PREVALENCE OF MOOD SYMPTOMS IN PATIENTS WITH CANNABIS USE ADMITTED TO THE ACUTE WARDS AT FREE STATE PSYCHIATRY COMPLEX WITH SCHIZOPHRENIA SPECTRUM AND RELATED DISORDERS

BY

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SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS IN RESPECT OF THE MASTER'S DEGREE (MMED) IN THE DEPARTMENT OF PSYCHIATRY IN THE FACULTY OF HEALTH SCIENCES AT THE UNIVERSITY OF THE FREE STATE

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DECLARATION OF AUTHORSHIP

I, Mmatjlata Thalita Pooe, declare that the coursework Master's Degree mini-dissertation and interrelated publishable article that I herewith submit for the degree in MMed (Psychiatry) at the University of the Free State are my own independent work and that I have not previously submitted it for a qualification at another institution of higher education. Where help was sought, it has been acknowledged.

I, Mmatjlata Thalita Pooe, hereby declare that I am aware that copyright of this mini-dissertation is vested in the University of the Free State.

I, Mmatjlata Thalita Pooe, hereby declare that all royalties in relation to intellectual property that was developed during the course of and/or in connection with the study at the University of the Free State will accrue to the University.

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DR MT POOE DATE

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ABSTRACT

Keywords: Cannabis, mania, depression, psychosis, hypomania, prospective study, Free State Psychiatric Complex, Bipolar mood disorder, major depressive disorder, acute

Background: Cannabis is the most commonly used drug among psychotic patients. Literature shows that the frequency and intensity of cannabis use, is a risk-factor for the development of schizophrenia-related psychosis. However, evidence for causality of mood disorders remain conflicting.

Aim: The purpose of this study was to compare the prevalence and severity of mood symptoms in patients with schizophrenia spectrum and related disorders with comorbid cannabis use and those that does not use cannabis.

Setting: This study was conducted in patients with schizophrenia spectrum and related disorders admitted at the acute wards at the Free State Psychiatric complex.

Methods: A prospective study was conducted among 30 non- cannabis users and 40 cannabis users. The Young Mania Rating Scale (YMRS)and Hamilton Depression (HAM-D) rating scale for depression was administered within three days of admission and repeated after 7-14 days.

Results: Among cannabis users, symptoms compatible with mania like symptoms was significantly more prevalent shortly after admission with ($p<0.01$). However, this difference declined to non-significance after 7 – 14 days with no clinical separation between the groups.

Conclusion: Seventy-five percent of schizophrenia spectrum and related disorders patients that used cannabis, scored ≥18 on the YMRS shortly after admission. Mania like symptoms were of mild-moderate severity. The study indicated a possible association between cannabis use and higher scores on the YMRS rating scale during the early phase of treatment. A causal link between mood symptoms and cannabis use could not be established and confounding factors were not excluded.

LIST OF ABBREVIATIONS

BD	Bipolar disorders
CEO	Chief Executive Officer
CNS	Central nervous system
DOH	Department of Health
FSPC	Free State Psychiatric Complex
DD	Depressive disorder
HAMD	Hamilton depressive rating scale
HOD	Head of Department
HSREC	Human Sciences Research Ethics Committee
PNS	Peripheral nervous system
YMRS	Young mania rating scale
Δ-9-THC	Delta-9-tetrahydracarbinnol

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LITERATURE REVIEW

1.1 INTRODUCTION

Cannabis was noted as one of the four frequently used illegal psychoactive substance around the world among adults after caffeine, alcohol and nicotine in the USA. Its use was around 19 million people in 2012 [4]. It is viewed as a drug that leads the user on to more addictive or dangerous drugs[2]. It was further classified as a frequent used illegal drug, after cocaine and ecstasy, in about (4) million people that use drugs[15]. In 2014, Colorado became the first state in the United State to legalise the cannabis for recreational purposes[3].

In South Africa, the Constitutional Court has decriminalised the use of cannabis for adults which can be used in their own private space[14]. However, using cannabis outside its allocated area and purchasing and trading still remain prohibited [13].

The Medical Research Council (MRC) conducted a longitudinal research study which reported 2.2 million cannabis users in 2004 and 3.2 million users in 2008 respectively across South Africa [12]. While in 2003, South Africa was rated by Interpol as the fourth biggest producers of cannabis around the globe, whereas the institute for Security Studies had assessed cannabis to have been mostly seized in the United Kingdom (UK) and on a global scale, the South origin was placed third[10].

Cannabis grows in almost every country in the world, but is not indigenous to Southern Africa[17]. However, it grows well in the South African`s climate[11].

The world use of cannabis was estimated at 192 million people worldwide in 2016 and about 3.9% of that global population was aged between 15 and 64 years of age[17]. The use of cannabis has increased over the past decade and more than 50% of adults are using it frequently[1]. In 2016, its usage was initiated by 2.6 million people of which 46% was from the age groups, ranging between 12 to 17 year olds [17].

According to American Diagnostic Association (APA) noted in the Diagnostic and

Statistical Manual of Mental Disorders, fourth edition (DSM IV) that the rates of cannabis abuse and cannabis dependence combined, which in DSM V is changed to cannabis use disorder, which rated around 3.4% and 1,5% among 12-17 years old and 18 years and older respectively[1]. The prevalence of cannabis use disorder, decreases with an increase in age. The highest rate of cannabis use disorder is 4.4% among 18-29 year olds and lowest amongst 65 years old and above[1]. The high rate of cannabis use disorder, explains why cannabis is considered as a frequent drug used illegal, in comparison to other drugs [1].

Chapman C, et al and Johnson RM et al, studies have shown that previously, the rate of cannabis use and that of cannabis use disorders has been more prevalent in men compared to women[6]. However recent studies show, more increase of cannabis use amongst female as compared to men[6]. According to Pacek et al there might have been several factors that contributed to higher use among women, such as legalisation, medical use of marijuana and a low risk associated with cannabis use[6].

Across ethnical subgroups within the United States, prevailing of cannabis use disorder, in 12 months differed moderately[1]. The race and ethnicity related to marijuana use, differ by age groups [4]. Looking at the ages 12 to 17 and 17 to 34, whites had a higher life time prevalence than Blacks. But above those who are 35 years and older, the prevalence is the same for both whites and Blacks [4]. It is more common amongst mixed race than African natives and American natives, with the African American classified the lowest [17]

The prevalence of cannabis use, amongst unemployed is 7.5% and that of part-time workers is 11.6 %, which is higher than those that are employed and those that are not on the labour market like students, retired and disabled [17]. However, the prevalence among college graduates, is lower at 6%, compared to those with less education at 8.3% to 11.3%[17]. There is a two threefold greater prevalence observed among adolescent with school experience [17].

The hemp plant, cannabis sativa has been refined and plowed for its psychoactive properties for over 2000 years and it was reported to cause mind altering effects [2].This plant can be described into two forms, which are male and female. Cannabis is the dried female flower of *Cannabis Sativa*[17]. The female form has the majority concentration of the cannabinoids, which are about 60 in number and this are unique to the Sativa plant [4]. It further contains several psychoactive substances, with the most significant one being the Delta-9-

tetrahydrocannabinol (Δ-9-THC)[4]. The content of the Δ-9-THC in the flower of the Sativa Plant is about 2mg and 5mg, and that in the bud is about 20mg of the content of harshish, which is the stronger extraction of cannabis plant[4]. There are still more stronger types of cannabis that have become available such as super skunk [4]. In South Africa," Swazi" is the most potent form [2].

Across the world, many names are commonly used for cannabis, e.g. Grass, Mary-jane, marijuana, pot, weed, and tea[4]. It can also be described by various strength type, which include chasra, hemp, dagga, ganja and sinsemila[4]. For the purpose of this study, all of the above-mentioned names and strength is included under the name, cannabis, which is the generic term.

The method of use for cannabis include smoking, sometimes in pipes or water pipe and at times as loosely rolled cigarette and it is called "joint" or "zol". Some brew it in tea or mix it with baked products and often unsuspecting individuals may suffer adverse effects unknowingly after consumption. [4].

When cannabis is smoked, there is 18% bio-availability of the Δ - 9 – THC and while 6% can be found in cakes[22]. This Δ – 9 – THC bind itself to Cannabinoid receptors found in the Nervous system [22].

The cannabinoid receptors are part of the components of endocannabinoid system (ECS) which are found in many areas around the human body, and play a significant role in the central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults[5].

There are two (2) cannabinoid receptors, CB1 and CB2 which are found within the Central Nervous System (CNS) and Peripheral Nervous System (PNS) respectively. The CB1 receptors mediates most of the cannabinoids in the central nervous system, while the CB2 mediates the peripheral nervous system. The CB1 receptor is a G-Protein coupled and is the most abundant in mammalian brain [22].

The highest concentration of the cannabinoid receptors is located in the basal ganglia, hippocampus and cerebellum, with fewer concentration around the cortex[4]. These receptors

are not located around the brainstem, therefore cannabis would have a minimal effect on respiratory and cardiac function [4].

There is no clear indication on cases of death caused by cannabis intoxication alone and this shows, cannabis`s lack of effects on the respiratory rate[4]. However, there is a potential adverse effects in users who smoked traditional tobacco, which contains potent cancerous hydrocarbons which can be found in cannabis, and researchers noted that, the excessive use of cannabis exposes an individual to develop long standing respiratory and lung diseases[4]. There is also a practice of smoking cannabis containing cigarette, which is named "roaches", which can cause an increase of tar intake[4]. Some reports show that there are long term effects with chronic use of cannabis related to impaired immune reactivity, chromosomal damage birth defects, seizure susceptibility, and cerebral atrophy[4]. However, this reports have not been extensively researched and repeated[4]. Therefore, the relationship between this findings and cannabis use still remain undetermined [4].

After smoking cannabis, it`s euphoric sequel presents in a short space of time and attain its peak within 30 minutes of use and might last for 2 - 4 hours, while motor and cognitive effects might last longer, five (5) to twelve (12) hours [23].

Most users also reported mild sedatives effects and describe a feeling of relaxation [17]. The use of cannabis further leads to decreased blood pressure, bloodshot eyes, dizzy feeling, and an increased appetite termed "munchies", in some cases memory and coordination can also be slightly affected [2].

Weinsten and Goreliats 2011, postulated that the THC binds to endogenous cannabinoids receptors on the cell membrane and this interaction between the endocannabinoids membrane and opioid system may be responsible for the cannabis dependence[2]. There are also neuro-anatomical findings that suggests that CB1 modulates and interact with the function of dopamine, a neurotransmitter and this evidence suggests that there is an interaction in which variety of arears are modulated including affect, appetite, learning and memory, however there is not much evidence available regarding the underlying molecular mechanisms. By understanding the underlying mechanism involved, one can be able to understand the presenting symptoms of cannabis use, for example euphoria, which is part of an affect dysregulation [2].

Cannabis might be used by some patients for different reasons, including anxiety, depression, GIT disorders, nausea due to chemotherapy chronic pain, multiple sclerosis, AIDS and glaucoma [2]. Furthermore, the use of cannabinoid was reported to have been used to for chronic treatment for pain and rigidity in multiple sclerosis [9]

The Medicine Control Council (MCC) which is the South African`s administrative body established for drugs regulation, at the beginning classified cannabis as a Schedule Seven drug[18, 19]. These meant that cannabis did not show any pharmaceutical value at that time and it was unlawful to plow, examine, posses, trade or purchase and for research use, without the permission from the Department of Health [18, 19]. Later on a decision was taken by the MCC to reclassify cannabinoid medicine as a schedule six drug, which meant that it would be used and available for pharmaceutical purposes [20].

By 2018, the Medicine Control Council was replaced by the South African Health Products Regulatory Authority (SAHPRA), where the authority then reclassified cannabinoid as a schedule four (4) substance or schedule zero (0) under certain criteria[12]. The reclassification also put the THC under schedule four (4) or zero (0) under certain conditions[12].

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM V) recognises the following cannabis associated disorders [1]:

- Cannabis-use disorder;
- Cannabis intoxication;
- Cannabis withdrawal;
- Other cannabis induced disorders, which include:
    - Psychotic disorders;
    - Anxiety disorders;
    - Sleep disorders;
    - Delirium; and
    - Unspecified cannabis related.

However, it does not recognise cannabis induced bipolar and depressive disorder[1].

The DSM – V classified the following disorders as schizophrenia spectrum related and related disorders [1].

- Schizophrenia
- Schizophrenic form

- Brief psychiatric disorder
- Substance induced psychotic disorder
- Delusional disorder
- Schizoaffective disorder

The above mentioned disorders were part of the psychotic disorders included in the study.

The withdrawal symptoms in individuals with cannabis use, appears commonly when a person suddenly discontinues its high intake. They predominately present with modest increase in irritability, restlessness, insomnia, anorexia[(4)]. The other symptoms can include cravings, nervousness, anxiety, vivid dreams, weight loss, depressed mood, headaches, stomach pains, chills, tremors and sweating [(4)]. Studies have indicated that the withdrawal symptoms appear within (one) to two (2) weeks after an individual has stopped smoking cannabis [(4)].

During intoxication with cannabis use or intake the user experiences a heightened sensitivity to external stimuli, and many reveal new details, which make colour appear brighter and richer and the individual reports slowness of time[(4)]. When taken in high doses, some users report a sense of depersonalisation and derealisation[(4)]. The motor skills remain present as reported by the users, even after euphoria has resolved and this affect operation of machinery eight (8) to twelve (12) hours after use [(4)].

There are several studies that have shown that cannabis is related to an increase in positive symptoms of psychosis and it exposes an individual to Schizophrenia and it is reported that they will be symptom improvement upon discontinuation [(7)]. Furthermore, Henquet et al suggested that cannabis has also been reported to affect mood [(7)]. However, in their knowledge, there was no longitudinal researches done, to examine the association between cannabis and manic symptoms in patients that presented with psychosis as a first episode[(7)].

The use of cannabis has been implicated in producing short impermanent, and mostly minimal psychotic and affective symptoms in healthy individual [(21)]. In one longitudinal study which was conducted, their results showed that the level of cannabis use was seen to be linked with young age at presentation, manic symptoms and disorganised thinking, however this was not shown to be related to hallucinations, delusions, negative symptoms or have affected an individual`s ability to function daily[(7)]. More et al, 2007 further reported

that the symptoms which prolong or occur separate from intoxication effects are of greater concern[16].

Bipolar mood disorders, including depressive episode and mania/hypomania episode is comorbid with cannabis use and cannabis use disorder[7]. The was a community-based study in adults that showed individuals with a lifetime mood disorder, were likely to have used cannabis during their life-time compared with individuals without any psychotic disorder [7]. According to Strakowski*et al*., 2007 and Van Rossum, *et al*., 2009, studies have reported that the use of cannabis is associated with depressive symptoms and has shown poor outcome in individual with bipolar-disorder [7].

In a cross sectional study that was conducted, 30% of patients that were diagnosed with bipolar mood disorder, it was found that 70% of them had used cannabis[24]. This shows that patients that are diagnosed with bipolar mood disorder are more prone to abuse cannabis[24]. Furthermore, related studies have proven that constant intake and chronic use of cannabis exposes an individual to psychotic disorders [24]. Among patients diagnosed with bipolar mood disorder, 70% had comorbid cannabis use, while 30% presented with comorbid cannabis abuse and dependence[24]. The use of Cannabis appears to be associated with first onset of mania at young age and also frequent depressive or manic episodes[24]. However, this evidence was found to be somehow inconclusive as to whether the use of cannabis comes before manic episode and this causal direction still remain a subject of debate[24]

In a meta-analysis and systematic review study conducted by Gibbs *et al*, supported the relationship between the use of cannabis and worsening of mania symptoms in patients previously diagnosed with bipolar mood disorder. In the same study a further meta-analysis of two studies, suggested that, there is a relationship between the use of cannabis, which increased the possibility of new onset for mania symptoms, with an approximation of three times increase[16]. Due to limited studies of variable quality their conclusion however remained preliminary[16].

Arseneault et al., 2004 and Van Os et al., 2002, postulated that there is strong evidence on the use of cannabis and psychosis, where cannabis can attribute to the onset of psychosis and it`s use result to poor outcome for individuals, who were with pre-existing susceptibility to psychosis [16]. Whereas Van Laar et al 2007, and Gruber et al study in 2012, noted that it is

not clear as to whether the use of cannabis has a significant role on the onset of mania affective symptoms and mania episodes [16]. However, Henquet et al 2006, suggested that the use of cannabis is comorbid in individuals with pre-existing bipolar mood disorder and noted that the relationship between the use of cannabis did not receive the same recognition as the use of cannabis and schizophrenia [16].

Leweke and Koete, 2008 co-morbid substance use is most common among patients with bipolar mood disorder as compared to other Axis I disorders [16] And Duffy et al 2012, noted that somehow there is a relationship which is difficult to understand between the use of cannabis and bipolar mood disorder which can be related.[16]

Grinspoon and Balcalar, 1998 noted in some anecdotal studies, evidence suggesting that patients with bipolar mood disorder may use cannabis with a hope of improving the symptoms of their condition[16]. Whereas several researches have indicated that individuals may start using cannabis earlier than the diagnosis of bipolar mood disorder and the reoccurrence of manic episodes this is according to Strakowski et al 1998 and Delbello, 2000, who further reported a possible relationship between the use of cannabis and bipolar mood disorder[16].

Van Rossym et al, 2009, classified bipolar mood disorder as a complex condition with symptoms cluster, which are diverse, including the manic and depressive episodes [16]. Strakowski et al 1998, Delbello, 2000 and Sarkar et al, 2003 further reported that, manic phases in bipolar mood disorder are more likely to be associated with cannabis use[16].

The manic symptoms are common in patients diagnosed with schizophrenia and whereas psychotic symptoms often occur in patients diagnosed with bipolar mood disorder as noted by Dunayevich and Keck, 2000 and Henquet et al 2006 [16]. Murray et al 2004, further indicated that manic and psychotic symptoms might have the same causal influence, potentially accountable to similar physiological mechanism [16]. Henquet et al 2006, made an example by stating that sensitization of the dopamine system might play a role in increasing the chances of acquiring schizophrenia and mania[16]. Furthermore, Murray et al 2004, noted that, whether the chances are increased in psychosis or mania disorder, the risk might depend on the relationship between genetic pre-disposition and environmental factors [16].

1.2 IDENTIFICATION OF GAPS – NEEDS FOR FURTHER RESEARCH

There is a need for a further longitudinal study to explore causality of cannabis use and mood symptoms, looking at the frequency and intensity of cannabis exposure and taking into consideration confounding factors.

1.3 RESEARCH QUESTION

Do patients who use cannabis, and are admitted for schizophrenia spectrum and related disorders present with more mood symptoms compared to those that do not use cannabis.

1.4 AIM

To determine the association between cannabis use and mood symptoms in patients admitted with schizophrenic spectrum and related disorders to acute wards at FSPC.

1.5 OBJECTIVES

i. *To determine the prevalence of mood symptoms in patients diagnosed with schizophrenic spectrum and related disorders comorbid cannabis use and those with no cannabis use at FSPC;*
ii. *To determine the severity of mood symptoms if present.*

1.6 HYPOTHESIS

Hypothesised that manic symptoms are prevalent among cannabis users.

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Keywords

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Introduction

Cannabis was noted as one of the four frequently used illegal psychoactive substance around the world among adults after caffeine, alcohol and nicotine in the USA. Its use was around 19 million people in 2012 [4]. It is viewed as a drug that leads the user on to more addictive or dangerous drugs [2]. It was further classified as a frequent used illegal drug, after cocaine and ecstasy, in about (4) million people that use drugs [5]. In 2014, Colorado became the first state in the United State to legalise the cannabis for recreational purposes [3].

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Cannabis grows in almost every country in the world, but is not indigenous to Southern Africa [17]. However, it grows well in the South African`s climate [13].

The use of cannabis varies according to age, with the highest prevalence reported among the young adult at 33% between the age of 18 to 26 yrs. The cannabis use is rare among those who are 65 years and older [18]. Men and women use cannabis, however men are almost twice as likely than women, with men at 11.3% compared to women at 6.7% [18]. However recent studies show, more increase of cannabis use amongst female as compared to men [8]. According to Pacek et al there might have been several factors that contributed to higher use among women, such as legalisation, medical use of marijuana and a low risk associated with cannabis use [8].

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Across the world, many names are commonly used for cannabis, e.g. Grass, Mary-jane, marijuana, pot, weed, and tea [4]. It can also be described by various strength type, which include chasra, hemp, dagga, ganja and sinsemila[4]. For the purpose of this study, all of the above-mentioned names and strength is included under the name, cannabis, which is the generic term.

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM V) recognises the following cannabis associated disorders namely: cannabis use disorder, cannabis intoxication, cannabis withdrawal, Other cannabis induced disorders, which include: psychotic disorders, anxiety disorders, sleep disorders, delirium and unspecified cannabis related. However, it does not recognise cannabis induced bipolar and depressive disorder [1].

The DSM – V classified the following disorders as schizophrenia spectrum related and related disorders: schizophreniform, brief psychotic disorder, substance induced psychotic disorder, delusional disorder and schizoaffective disorder [1]
The above mentioned disorders were part of the psychotic disorders included in the study.

There have been accumulating data which has shown that increasing the frequency and intensity of cannabis, increase the risk of psychotic disorders [10]**.** However, the use of cannabis is less associated with mood disorders [10]**.**

There has not been available information regarding the neurobiological mechanism accountable for the effects of cannabis on psychiatric disorders [6]. As more research is conducted in the endocannabinoid system the neurobiological effect of cannabis is constantly being looked at and given attention in the development of mental illness for individuals who may be genetically predisposed [6]. In other longitudinal studies, there have been some data which highlighted that the use of substance mostly occurs before the onset

of bipolar mood disorder [25]. However, how the use of cannabis can be the underlying consequence of psychiatric symptomology still remain the subject of debate [25].

Inversen in 2000, noted that Delta – 9- tetrahydrocannabinol (Δ - 9 – THC) as the primary psycho-active property found in cannabis, which has short-term effects, that include feeling of intense excitement, disinhibition, impulsivity, change in perception, desire to eat more and cognitive fall outs [25]**.** In support of the statement mentioned above a study was conducted by D`Souza et al in 2014, where individuals in good health were injected with Δ-9-THC, and this resulted in subjects presenting with psychotic symptoms, which include delusions and perceptual disturbances including hallucinations [25]. Moore et al further said patients that presented with symptoms post intoxication independently are worrisome and raised a bigger concern [17]

When cannabis is smoked, there is 18% bio-availability of the Δ - 9 – THC and while 6% can be found in cakes [23]. This Δ – 9 – THC bind itself to Cannabinoid receptors found in the Nervous system [23]. The cannabinoid receptors are part of the components of endocannabinoid system (ECS) which are found in many areas around the human body, and play a significant role in the central nervous system development, synaptic plasticity, and the response to endogenous and environmental insults[7].
There are two (2) cannabinoid receptors, CB1 and CB2 which are found within the Central Nervous System (CNS) and Peripheral Nervous System (PNS) respectively [23]. The CB1 receptors mediates most of the cannabinoids in the central nervous system, while the CB2 mediates the peripheral nervous system. The CB1 receptor is a G-Protein coupled and is the most abundant in mammalian brain [23]

A study that was conducted by Di Chiara (1995) and Oleson and Cheer (2012) concluded that the effects of THC on the mesolimbic dopaminergic pathways, promote addiction in cannabis users [25]. Furthermore, Carlson (1988) and Coque (2011) indicated that over excitability of mesolimbic dopaminergic pathway was associated with psychosis and mania symptoms [25]. Van Laar et al, 2007 also commented that THC increases the level of glutamate, in the left dorsolateral prefrontal cortex, which leads to acute mania [25].

Weinsten and Goreliats 2011, postulated that the THC binds to endogenous cannabinoids

receptors on the cell membrane and this interaction between the endocannabinoids membrane and opioid system may be responsible for the cannabis dependence [2]. There are also neuro-anatomical findings that suggests that CB1 modulates and interact with the function of dopamine, a neurotransmitter and this evidence suggests that there is an interaction in which variety of arears are modulated including affect, appetite, learning and memory, however there is not much evidence available regarding the underlying molecular mechanisms. By understanding the underlying mechanism involved, one can be able to understand the presenting symptoms of cannabis use, for example euphoria, which is part of an affect dysregulation [2].

Bipolar disorder has the highest rate of substance abuse amongst mood disorders and cannabis being the most commonly-used illegal substance amongst bipolar disorders [27]. And the abuse of cannabis, has shown to have significant impact on first-episode mania and the course of the illness, way before a diagnosis of bipolar mood disorder is given and other studies reported that, at baseline using cannabis significantly increase the risk of mania when patients are followed up [1].

The manic symptoms are common in patients diagnosed with schizophrenia and whereas psychotic symptoms often occur in patients diagnosed with bipolar mood disorder as noted by Dunayevich and Keck, 2000 and Henquet et al 2006 [17]. Murray et al 2004, further indicated that manic and psychotic symptoms might have the same causal influence, potentially accountable to similar physiological mechanism [17]. Henquet et al 2006, made an example by stating that sensitization of the dopamine system might play a role in increasing the chances of acquiring schizophrenia and mania [17]. Furthermore, Murray et al 2004, noted that, whether the chances are increased in psychosis or mania disorder, the risk might depend on the relationship between genetic pre-disposition and environmental factors [17].

Whiteford et al (2013) described depression as a usual psychiatric disorder which has a huge impact on burden of diseases worldwide [10]. Cross-sectional studies have reported high depression rate among cannabis users and the other way around [10]. However, other longitudinal researches conducted, have demonstrated contradicting reports relating to the relationship between the use of cannabis and depression [10]. While other studies by Bosson, Fergusson and Horwood reported an important relationship between the use of cannabis at

baseline and possible development of depression, and other researchers have reported that the likelihood of developing depressive disorder (|DD) among cannabis users and non-users at follow-up will be the same [10].

There are several studies that have shown that cannabis is related to an increase in positive symptoms of psychosis and it exposes an individual to Schizophrenia and it is reported that they will be symptom improvement upon discontinuation [9]. Furthermore, Henquet et al suggested that cannabis has also been reported to affect mood [9]. However, in their knowledge, there was no longitudinal researches done, to examine the association between cannabis and manic symptoms in patients that presented with psychosis as a first episode [9]. The use of cannabis has been implicated in producing short impermanent, and mostly minimal psychotic and affective symptoms in healthy individual [22]. In one longitudinal study which was conducted, their results showed that the level of cannabis use was seen to be linked with young age at presentation, manic symptoms and disorganised thinking, however this was not shown to be related to hallucinations, delusions, negative symptoms or have affected an individual`s ability to function daily [9]. More et al, 2007 further reported that the symptoms which prolong or occur separate from intoxication effects are of greater concern [17].

Though different study designs were used, proof relating to the longitudinal relationship between the use of cannabis and depressive disorder (MDD/DD) still remain a subject of controversy [10]. To examine the relationship between the use of cannabis and depressive disorders, it requires a longitudinal study to show that, increased exposure to cannabis can lead to an increased episode of depressive disorder [10]. However, Gruber *et al.* (1997), pointed to the reverse direction of causality, stating "that depressive symptoms may lead to cannabis use as a means to self-medicate" [10].

This study aims to evaluate the prevalence of mood symptoms including mania like symptoms and depression, in patient with psychotic disorders who used cannabis. If mood symptoms are prevalent, we aim to explore their severity.

We hypothesise that manic symptoms are prevalent among cannabis users with psychotic disorders, with increased symptom severity within the first three days of admission.

Research methods and design

Study design

This study followed a quantitative, analytical and a prospective design to assess the prevalence of mood symptoms in patients diagnosed with psychotic disorders with cannabis use.

Study setting

The study was conducted at Free State Psychiatric Complex (FSPC) inpatient acute wards.

Study population

The study was conducted on psychotic patient admitted at the acute wards of females and male's admission wards. The study had 70 patients in total, where 40 were the study group and 30 were the study controls. All study participants had either of the following schizophrenic spectrum and related disorders as specified in DSM 5. These include psychotic disorder, schizophrenic-form disorder, schizophrenia, schizoaffective disorder, substance induced psychotic disorder and delusional disorder.

The study group had the following inclusion, positive cannabis results on urine, recent history of cannabis use during the past 10 days or more. The control group has the following inclusion: patients without positive cannabis screening on urine, with no recent history of cannabis use during the past 10 days or longer.

The following patients were excluded from the study: patients diagnosed with bipolar mood disorder and related disorders, depressive-disorders, patients who used other substances or medication that induce mood symptoms and patients who were on mood stabilisers.

Data collection

Data was collected at two points in time, within three days of hospital admission and 7-14 days after.

The Young Mania Rating Scale (YMRS) was administered to measure and detect the symptoms of mania. YMRS is a clinical tool designed to measure the severity of manic symptoms, and assess the effects of treatment and detect relapses of manic symptoms. YMRS has a checklist of 11 items that are ranked on a scale of 0-4 or 0-8. A score on the YMRS of 13-19 indicates minimum symptoms, a score of 20-25 indicates mild symptoms, 26-37 moderate symptoms and a score of ≥ 38 indicates severe symptoms.

The Hamilton rating scale for depression (HAM-D) was used to measure and detect depressive symptoms. It consists of 17 items and are ranked on a scale of 0-2 and 0-4. The following was expected outcomes, less than 13 is normal, 14-18 mild symptoms, 19-22 moderate and >22 severe symptoms [16].

The biggest challenge encountered during collection was the psychotic symptoms as patients have lost insight and judgement into themselves and one might question the accuracy and the truthful of their symptoms. One had to pay close and careful attention to those symptoms, to make a clinical judgement isolated of psychotic answers.

Data analysis

The collected data was analysed by the Department of Biostatistics, Faculty of Health Sciences, University of the Free State.

The results were summarised by frequencies and percentages (categorised variables), mean and standard deviations (numerical variables). The groups were compared using the 95% confidence intervals for differences in percentages, mean or medians with appropriate hypothesis testing.

Ethical considerations

The study was approved by the Health Science Research Ethics Committee (HSREC) of the University of the Free State. The Department of Health (DOH) Free State, also approved the study. Permission and approval was granted by the FSPC clinical management to conduct the study on psychotic patients admitted at FSPC.

Results

The mean age in the study group, cannabis users, was 24 years (integrative range of 21-30.5) compared to 33 years (integrative range of 28-41) in the non-cannabis users with a $p<0.01$.

Table 1a shows the demographic screening that 77.5% of cannabis users were males and 22.5%, female. However, it shows an equal distribution of non-cannabis users.

Table 1a. Demographic characteristics and screening (P.value<0.02)

GENDER	**GROUP A: CANNABIS USERS**	**GROUP B: NON-CANNABIS USERS**
Male	31 (77.5%)	15 (50%)
Female	9 (22.5%)	15 (50%)

Of the cannabis users, 87.5% reached secondary education (cf. Table 1b) and 72.5% were unemployed (cf. Table 1c). These demographics show evidence of clear, consistent and a significant P.value.

Table 1b. Education (P.value<0.01)

EDUCATION	**GROUP A: CANNABIS USERS**	**GROUP B: NON-CANNABIS USERS**
Never	0 (0%)	1 (3.3%)
Primary	2 (5%)	9 (30%)
Secondary	**35 (87.5%)**	19 (63%)
Tertiary	3 (7.5%)	1 (3.3%)

Table 1c. Employment (P.value<0.01)

EMPLOYMENT	GROUP A: CANNABIS USERS	GROUP B: NON-CANNABIS USERS
Scholar	6 (15%	0 (0%)
Employed	4 (10%)	3 (10%)
Unemployed	29 (72.5%)	11 (36.6%)
Pensioner	0 (0%)	2 (6.6%)
Disability grant	1 (2.5%)	14 (46.6%)

Table 1d shows that within three (3) days of admission, 75% of cannabis users and 46.7% of non-cannabis users presented with mania like symptoms on YMRS. Therefore, this has shown significant p-value (p0.01). However, after day 14, only 17.5% and 0% of cannabis users and non-cannabis users respectively showed a decrease in symptom score with non-significant p-value.

Table 1d. Symptom score

YMRS	GROUP A: CANNABIS USERS	GROUP B: NON-CANNABIS USERS	P.value
Day 3	30 (75%)	14 (46.7%)	<0.01
Day 14	7 (17.5%)	0 (0%)	N/A
HAMD	**GROUP A: CANNABIS USERS**	**GROUP B: NON-CANNABIS USERS**	**P.value**
Day 3	2 (5%)	6 (20%)	0.02
Day 14	1 (2.5%)	0 (0%)	1.00

Within three (3) days of admission, 5% of cannabis users and 20% of non-cannabis users, showed depressive symptoms on-hand with a significant p-value of ($p<0.02$). After day 14, only 2.5% and 0% of cannabis users and non-cannabis users, statistically these results are not significant, they have a P-value of >0.05.

Discussion

In this study, we explored the effect of cannabis use on psychotic patients, within three (3) days of admission and also after 14 days. To investigate if mood symptoms is common, and if present, how severe they are. Our study found significantly higher YMRS scores in the patients that used cannabis. Mania like symptoms cleared relatively quickly, with no difference in YMRS scores after 14 days.

There was a study by Henquet et al 2007, that showed that the use of cannabis is linked with patients presenting with positive effects such as signs of relaxation, cheerfulness, happiness, enthusiasm and a sense of satisfaction among people that used it [(9)].

While studies have shown from clinical population that the use of cannabis inform us about the cause and severity of bipolar-disorder, there is a need of non-clinical population to understand whether there is consistency and signals with regard to causality [(17)]. A study on high-risk offspring population studies and community studies is needed to further explore causality [(17)].

Conclusion

Very few studies have been done on whether cannabis can induce mood disorders. Therefor the findings of this study will contribute to the limited clinical knowledge on this topic. More longitudinal studies are required to determine causality of mood disorders with cannabis use.

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Competing interests

No competing interest exist.

Disclaimer

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APPENDICES