | N/A | N/A | Groups did not differ on the number of days spent in hospital during the index at admission or total during the first two years of illness. |
| Oluwoye et al., 2019 | 80 (404) | PS: | | | | | |
| | | CV: | | | | | |
| | | Alc: Self-reported current use. | No significant difference between those who misused and those who never misused as measured by | No significant difference between those who misused and those who never misused as measured by | N/A | No significant difference between those who misused and those who never misused (measured by | N/A |

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| | | | the PANSS Scale. | the PANSS Scale. | | the QLS scale). | |
| | | Can: Self-reported current use. | Cannabis misusers had significantly higher positive symptoms compared to non-users as measured by the PANSS Scale. | No significant difference between those who misused and those who never misused as measured by the PANSS Scale. | N/A | No significant difference between those who misused and those who never misused (measured by the QLS scale). | N/A |
| Ouellet-Plamondon et al., 2017 | 67* (176) | PS: Grouped by poly-substance use disorder (poly-SUD), which included those with at least two SUD [alcohol and drug(s) or at least two different drugs]. | At baseline, no differences between groups. At 1 year follow-up but not 2 years, those in the poly-group had higher positive symptoms than those who did not misuse (measured by PANSS). | At baseline, no differences between groups. At the 1 year and 2-year follow-up, those in the poly-group had increased negative symptoms compared to those who did not misuse (measured by PANSS). | At baseline, no differences between groups. At the 1 year and 2-year follow-up, those in the poly-group had lower GAF scores compared to those who did not misuse (measured by Global Assessment of Functioning Scale). | Compared to the no misuse group, the poly-group had lower QOL scores. At the 1 year and 2-year follow-up, those in the poly-group had lower QOL scores compared to those who did not misuse (measured by QLS). | At 1- and 2-years follow-up, those in the poly-group had more hospitalizations than those who did not misuse. |
| | | CV: N/A | | | | | |
| | | Alc: Participants were grouped by | No differences between | No differences between groups | At baseline, no differences | At baseline, no differences | At 2 years follow-up, |

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| | | substance use disorder (SUD) status: 'no-SUD', 'Alcohol use disorder' (AUD), which included those who had AUD only and not another SUD. | groups (measured by PANSS). | (measured by PANSS). | between groups. At 1 year follow-up, those who misused alcohol had lower GAF scores (measured by the Global Assessment of Functioning Scale). | between groups. At 1 year follow-up, those who misused alcohol had lower QOL scores (measured by the QLS). | those who misused alcohol had more hospitalization than those who did not misuse. |
| | | Can: Participants were grouped by substance use disorder (SUD) status: 'no-SUD', Cannabis use disorder (CUD) | At baseline, no differences between groups. At the two-year follow-up, compared to those who did not misuse, those who continued to misuse cannabis had increased positive symptoms (as measured by PANSS). | No differences between groups (as measured by PANSS). | Compared to the no misuse group, the cannabis-group had lower GAF scores as measured by the Global Assessment of Functioning scale. At the two-year follow-up, compared to those who did not misuse, those who continued to misuse cannabis had | At the two-year follow-up, compared to those who did not misuse, those who continued to misuse cannabis had lower QOL (as measured by QLS). | No differences between groups. |

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| | | | | | lower GAF scores. | | |
| Seddon et al., 2016 | 89* (1027) | PS: N/A | | | | | |
| | | CV: N/A | | | | | |
| | | Alc: N/A | | | | | |
| | | Can: Current substance use was defined as any use of drugs within the previous 3 months as assessed by a revised version of the Kavanagh Drug Check scale | The use of cannabis at baseline or at the 12-month assessment was associated with significantly higher positive symptoms (measured by PANSS). | Continued misuse of cannabis was associated significantly greater PANSS negative symptoms. | The use of cannabis at baseline or at the 12-month assessment was associated with significantly lower GAF scores (measured by Global Assessment of Functioning Scale). Continued misuse of cannabis was associated significantly lower GAF scores. | N/A | N/A |
| Wade et al., 2007 | 75 (92) | PS: N/A | | | | | |
| | | CV: Coded as heavy substance use disorder, mild substance use disorder, no | Heavy substance use disorder had significantly more severe | Heavy substance use disorder was not associated with negative symptoms | Heavy substance use disorder had significantly poorer social | Heavy substance use disorder was not associated with QOL | |

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| | | substance use disorder using the Case Manager Rating Scale and DSM-IV diagnosis of substance use disorder. | positive symptoms compared to mild substance use disorder and no substance use disorder at 15-months when controlling for durations of untreated psychosis, gender, and medication adherence (as measured by PANSS). | compared to mild substance use disorder but not compared to no substance use disorder when controlling for durations of untreated psychosis, gender, and medication adherence (as measured by PANSS). | functioning compared to mild substance use disorder and no substance use disorder when controlling for durations of untreated psychosis, gender, and medication adherence (as measured by SOFAS). | compared to mild substance use disorder and no substance use disorder when controlling for durations of untreated psychosis, gender, and medication adherence (as measured by the QLS). | |
| | | Alc: N/A | | | | | |
| | | Can: N/A | | | | | |
| Weibell et al., 2017 | 86*(266) | PS: | | | | | |
| | | CV: Substance and alcohol use were measured by the Alcohol and Drug Use Scale. Patients were grouped into one of four groups: nonusers, stop-users (discontinued | Nonusers and stopped users statistically predicted overall lower positive symptoms scores compared to persistent users across 10 years | No significant group differences (measured by PANSS). | Across 10 years, the non-users and stopped users had significantly lower GAF symptoms compared to the persistent user groups. However, GAF | N/A | Episodic users spent the most time hospitalized, which was significantly longer than the non-user group. |

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| | | misuse), episodic users, and persistent users. All commonly used illegal psychoactive substances were included. Alcohol was classified as a separate variable and used as a covariate. Tobacco was not included. | (measured by PANSS). | | functioning was significantly higher in the non-user and stopped user groups compared to the persistent user group (measured by the Global Assessment of Functioning Scale). | | |
| | | Alc: N/A | | | | | |
| | | Can: N/A | | | | | |

* Includes an unknown number of schizoaffective patients
PS: Polysubstance misuse
CV: Composite variable substance misuse
Alc: Alcohol misuse
Can: Cannabis misuse