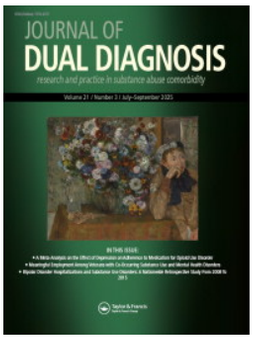

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Pain Is Not a Predictor of Cannabis Use in People With Psychotic Disorders

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ABSTRACT

Objective: People with a psychotic disorder are more likely to experience pain and interference from pain in their daily lives. There is also a high prevalence of cannabis use among people with psychotic disorders, which is known to be effective in pain management. This study investigates whether pain is a predictor of cannabis use in people with psychosis. Since sedating antipsychotics may also suppress pain, this is included as a covariate. **Methods:** This sample included 108 Dutch people with a psychotic disorder, participating in the VAT observational cohort study. Cross-sectional regression analyses were performed with cannabis use (yes/no and units per week) as outcomes, and pain and the degree of interference from pain (RAND-36-SF items 7 and 8) as predictors. Covariates included were age, sex, severity of psychosis, and use of sedating antipsychotics. **Results:** In this sample, 59% experienced some degree of pain and 18.5% used cannabis. Pain and interference from pain were not significant predictors of cannabis use, nor of the amount of cannabis use. However, the use of antipsychotics with low sedating effects was associated with a greater amount of cannabis use in our participants (p = .028). **Conclusions:** We found no direct link between pain experience and cannabis use in people with psychotic disorders. It is possible that cannabis effectively suppresses the pain, and participants using cannabis therefore did not report experiencing pain. Furthermore, our finding that participants who were prescribed antipsychotic drugs with low sedating effects use more cannabis warrants further investigation. It is possible that people with psychotic disorders who experience numbness and sedation from their antipsychotics, may be less inclined to attempt to reach these effects using cannabis, which could potentially influence the choice of prescribed antipsychotics in the treatment of psychotic disorders in the future.

KEYWORDS

Cannabis; psychiatry; illicit drugs; antipsychotics; substance use; schizophrenia; marijuana

The prevalence of cannabis use among people with a psychotic disorder is relatively high, with approximately 28% current and 44% lifetime users (Hasan et al., 2020), compared to 4% current users in the general European population (Manthey et al., 2021). Cannabis use negatively impacts the course of psychotic disorders with more relapses, more hospitalizations, and increasing severity and persistence of psychotic symptoms (Seddon et al., 2016). Quitting the use of cannabis should therefore be an important treatment goal for people with psychotic disorders.

People with a severe mental illness report using cannabis for various reasons, but most of them do not use it solely for recreational effects (Bruins et al., 2023). One important reason for their cannabis use is self-medication (Bruins et al., 2023; B. Green et al., 2004; Henquet et al., 2010; Kolliakou et al., 2015). The self-medication hypothesis assumes drug use begins as a partially successful attempt to reduce unpleasant feelings, as it provides people with temporary relief from their suffering (Khantzian, 1997). In support of this theory, cannabis has been used as a medicinal plant for thousands of years. Among others, there is substantial evidence that cannabis effectively relieves chronic pain in adults (Byars et al., 2019; Hutchinson et al., 2019; Maharajan et al., 2020; Romero-Sandoval et al., 2018). Cannabis has even been included as a formal treatment recommendation in medical guidelines for chronic pain (Sutherland et al., 2018).

Several studies have indicated that people with psychotic disorders experience pain more frequently than those in the general population (König et al., 2007; Koyanagi & Stickley, 2015; Strassnig et al., 2003). One study found that 44% of people with psychotic disorders experienced pain and discomfort, compared to

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27.9% in the general population (König et al., 2007). This high prevalence of pain experienced by individuals with psychosis could stem from the inflammatory processes involved in the pathogenesis of psychosis, since inflammation has also been associated with hyperalgesia (Koyanagi & Stickley, 2015). Moreover, people with psychotic disorder have a relatively high risk of developing painful conditions, such as fractures and tooth problems (Morales-Chávez et al., 2014; Stubbs et al., 2015). At the same time, these patients often demonstrate a reduced reactivity to pain (Stubbs et al., 2014). It is possible, however, that people with psychotic disorders simply have more difficulties in expressing their pain, instead of having a reduced perception of pain (Bonnot et al., 2009).

Pain is defined by the criteria of The International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Raja et al., 2020). In relation to cannabis use, this suggests it may not necessarily be experiencing pain, but the extent to which this pain interferes with people's lives that influences the potential urge to self-medicate (Koyanagi et al., 2016).

There is likely a three-way bidirectional relationship between pain, cannabis, and psychosis. Firstly, people with psychosis have an increased risk of experiencing conditions that may induce pain (König et al., 2007; Oh & DeVylder, 2015). At the same time, people with chronic pain conditions are more likely to develop psychiatric symptoms (Demyttenaere et al., 2007; Scott et al., 2007). It has been suggested that several neurotransmitters, such as norepinephrine and serotonin, are involved in both pain perception and psychiatric symptoms (Campbell et al., 2003; Dersh et al., 2002).

Secondly, cannabis use can trigger the onset of a psychotic disorder (Lowe et al., 2019), but people who are already diagnosed with a psychotic disorder are also known to use cannabis as self-medication to find temporary relief from their psychotic symptoms (Bruins et al., 2023; Quach et al., 2009).

Finally, long term cannabis use builds up a tolerance, which means increasing amounts of cannabis are needed to reach a stage of temporary relief. Thus, prolonging and increasing the severity of psychotic symptoms (Bruins et al., 2016; Lowe et al., 2019). Similarly, using cannabis for pain relief has a short-term positive effect, but may eventually result in a reduced pain tolerance, thus worsening the pain over time (Zhang-James et al., 2023). Consequently, experiencing higher levels of pain and a greater degree of interference from pain may be associated with a greater amount of cannabis intake in people with psychotic disorders.

Overall, there is a high prevalence of both pain and cannabis use in people with psychotic disorders. Considering the effectiveness of cannabis use in pain management, we hypothesize that experiencing pain might be a reason for people with psychotic disorders to self-medicate with cannabis. Additionally, it has been suggested that antipsychotic drugs may be responsible for a reduced pain sensitivity in people with psychotic disorders (Seidel et al. 2010). Certain antipsychotic drugs, such as clozapine, are known to have sedating effects and may inadvertently serve as both an antipsychotic and pain killer (Leucht et al., 2013; Shin et al., 2019). People with a psychotic disorder who are prescribed these antipsychotics may therefore not need to self-medicate with cannabis to relieve their pain. Therefore, the hypothesized association between experienced pain and cannabis use may depend on whether people are using antipsychotics with known sedating effects.

Aim of the study

In this study, we will examine the association between cannabis use and pain in people with psychotic disorders in a cross-sectional design. We hypothesize that experiencing pain and interference from pain is associated with cannabis use in people with a psychotic disorder. We will correct these associations for type of antipsychotic medication, categorized based on sedating effects, as well as the following known factors associated with cannabis use in psychosis: age, sex, and severity of psychosis (Bruins et al., 2016).

Methods

Participants

Participants in this study are enrolled in the Voices, Attachment and Trauma (VAT) observational cohort study, a research project focused on finding determinants of recovery in people with psychosis, approved by the Medical Ethical Review Committee of the University Medical Center Groningen (METc number: 2017.456). Participants were included in the current study if they: (1) were diagnosed with a psychotic disorder according to the *DSM-V* criteria (i.e. schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, substance induced psychosis, or psychosis NOS); (2) were ≥ 18 years old; (3) disclosed information about potential cannabis use; (4) disclosed information about experiencing

pain, and (5) had available information about any prescribed antipsychotic drugs.

Study design

VAT participants were recruited through mental health care workers at Lentis Psychiatric Institute in the northern Netherlands. Written informed consent was obtained after a complete discussion of the study with each potential participant, and prior to participation. Patients participated on a voluntary basis and could withdraw from the study at any given time without consequences. Participants received a €10 gift card after each completed measurement, which consisted of a clinical interview by a trained clinical psychologist and self-report questionnaires.

Measures

Demographic information regarding age, sex, and illness duration was provided by the patients through autobiographical questions. Information about the psychiatric diagnosis was obtained from the electronic patient records with consent from participants.

Cannabis use

Self-reported data included two points: current cannabis use (yes/no), and for those reporting "yes," the frequency of use (average number of units per week during the last 6 months). In the analyses examining the association between pain and the amount of cannabis intake, frequency of use for the non-users was set to zero to include the full study sample in the analyses.

Pain and pain interference

The RAND-36 short form was used to obtain information about pain experience (van der Zee & Sanderman, 1992). The RAND-36 short form is a reliable, valid, and sensitive measure of general health. We used two items of the RAND-36 short form to measure pain. Firstly, item 7 inquired about the degree to which people experience pain on a 6-point Likert scale (1 = none to 6 = very severe). Secondly, item 8 inquired to what extent this pain interfered with their normal work, both work outside the home as well as housework, on a 5-point Likert scale (1 = not at all to 5 = extremely).

Use of antipsychotic drugs

Information on the use of antipsychotic drugs was obtained from the electronic patient records. The different types of antipsychotics that are registered in the VAT study are: clozapine, olanzepine, risperidone, quetiapine, aripiprazole, haloperidol, and "other." These antipsychotic drugs were categorized based on their sedating effects as described by Leucht et al. (2013): (1) antipsychotics with no/low sedating effect (aripiprazole), (2) antipsychotics with moderate sedating effect (risperidone, haloperidol, olanzepine, and quetiapine), and (3) antipsychotics with high sedating effect (clozapine). In case of polypharmacy ($n = 12$ participants), participants were assigned to a category based on their prescribed antipsychotic with the highest sedating effect.

Psychotic symptoms

Information about the severity of psychotic symptoms was measured using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a clinical interview, where 30 symptoms are scored on a 7-point Likert scale (1 = absent, 2–7 = increasing symptom severity, 7 = extremely severe presence of a symptom). Higher PANSS scores represent greater severity of psychotic symptoms. The total score on the PANSS is included in the analysis as a covariate.

Statistical analysis

Differences in pain experience, antipsychotic drugs, age, sex, illness duration, and psychotic symptom severity between cannabis users and non-users were examined using chi-squared tests (dichotomous variables) and independent sample t-tests (continuous variables).

We performed two separate logistic regression analyses, with cannabis status (user/non-user) as the dependent variable and the scores of RAND-36-SF items 7 and 8 as individual independent predictors. Scores on RAND-36-SF item 8 (pain interference) were dichotomized into yes/no interference for analysis purposes due to the skewed distribution in scores (96.3% scored ≤ 3).

Secondly, we investigated whether the amount of cannabis use was predicted by the degree of experienced pain (RAND-36-SF item 7) and experience of pain interference (RAND-36-SF item 8) using two separate linear regression analyses.

All regression analyses were subsequently corrected for the following covariates in a single step: use of sedating antipsychotic drugs, age, sex, and severity of psychosis. Patients with a diagnosis for substance-induced psychosis ($n = 2$) were excluded

from the regression analyses. Significance was tested against $\alpha = 0.05$.

Results

Sample characteristics

There was a total of 110 participants in the VAT study at the time of assessment. Two participants did not provide information about their cannabis use so were excluded from analysis. Therefore, 108 patients were included in the final analysis, of which 18.5% used cannabis. Two participants were diagnosed with substance-induced psychotic disorder and were excluded from the regression analyses. Frequency of cannabis use among the users ranged between 1–28 units per week, with an average of 9.4 units per week ($SD = 9.36$). Ages of the participants ranged from 19–78 years, with 85% being > 30 years old. Mean duration of illness was 21 years, ranging from 1 to 59 years. Cannabis users were younger, had a shorter illness duration, and experienced mild pain more often compared to non-users. An overview of the study sample is provided in Table 1.

Pain experience

Of all included participants, 59.4% ($n = 63$) reported that they experienced some degree of pain. Of the participants experiencing pain, 68.3% ($n = 43$) indicated that their pain interfered with their normal work (see Table 1).

Pain and cannabis use

The logistic regression analysis showed that the degree of experienced pain was not a significant predictor for cannabis use (unstandardized $B = 0.161$, $SE = 0.17$, $OR = 1.17$, 95% CI [0.84, 1.65], $p = .352$). Adjusting for the covariates did not significantly affect this association (unstandardized $B = 0.43$, $SE = 0.24$, $OR = 1.53$, 95% CI [0.95, 2.47], $p = .079$).

Experiencing interference from pain during normal work was also not a predictor for cannabis use (unstandardized $B = 0.32$, $SE = 0.24$, $OR = 1.37$, 95% CI [0.86, 2.18], $p = .181$). Adjusting for covariates did not significantly affect this association (unstandardized B = 0.42, $SE = 0.35$, $OR = 1.52$, 95% CI [0.77, 2.99], $p = .405$).

Of the included covariates, only age showed a significant negative association, with older age predicting lower odds of being a cannabis user (unstandardized $B = -0.09$, $SE = 0.03$, $OR = 0.91$, 95% CI [0.86, 0.96], $p = .002$). A post hoc analysis also showed a significant positive correlation between age and the degree of experienced pain ($r = .25$, $p = .011$).

Association between amount of pain and cannabis intake

The linear regression analysis showed that the degree of experienced pain was not a significant predictor of the amount of cannabis use (unstandardized $B = 0.15$, standardized $\beta = 0.05$, $SE = 0.32$, $p = .647$). Adjusting for covariates did not significantly affect

Table 1. Differences in sample characteristics between cannabis users and non-users.

	Total	Cannabis users ($n = 20$)	Non-users ($n = 88$)	t/χ^2	p
Age, *M (SD)*	48.39 (15.10)	35.11 (9.95)	51.06 (14.51)	5.79	<.001*
Sex, % (*n*) male	60.0 ($n = 66$)	75.0 ($n = 15$)	58.0 ($n = 51$)	1.99	.158
Illness duration, *M (SD)*	20.92 (14.40)	13.47 (10.15)	22.55 (14.72)	3.23	.003*
Pain experience (RAND-SF 7), *M (SD)*	2.41 (1.44)	2.68 (1.25)	2.34 (1.48)	−0.93	.354
Very mild pain, % (*n*)	16.7 ($n = 18$)	10.0 ($n = 2$)	18.2 ($n = 16$)	0.79	.375
Mild pain, % (*n*)	14.8 ($n = 16$)	35.0 ($n = 7$)	10.2 ($n = 9$)	7.93	.005*
Moderate pain, % (*n*)	15.7 ($n = 17$)	20.0 ($n = 4$)	14.8 ($n = 13$)	0.34	.562
Severe pain, % (*n*)	11.1 ($n = 12$)	5.0 ($n = 1$)	12.5 ($n = 11$)	0.93	.335
Pain interference (RAND-SF 8), *M (SD)*	1.64 (0.95)	1.90 (1.07)	1.58 (0.92)	−1.37	.175
A little bit, % (*n*)	22.2 ($n = 24$)	30.0 ($n = 6$)	20.5 ($n = 18$)	0.86	.354
Moderately, % (*n*)	13.9 ($n = 15$)	20.0 ($n = 4$)	12.5 ($n = 11$)	0.77	.381
Quite a bit, % (*n*)	0.9 ($n = 1$)	0.0 ($n = 0$)	1.1 ($n = 1$)	0.23	.630
Extremely, % (*n*)	2.8 ($n = 3$)	5.0 ($n = 1$)	2.3 ($n = 2$)	0.45	.503
Antipsychotic drug use, % (*n*)	77.1 ($n = 84$)	75.0 ($n = 15$)	78.4 ($n = 69$)	0.11	.741
Low sedative, % (*n*)	33.9 ($n = 37$)	45.0 ($n = 9$)	30.7 ($n = 27$)	1.50	.220
Moderate sedative, % (*n*)	41.3 ($n = 45$)	35.0 ($n = 7$)	43.2 ($n = 38$)	0.45	.503
High sedative, % (*n*)	24.8 ($n = 27$)	20.0 ($n = 4$)	26.1 ($n = 23$)	0.33	.567
PANSS total	57.75 (14.81)	56.29 (9.07)	58.04 (15.73)	0.44	.660
PANSS Positive subscale	13.72 (4.89)	13.59 (3.74)	13.74 (5.11)	0.12	.907
PANSS Negative subscale	14.04 (4.81)	14.18 (5.34)	14.01 (4.73)	−0.13	.898
PANSS General Psychopathology	29.99 (8.22)	28.53 (4.74)	30.28 (8.74)	0.80	.425

Note. *M* = mean; *SD* = standard deviation; *n* = number; RAND-SF = RAND Short Form; PANSS = Positive And Negative Syndrome Scale.
*Significance at $\alpha = 0.05$.

this association (unstandardized $B = 0.37$, standardized $\beta = 0.12$, $SE = 0.33$, $p = .263$).

Experiencing interference from pain during normal work was also not a significant predictor for the amount of cannabis use (unstandardized $B = 0.37$, standardized $\beta = 0.08$, $SE = 0.50$, $p = .463$). Adjusting for covariates did not significantly affect this association (unstandardized $B = 0.40$, standardized $\beta = 0.08$, $SE = 0.50$, $p = .421$).

Of the included covariates, a younger age (unstandardized $B = -0.07$, standardized $\beta = -0.23$, $SE = 0.03$, $p = .021$) and use of low sedating effects of antipsychotic drug use (unstandardized $B = 2.34$, standardized $\beta = 0.24$, $SE = 1.05$, $p = .028$) were significantly associated with a greater amount of cannabis use.

Discussion

In this study, we found that 59% of the people with a psychotic disorder experienced some degree of pain, and 68% of these indicated this pain interfered with their normal work. However, neither experienced pain, nor pain-related work interference significantly predicted cannabis use. We also found no association between the amount of cannabis use and experienced pain. It was noted that the use of antipsychotics with low sedating effects was associated with a greater amount of cannabis use. Age was anticipated as a potential confounding variable, and results showed younger participant using cannabis more frequently and in greater amounts.

There is limited research on pain experience in people with psychotic disorders. Our findings were similar to the study of König et al. (2007), who reported 44% of their participants with a psychotic disorder experienced pain and discomfort, even though they used a different instrument to measure pain. We found no significant associations between cannabis use and pain in people with psychotic disorders, unlike the recent study of Wilson et al. (2022), which demonstrated that young cannabis users experience more psychotic complaints and report significantly more pain. An important factor in understanding the discrepancy between our findings and those of Wilson et al. may be the varying age composition of the samples. Wilson et al. (2022) included a young sample with a mean age of 19 years (range 16–25), whereas our participants had a mean age of 49 years, and only 6.5% of our sample was in the age range of 18–25 years. Older age has been associated with less cannabis use in people with psychotic disorders in both our study and previous research (Bruins et al., 2016; Seddon et al., 2016), yet older age was also associated with increased reports of pain in our sample.

The association between cannabis use and pain was not significant in our sample. The current findings suggest a lack of direct association between cannabis use in individuals with psychotic disorders and reported experienced pain. However, consistent with the self-medication theory, it remains plausible that cannabis use may serve to mitigate perceived pain among users. As a result, cannabis-induced pain suppression may have resulted in an underestimation of reported pain and subsequent interference with daily activities. Considering the demonstrated effectiveness of cannabis in pain management (Hutchinson et al., 2019; Maharajan et al., 2020), experiencing pain could therefore still contribute to the explanation for the relatively high prevalence of cannabis use in people with psychotic disorders. This alternative explanation suggests we may have inadvertently measured the *effect* of cannabis use on pain, rather than pain as a cause of cannabis use.

Originally, we hypothesized sedating antipsychotics may already provide patients with sufficient relief from experiencing pain, thus eliminating the need to self-medicate with cannabis. While no associations were found between cannabis use and pain, low sedating antipsychotics were associated with greater amounts of cannabis use in this study. Therefore, we suggest that the sedative effects of certain antipsychotics may contribute to cannabis self-medication for reasons other than pain alleviation. A previous study reported that individuals with psychotic disorders often use cannabis as a form of sedation to numb themselves, and to repress negative emotions (Bruins et al., 2023). It is possible that patients who do not experience numbness and sedation from antipsychotic drugs, are more inclined to use cannabis to numb and sedate themselves. Previous literature offers partial support for this theory, however, a more nuanced approach to categorizing sedative effects of antipsychotics, including the influence of dosage and polypharmacy, is warranted. Previous studies showed that people with psychotic disorders who took clozapine (highly sedating) had a greater reduction in cannabis cravings compared to patients taking risperidone (moderately sedating; Machielsen et al., 2014; Machielsen et al., 2018). Patients using olanzapine also had less cannabis cravings than patients taking risperidone, even though both are considered to have moderately sedating effects (Machielsen et al., 2012).

Strengths and limitations

In this cross-sectional study, we were able to examine the relationship between pain, cannabis use, and the use of antipsychotics in a representative sample of people with a broad spectrum of psychotic disorders, ranging from first-onset psychosis to chronic conditions. In contrast, most studies investigating cannabis use focus on the first psychotic episode or the prodromal phase.

Information about cannabis was collected using self-report measures, which may result in the participant providing socially desirable answers resulting in underestimations of cannabis use. However, self-report and objective measures of cannabis use have previously been found to be nearly equally reliable in people with a psychotic disorder (van der Meer & Velthorst, 2015).

Furthermore, details about cannabis use were limited to the self-reported number of units used per week. No information was collected concerning the method of cannabis intake (inhalation, edible, etc.), the amount of cannabis in grams, or the compound of the cannabis plants. More detailed information on cannabis components and dosages would have been beneficial, since different components and dosages of cannabis can have different effects (Bonaccorso et al., 2019; Boyaji et al., 2020; Tamba et al., 2020). For example, cannabidiol (CBD) and tetrahydrocannabinol (THC) are two important components of the cannabis sativa plants. THC is known for its psychedelic qualities, which is mostly relevant for recreational use of cannabis. However, CBD appears to be more helpful in alleviating pain, which makes cannabis with a high CBD content more appealing for those using it for pain management (Bonaccorso et al., 2019).

Because of the cross-sectional design and inclusion criteria of the VAT study, there is no available data regarding participants' pain experience prior to their cannabis use. The question therefore remains whether the association between pain and cannabis use is non-existent in psychosis, or whether cannabis has the intended effect of self-medication against pain. Our sample includes people with psychotic disorders specifically from the northern Netherlands, which may limit the generalizability of our findings to other populations. Although our study had sufficient power (>86%), we emphasize caution regarding the interpretation of our findings.

Clinical implications and future research

Experiencing pain and interference with daily life from pain appears to be a common occurrence among people with a psychotic disorder, which deserves attention during treatment. We found no evidence for an association between pain experience and cannabis use. However, due to the potential for cannabis self-medication in pain management and the cross-sectional nature of this study, we cannot draw definitive conclusions about the relationship between pain experience and cannabis use in individuals with psychotic disorders. We recommend future longitudinal studies to further examine this association. Ideally, future studies should incorporate baseline data on pain experience collected prior to cannabis use. Examining fluctuations in pain experience and cannabis use over time may provide insight to a potential causal relationship between pain and cannabis use in psychosis, if such an association exists. Future studies should include a sample with a larger representation of patients in the 18–25 age range, and detailed information regarding the use of sedating antipsychotics. We also recommend further exploration of the sedating effects of antipsychotics in relation to cannabis use, since this could influence the choice of prescribed antipsychotics in the treatment of psychotic disorders in the future. A targeted approach, prescribing antipsychotics with higher sedating effects in patients with psychosis at risk for self-medicating with cannabis, could potentially help reduce cannabis use in these patients.

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Authors' contributions

MHS and JB were both involved in study conceptualization, formal analysis, and methodology. MHS was involved in data collection and writing the original draft. JB was acting supervisor and involved in writing, reviewing and editing.

Disclosure statement

The authors MHS and JB report there are no competing interests to declare.

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Data availability statement

Data is available upon request through primary investigator and coauthor of this study Dr. Jojanneke Bruins.

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