# Smoking Status and its Relationship to Demographic and Clinical Characteristics in First Episode Psychosis

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Abstract

Elevated rates of cigarette smoking are observed prior to the onset of psychosis and remain stable early in the illness. Cannabis use frequently co-occurs with cigarette smoking and is independently associated with distinct clinical outcomes. However, past research has not controlled for cannabis use in cigarette smokers with first episode psychosis (FEP), limiting conclusions on the unique relationship of cigarette smoking to the demographic and clinical profiles of these patients. The present study therefore aimed to: (1) Determine the prevalence and patterns of cigarette smoking and its co-use with cannabis in FEP, and (2) Examine the demographic, clinical, cognitive, and functional characteristics associated with cigarette smoking status, after adjusting for frequency of cannabis use. Patients entering specialized treatment for FEP ($N$ = 140) were divided into groups according to their current smoking status: 66 non-smokers (0 cigarettes/day), 47 light/moderate smokers (1-19 cigarettes/day; $M$ = 9.81, $SD$ = 3.93), and 27 heavy smokers (≥ 20 cigarettes/day; $M$ = 26.39, $SD$ = 6.31). The prevalence of cigarette smoking was 53% and smoking status was highly associated with frequency of cannabis use. After adjusting for cannabis use, significant between-group differences emerged. Heavy smokers were older at program entry and had a later age of onset of psychosis than light/moderate and non-smokers. Non-smokers had more education, better neurocognitive performance, and higher levels of functioning than light/moderate and heavy smokers. Prospective, longitudinal studies are needed to better understand the clinical significance of tobacco use and factors that contribute to the initiation and continuation of smoking behaviours in FEP.

*Keywords*: first episode psychosis, smoking, tobacco, cannabis, symptoms, cognition

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## 1. Introduction

The prevalence and intensity of tobacco use is remarkably high in first episode psychosis (FEP), with rates of daily cigarette smoking ranging from 52% to 77% (Kotov et al., 2010; Wade et al., 2005). Although estimates vary across studies and countries, FEP patients consistently demonstrate elevated rates of cigarette smoking relative to age-matched controls (Barnett et al., 2007) and less success with quitting compared to smokers in the general population (de Leon and Diaz, 2005). Regular cigarette use typically precedes the onset of psychosis (Myles et al., 2012b) and remains stable (Wade et al., 2006) or slightly increases (Harrison et al., 2008) during the early course of illness.

Several theories have been proposed to explain why individuals with psychosis are more vulnerable to initiate and maintain tobacco use. Common genetic factors and neurobiological mechanisms, such as abnormalities in the cholinergic and dopaminergic systems, are implicated in the pathophysiology of psychosis and nicotine dependence (Wing et al., 2012). Because nicotine stimulates dopamine release in the prefrontal cortex and reward mechanisms of the brain, the effects of cigarette smoking may be highly reinforcing for patients who experience prominent negative symptoms, which arise, in part, from diminished reward system activity (Glassman, 1993). It is also plausible that psychosis could lead to increased rates of tobacco use through attempts to self-medicate, given that cigarette smoking may ameliorate psychiatric symptoms, cognitive deficits, and/or side effects of antipsychotic medication (Kumari and Postma, 2005; Winterer, 2010). In support of this latter proposition, lower levels of negative

symptoms (Jiang et al., 2013; Smith et al., 2001) and higher neurocognitive performance across multiple neurocognitive domains (Morisano et al., 2013; Wing et al., 2011), especially working memory and attention (Ahlers et al., 2014; Jacobsen et al., 2004; Sacco et al., 2005), have been documented in cigarette smokers with chronic psychosis relative to non-smoking patients. On the other hand, tobacco use has also been associated with increases in positive (Uçok et al., 2004), negative (Cooper et al., 2012; Patkar et al., 2002), or both types of symptoms (Goff et al., 1992), as well as poorer global functioning (Vanable et al., 2003) and social adjustment (Krishnadas et al., 2012), suggesting that cigarette smoking could serve as a marker of severity in psychotic illness (Aguilar et al., 2005). Nevertheless, the clinical outcomes of patients who are chronically ill may not be representative of those in the earlier stages of psychosis.

An emerging literature has begun to examine the association between tobacco use and clinical characteristics of patients with FEP, yet findings are inconclusive and to some extent contradictory. In a study by Kotov et al. (2010), smokers exhibited greater functional impairment than non-smokers, and depressive symptoms positively covaried with cigarette smoking over a 10-year period. However, smoking was not associated with psychotic symptoms. Zhang et al. (2013) demonstrated a positive relationship between tobacco use and positive and global psychotic symptoms, whereas Berk et al. (2010) found that smoking status was unrelated to clinical course and functional outcomes over a 7.5-year follow-up. More recently, Misiak et al. (2015) reported that cigarette smokers with FEP had lower negative and depressive symptoms relative to non-smokers with FEP.

Investigations of neurocognitive performance as a function of smoking status in FEP have also yielded mixed results. Zabala et al. (2009) indicated that, compared to non-smokers at baseline, smokers ($\geq$ 20 cigarettes/day) displayed significantly better sustained attention and

working memory, but not executive functioning. However, these group differences were not maintained at a 12-month follow up (Segarra et al., 2011). Zhang et al. (2013) also failed to detect neurocognitive differences between smoking (> 1 cigarette/day) and non-smoking patients.

Methodological limitations may partly explain these inconsistent findings. For instance, smoking status is often imprecisely defined in the psychosis literature. Nearly all studies simply classified patients as "smoker" and "non-smoker" or removed light/moderate smokers (1-19 cigarettes/day) from analyses to compare non-smokers with heavy smokers (≥ 20 cigarettes/day), thereby reducing the variability associated with smoking status. Another explanation for the inconsistent findings could be the largely overlooked confound of concurrent cannabis use among cigarette smokers (Myles et al., 2012b). Cannabis and cigarette use are strongly correlated in psychotic disorders (Margolese et al., 2004) and can be equally predictive of subclinical psychotic symptoms in young adults (van Gastel et al., 2013). Moreover, cannabis is among the most commonly abused substances in FEP (Addington and Addington, 2007; Faridi et al., 2012) and may complicate the clinical presentation of psychosis through its association with more severe positive symptoms (Large et al., 2014), increased relapse rates, and treatment non-adherence (Faridi et al., 2012; Zammit et al., 2008). The failure of all previous studies to control for cannabis use in cigarette smokers makes it difficult to isolate the unique relationship of tobacco use to clinical characteristics in FEP. Finally, only one of the previous studies (Zhang et al., 2013) assessed the impact of smoking status on global neurocognitive functioning in FEP. This may be important to examine given that a more generalized neurocognitive impairment seems to contribute to a range of neurocognitive difficulties observed in schizophrenia (Dickinson et al., 2006).

By addressing these key limitations, the present study therefore aimed to: (1) Determine the prevalence and patterns of cigarette smoking and its co-use with cannabis at the time of initiation of treatment for FEP, and (2) Examine the demographic, clinical, global neurocognitive, and functional characteristics associated with cigarette smoking status, after adjusting for frequency of cannabis use.

## 2. Method

### 2.1. Participants and treatment setting

All participants were part of a larger prospective study of FEP at the Prevention and Early Intervention Program for Psychoses (PEPP-Montréal) in Montréal, Canada. PEPP-Montréal is a specialized early intervention program that provides intensive medical and psychosocial treatment for affective or non-affective FEP. Individuals aged 14 to 35 from the local catchment area consecutively admitted between 2008 and 2015 were eligible for participation in the study. The exclusion criteria were as follows: primary diagnosis of substance abuse or dependence, antipsychotic treatment for more than one month, IQ < 70, a history of neurological disorders (e.g., epilepsy), and an inability to speak either English or French (Iyer et al., 2015). Research protocols were approved by the Douglas Institute Human Ethics Review Board and written informed consent was obtained from all participants, with parental consent obtained from those under the age of 18.

### 2.2. Measures

#### 2.2.1. Demographic and clinical assessments

At program entry, trained research staff collected detailed information on participants' sex, age, education, socio-economic status (SES), age of onset, and duration of untreated psychosis (DUP). SES was determined based on the Hollingshead (1965) two-factor index of

social status, which is a weighted average of years of formal education and occupational prestige of participants. DUP was defined as the time period from onset of psychotic symptoms to adequate treatment with antipsychotic medication. Age of onset and DUP were determined using the Circumstances of Onset and Relapse Schedule (Malla et al., 2006). Baseline diagnoses were established with the Structured Clinical Interview for DSM-IV (First et al., 1995). From this interview, participants were classified into two primary diagnostic categories: Schizophrenia-Spectrum or Non-Affective Psychotic Disorder (Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder, Brief Psychotic Episode, and Psychosis NOS) or Affective Psychotic Disorder (Bipolar Disorder with Psychotic Features and Major Depressive Disorder with Psychotic Features). Secondary substance abuse or dependence diagnoses (past and current) were also established with this interview. Positive and negative symptoms were assessed with the Scale for the Assessment of Positive Symptoms (Andreasen, 1984b) and Scale for the Assessment of Negative Symptoms (Andreasen, 1984a), respectively. Other symptom measures included the Calgary Depression Scale for Schizophrenia (Addington et al., 1990) and the Hamilton Anxiety Rating Scale (Hamilton, 1969). Antipsychotic medication and dosage were recorded and converted into chlorpromazine equivalents according to the literature (Leucht et al., 2014). All diagnostic ratings and estimation of DUP were confirmed by consensus between research staff and a senior research psychiatrist (A.M. or R.J.).

**2.2.2. Smoking status**

The Chemical Use, Abuse, and Dependence Scale (CUAD; McGovern and Morrison, 1992), a brief semi-structured interview, was administered to ascertain the presence and frequency of tobacco and cannabis use. Tobacco use frequency was based on the number of self-reported cigarettes smoked per day for individuals who identified as a non-smoker or daily

smoker. Intermittent smokers (i.e., those who reported tobacco use from < 1 time/month to ≤ 3 times/week) were excluded from the analyses due to their low numbers ($n$ = 17). Participants were subsequently categorized (Health Canada, 2008) as non-smokers (0 cigarettes/day), light/moderate smokers (1-19 cigarettes/day), or heavy smokers (≥ 20 cigarettes/day). This classification, based on the cut-off of one pack of 20 cigarettes/day, is also supported in the tobacco literature (Alati et al., 2004; Chin et al., 2012; Kay-Lambkin et al., 2013; Shelef et al., 2009).

Cannabis use frequency was determined using CUAD criteria: non-user, < 1 time/month, ≥ 1 time/month, ≤ 1 time/week, ≤ 3 times/week, and daily user. Only participants reporting stable tobacco and cannabis smoking status for ≥ 1 month were included.

**2.2.3. Neurocognitive assessment**

Neurocognitive testing was completed following stabilization of acute psychotic symptoms, usually within three months of entry to the program. Supervised by a neuropsychologist (M.L.), trained research staff administered a neuropsychological battery that assessed six cognitive domains found to be consistently impaired and related to outcome in psychosis (Nuechterlein et al., 2004). These domains were: (1) *Verbal Learning and Memory*, (2) *Visual Learning and Memory*, (3) *Working Memory*, (4) *Speed of Processing*, (5) *Reasoning/Problem Solving*, and (6) *Attention*. Due to modifications to the assessment protocol over the course of the study, participants received either a traditional paper-and-pen battery or a computerized battery (CogState Research Battery) to measure the six cognitive domains. The paper-and-pen battery included the following neurocognitive tests: (1) the Logical Memory subtests of the Wechsler Memory Scale III (WMS-III; Wechsler, 1997b); (2) the Visual Reproduction subtests of the WMS-III; (3) the Spatial Span subtests of the WMS-III and Digit

Span subtests of the Wechsler Adult Intelligence Scale III (WAIS-III; Wechsler, 1997a); (4) the Trail Making Test-Part A (Reitan, 1992) and the Digit Symbol subtest of the WAIS-III; (5) the Trail Making Test-Part B (Reitan, 1992) and the Block Design subtest of the WAIS-III; and (6) the Concentration Performance score on the d2 Test of Attention (Brickenkamp and Zillmer, 1998). The individual tests that comprised each of the domains for the computerized battery are reported elsewhere (Benoit et al., 2015). Raw scores for all of the neurocognitive tests were converted to standard scores based on normative data from a group of age- and gender-matched healthy controls recruited from the same catchment area (Benoit et al., 2015). Although six cognitive domains were separately calculated for each battery, a neurocognitive composite score was the primary outcome measure, given that a more generalized impairment may better account for the range of neurocognitive difficulties observed in schizophrenia (Dickinson et al., 2006).

### 2.2.4. Functional assessment

Global functioning was measured with the Strauss Carpenter Level of Functioning Scale (SCLFS; Strauss and Carpenter, 1972). The SCLFS evaluates functioning over a 12-month period in four areas: severity of psychiatric symptoms, duration of non-hospitalization, percentage of time employed or engaged in education, and frequency of social contacts. Each area was rated on a 5-point Likert scale from 0 (worst functioning) to 4 (best functioning). A global functioning score was calculated by averaging the four item scores.

## 3. Data Analysis

Due to the non-normality of the cannabis frequency data, a Kruskal-Wallis test was conducted to evaluate group differences in reported cannabis use, and post-hoc comparisons were applied using Mann-Whitney *U* tests. Group comparisons of demographic and clinical characteristics were performed using Pearson chi-square tests for categorical variables and

ANCOVAs for continuous variables after adjusting for frequency of cannabis use. Results from the analyses before adjusting for frequency of cannabis use are presented in supplementary material. Given the exploratory nature of the analyses, a *p*-value of ≤ .05 was considered statistically significant for all omnibus tests and post-hoc comparisons. Independent samples *t*-tests were performed to compare participants who received the paper-and-pen battery with those who received the computerized battery on demographic and clinical characteristics.

Effect sizes were represented with partial eta squared, and conventional definitions of small (.01), medium (.06), and large (.14) effects were used to interpret the findings (Cohen, 1988).

## 4. Results

### 4.1. Smoking status

The sample included 140 FEP patients ($M_{age}$ = 24.16, *SD* = 4.68) who entered the program between May 2008 and March 2015 and provided informed consent. Of these 140 patients, 66 (47%) were non-smokers (0 cigarettes/day), 47 (34%) were light/moderate smokers (1-19 cigarettes/day), and 27 (19%) were heavy smokers (≥ 20 cigarettes/day). The prevalence of cigarette smoking (≥ 1 cigarettes/day) was 53% (*n* = 74).

Frequencies of tobacco and cannabis use for participants at baseline are displayed in Table 1. Light/moderate and heavy smokers consumed, on average, 9.81 and 26.39 cigarettes/day (*SD*s = 3.93 and 6.31) and accounted for 64% and 36% of the smokers, respectively.

Fourty-four percent of the sample did not report smoking cannabis, whereas thirty-four percent reported smoking cannabis daily. A Kruskal-Wallis test was conducted to evaluate differences among the three smoking groups (non-smoker, light/moderate, heavy) on median

frequency of cannabis use (non-user, < 1 time/month, ≥ 1 time/month, ≤ 1 time/week, ≤ 3 times/week, or daily user). The test revealed significant group differences in frequency of cannabis use, $\chi^2(2, N = 140) = 33.69$, $p < .001$. Results of follow-up tests indicated that heavy cigarette smokers (*Mdn* = daily cannabis user) used cannabis significantly more often than light/moderate cigarette smokers (*Mdn* = ≤ 1 time/week cannabis user), $U = 375$, $p = .001$, $r = .37$, and non-cigarette smokers (*Mdn* = non-cannabis user), $U = 274$, $p < .001$, $r = .58$. Similarly, light/moderate cigarette smokers used cannabis more often than non-cigarette smokers, $U = 1{,}057$, $p = .002$, $r = .29$.

**4.2. Demographic and clinical characteristics**

Between May 2008 and March 2015, 286 patients entered the program and consented for their data to be used for research. Patients were excluded if they identified as intermittent smokers ($n = 17$) or had missing data for any demographic and clinical ($n = 68$) or smoking status variables ($n = 61$), yielding a final sample of 140 participants. After comparing the characteristics of participants and non-participants, the only significant differences observed were higher baseline antipsychotic dosage and anxiety symptoms for participants relative to non-participants (see Table 2).

See Table 3 for demographic and clinical characteristics according to baseline smoking status. After adjusting for frequency of cannabis use, smoking status was not significantly related to sex, primary diagnosis, and SES. However, group differences were observed on other characteristics. Non-smokers were less likely to have a secondary substance abuse or dependence diagnosis (in reference to any substance) than light/moderate smokers, $\chi^2(1, N = 113) = 20.57$, $p < .001$, and heavy smokers, $\chi^2(1, N = 93) = 26.92$, $p < .001$ (see Table 4 for a summary of past and current substance abuse or dependence diagnoses). Non-smokers also had more years of

education than light/moderate smokers, $F(1, 136) = 5.92$, $p = .02$, and heavy smokers, $F(1, 136) = 3.89$, $p = .05$. Heavy smokers were older than light/moderate smokers, $F(1, 136) = 7.50$, $p = .01$, and non-smokers, $F(1, 136) = 9.72$, $p = .002$, and had a later age of onset of psychosis than light/moderate smokers, $F(1, 136) = 4.16$, $p = .04$, and non-smokers, $F(1, 136) = 8.37$, $p = .004$. No differences emerged between groups on DUP, level of positive, negative and anxiety symptoms, and antipsychotic dosage. There was a non-significant trend for heavy smokers to have higher depressive symptoms than light/moderate smokers and non-smokers, $F(2, 135) = 2.43$, $p = .09$. Non-smokers showed better overall functioning than light-moderate smokers, $F(1, 116) = 7.03$, $p = .01$, and heavy smokers, $F(1, 116) = 4.70$, $p = .03$.

**4.3. Neurocognition**

A neurocognitive composite score was calculated for each battery by averaging the *z*-scores of all individual tests, and this composite score was our main neurocognitive variable of interest. Data from 106 participants who completed all of the tests in the paper-and-pen ($n = 38$) or computerized battery ($n = 48$) were used to construct the neurocognitive composite. Participants assessed with the paper-and-pen battery had lower anxiety symptoms ($M = 10.94$, $SD = 7.22$) compared to participants assessed with the computerized battery ($M = 14.41$, $SD = 7.47$), $t(104) = 2.42$, $p = .02$. Additionally, participants who received the paper-and-pen battery performed worse ($M = -.25$, $SD = .78$) than those who received the computerized battery ($M = -.01$, $SD = .39$), $t(104) = 2.11$, $p = .04$, which was anticipated based on previous research (Benoit et al., 2015). We therefore included type of battery as a covariate while examining between group differences on the neurocognitive composite based on smoking status. Type of battery emerged as a significant covariate for this analysis, $F(1, 101) = 5.40$, $p = .02$.

Neurocognitive performance was found to be associated with smoking status (see Table 3). Light/moderate smokers exhibited poorer performance on global neurocognition relative to non-smokers, $F(1, 101) = 5.58$, $p = .02$. Similarly, heavy smokers exhibited poorer performance on global neurocognition relative to non-smokers, $F(1, 101) = 4.25$, $p = .04$. Light/moderate and heavy smokers did not differ in their neurocognitive performance.

## 5. Discussion

### 5.1. Smoking status, demographic, and clinical characteristics

Tobacco use remains a critical, yet understudied issue in FEP. At 53%, the prevalence of cigarette smoking in our study was comparable to what has been reported in other FEP samples from different geographic regions and time periods (e.g., 52%; Kotov et al., 2010), but more than two times greater than those of young adults (aged 20-24) sampled from the general population in the same geographic region (e.g., 22%; Health Canada, 2013). Cigarette smoking was also highly associated with frequency of cannabis use and substance abuse or dependence status, which further supports the co-occurrence of tobacco and cannabis use in FEP, and the need to account for the confounding effects of other substances when evaluating outcomes associated with tobacco use.

Heavy cigarette smokers had a later age of onset and were significantly older at program entry than light/moderate smokers and non-smokers. In accordance with the self-medication hypothesis (Kumari and Postma, 2005; Winterer, 2010), heavy tobacco use may reflect an attempt to manage subclinical psychotic symptoms or more general prodromal psychopathology. While it is reasonable to assume that delays in help-seeking might be responsible for heavy smokers' older age at program entry, smoking status showed no association with DUP. Nevertheless, these interpretations require further investigation through studies examining

patterns of tobacco and cannabis use prior to onset of psychosis, given that some (Ma et al., 2010; Misiak et al., 2015) but not all studies (Gurillo et al., 2015; Myles et al., 2012a) have reported a later age of psychosis onset among smokers.

The relationship found between smoking status and psychotic symptoms was not statistically significant, although there was a trend for heavy smokers to exhibit higher depressive symptoms than light/moderate and non-smokers. We noted poorer performance on global neurocognition among light/moderate and heavy smokers relative to non-smokers, with a medium effect size. Light/moderate smokers had higher global neurocognitive functioning than heavy smokers, although the difference was not statistically significant. Taken together, these results may suggest an exposure-response relationship between smoking and global neurcognition, when accounting for cannabis use, such that linear increases in tobacco use may correspond with linear decreases in neurocognitive performance. However, this will need to be tested in future studies with larger sample sizes before any firm conclusions can be drawn.

Similar to neurocognition, functional impairment was also associated with smoking status. These findings are consistent with those from recent studies that demonstrated current smokers with schizophrenia exhibit greater working memory impairments than non-smokers (Lee et al., 2015) and worse cognitive and functional outcomes than past smokers or those who had never smoked (Depp et al., 2015). While selective improvements in working memory and attention have been identified in first episode (Zabala et al., 2009) and chronic patients who smoke cigarettes (Ahlers et al., 2014; Jacobsen et al., 2004; Sacco et al., 2005), evidence also suggests that these cognition-enhancing effects of smoking might be due to the reversal of nicotine withdrawal (Sacco et al., 2005), especially since smoking cessation is known to impair working memory in schizophrenia (George et al., 2002).

### 5.2. Limitations

Because participants were asked their current smoking status, lifetime smokers who were not actively smoking at program entry could have been categorized as non-smokers. Secondly, cannabis use frequency was measured with a single item rated on an ordinal scale rather than continuously, possibly limiting the reliability of the score and causing the underestimation of effect sizes. Also, tobacco and cannabis use frequency, being self-reported, may have been subject to reporting bias. While self-reported measures were not corroborated with toxicological evaluations, research suggests that adults with schizophrenia are generally willing and able to accurately self-report drug use (Van Dorn et al., 2012). Using archival data also constrained the present analyses by the types of data that were collected for the larger study. For example, two different neuropsychological test batteries were used over time, which could arguably have impacted the interpretation of neurocognitive data. To account for this, we included type of battery as a covariate in our analyses and only examined global neurocognition (and not individual neurocognitive domains), thus increasing confidence in our findings. Further, although a substantial number of patients were not included in our study due to missing data, the final sample was more thoroughly characterized than in most studies. Importantly, cannabis use frequency was adjusted for in all of the analyses. Other substances which may obscure the relationship between tobacco use and clinical outcomes (Archie and Gyömörey, 2009), such as alcohol, cocaine, hallucinogens, and stimulants, were not accounted for given their low prevalence in our sample.

### 5.3. Conclusions and future directions

The present study supports and extends past research by demonstrating that patients with FEP use tobacco and cannabis at high rates, and exhibit differential demographic and clinical

profiles depending on their cigarette smoking status, even after adjusting for frequency of cannabis use. Notably, neurocognitive and functional impairments are more pronounced in light/moderate and heavy cigarette smokers with FEP relative to non-smoking patients at initial presentation for treatment, lending support to the theory that cigarette smoking may be indicative of greater illness severity. Nevertheless, the mechanisms underlying these effects are still not clearly understood. Because of the shared genetic, environmental, and socioeconomic factors associated with tobacco and cannabis use (Agrawal et al., 2012), more should be done to address the influence of these factors on smoking status and clinical course in FEP (Gage et al., 2014). Larger, prospective studies can provide important information on smoking status and its relationship with illness onset and progression, and help determine whether reducing the frequency of tobacco and cannabis co-use is associated with improved long-term outcomes.

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Table 1. Frequency of cannabis and tobacco use at baseline for participants ($N$ = 140).

| Frequency of Cannabis Use | Frequency of Tobacco Use | | |
|---|---|---|---|
| | Non-Smokers ($n$ = 66) | Light/Moderate ($n$ = 47) | Heavy ($n$ = 27) |
| Non-user | 41 | 18 | 3 |
| < 1 time/month | 6 | 1 | 0 |
| ≥ 1 time/month | 4 | 2 | 1 |
| ≤ 1 time/week | 1 | 3 | 1 |
| ≤ 3 times/week | 5 | 5 | 1 |
| Daily user | 9 | 18 | 21 |

Table 2. Comparison of baseline demographics and clinical characteristics between participants and non-participants.

| Characteristic | Participants ($N$ = 140) | Non-participants ($N$ = 146) | Test statistic | $p$ value |
|---|---|---|---|---|
| Sex, frequency (%) | | | | |
| Male | 99 (70.71) | 102 (70.83) | $\chi^2(1) < .01$ | .98 |
| Female | 41 (29.29) | 42 (29.17) | | |
| | | [144] | | |
| Primary Diagnosis, frequency (%) | | | | |
| Non-Affective Psychotic Disorder | 93 (66.43) | 75 (67.57) | $\chi^2(1) = .04$ | .85 |
| Affective Psychotic Disorder | 47 (33.57) | 36 (32.43) | | |
| | | [111] | | |
| Secondary Substance Abuse or Dependence Diagnosis, frequency (%) | | | | |
| | 83 (59.29) | 50 (62.50) | $\chi^2(1) = .22$ | .64 |
| Yes | 57 (40.71) | 30 (37.50) | | |
| No | | [80] | | |
| Age at program entry (years) | 24.16 (4.68) | 23.94 (5.17) | $t(278) = .38$ | .71 |
| | | [140] | | |
| Education (years) | 11.73 (2.86) | 11.92 (2.95) | $t(242) = .52$ | .60 |
| | | [104] | | |
| Patient SES[a] | 3.83 (1.13) | 3.78 (1.11) | $t(160) = .28$ | .78 |
| | [99] | [63] | | |
| Age of onset (years) | 23.16 (4.93) | 23.07 (5.11) | $t(248) = .14$ | .62 |
| | | [110] | | |
| DUP[b] | 2.82 (1.73) | 2.75 (1.74) | $t(216) = .28$ | .78 |
| | [131] | [87] | | |
| Antipsychotic dosage (mg/day in CPZeq) | 285.72 (409.70) | 173.36 (237.96) | $t(221.28) = 2.82$ | **.01** |
| SAPS total | 37.89 (16.12) | 35.18 (13.93) | $t(268.65) = 1.49$ | .14 |
| | | [133] | | |

| | | | | |
|---|---|---|---|---|
| SANS total | 30.03 (14.52) | 28.87 (15.75) [127] | *t*(265) = .63 | .53 |
| CDSS | 4.98 (4.29) | 5.09 (4.62) [121] | *t*(259) = .20 | .84 |
| HARS | 12.79 (7.59) | 10.17 (7.18) [107] | *t*(245) = 2.76 | **.01** |
| SCLFS | 2.23 (.71) [121] | 2.32 (.63) [95] | *t*(214) = .91 | .36 |
| Neurocognition composite (*z*-score) | -.09 (.59) [106] | -.07 (.55) [91] | *t*(195) = .31 | .76 |

*Note*: Values reported as mean (standard deviation) unless stated otherwise. The critical *p*-value was set at .05 with significant results highlighted in bold. [*n*] denotes number of patients with available data. SES, socioeconomic status; DUP, duration of untreated psychosis; CPZeq, chlorpromazine equivalents; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; HARS, Hamilton Anxiety Rating Scale; SCLFS, Strauss Carpenter Level of Functioning Scale.

[a]Hollingshead index scores range from 1 to 5, and higher scores correspond with lower SES.

[b]DUP required a logarithmic transformation to achieve normal distribution.

Table 3. Baseline demographics and clinical characteristics of participants ($N$ = 140) according to their smoking status after adjusting for frequency of cannabis use.

| Characteristic | Smoking Status | | | Test statistic | $p$ value | Partial $\eta^2$ | Post-hoc contrasts |
|---|---|---|---|---|---|---|---|
| | Non-Smokers ($n$ = 66) | Light/Moderate ($n$ = 47) | Heavy ($n$ = 27) | | | | |
| Sex, frequency (%) | | | | | | | |
| Male | 41 (62.1) | 37 (78.7) | 21 (77.8) | $\chi^2(2) = 4.46$ | .11 | | |
| Female | 25 (37.9) | 10 (21.3) | 6 (22.2) | | | | |
| Primary Diagnosis, frequency (%) | | | | | | | |
| Non-Affective Psychotic Disorder | 46 (69.7) | 30 (63.8) | 17 (63) | $\chi^2(2) = .60$ | .74 | | |
| Affective Psychotic Disorder | 20 (30.3) | 17 (36.2) | 10 (37) | | | | |
| Secondary Substance Abuse or Dependence Diagnosis, frequency (%) | | | | | | | |
| Yes | 22 (33.3) | 36 (76.6) | 25 (92.6) | $\chi^2(2) = 36.66$ | **<.001** | | NS < LM, Heavy |
| No | 44 (66.7) | 11 (23.4) | 2 (7.4) | | | | |
| Age at program entry (years) | 23.25 (.60) | 23.84 (.67) | 26.97 (.96) | $F(2, 136) = 5.18$ | **.007** | .07 | NS, LM < Heavy |
| Education (years) | 12.44 (.35) | 11.13 (.40) | 11.05 (.57) | $F(2, 136) = 3.48$ | **.03** | .05 | NS > LM, Heavy |
| Patient SES[a] | 3.86 (.17) [50] | 3.75 (.20) [31] | 3.88 (.28) [18] | $F(2, 95) = .12$ | .89 | .002 | |
| Age of onset (years) | 22.05 (.63) | 23.24 (.71) | 25.71 (1.01) | $F(2, 136) = 4.18$ | **.02** | .06 | NS, LM < Heavy |
| DUP[b] | 2.64 (.23) [64] | 2.83 (.27) [41] | 3.23 (.37) [26] | $F(2, 127) = .84$ | .44 | .01 | |
| Antipsychotic dosage (mg/day in CPZeq) | 336.35 (53.68) | 219.54 (60.11) | 277.16 (85.90) | $F(2, 136) = 1.02$ | .36 | .02 | |
| SAPS total[c] | 36.56 (2.17) | 38.16 (2.35) | 40.69 (3.46) | $F(2, 135) = .46$ | .63 | .01 | |
| SANS total[c] | 28.78 (1.90) | 30.76 (2.11) | 31.80 (3.10) | $F(2, 135) = .38$ | .69 | .01 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CDSS[c] | 4.32 (.56) | 4.84 (.62) | 6.82 (.92) | $F(2, 135) = 2.43$ | .09 | .04 | |
| HARS[c] | 12.28 (1.00) | 12.42 (1.11) | 14.72 (1.64) | $F(2, 135) = .82$ | .44 | .01 | |
| SCLFS[c] | 2.45 (.10) [56] | 2.06 (.11) [40] | 2.02 (.16) [25] | $F(2, 116) = 4.15$ | **.02** | .07 | NS > LM, Heavy |
| Neurocognition composite (*z*-score)[d] | .05 (.08) [52] | -.26 (.10) [ 36] | -.32 (.15) [18] | $F(2, 101) = 3.48$ | **.03** | .07 | NS > LM, Heavy |

*Note*: Values reported as adjusted mean (standard error) unless stated otherwise. The critical *p*-value was set at .05 with significant results highlighted in bold. [*n*] denotes number of patients with available data. Smoking status was defined as follows: Non-Smokers (NS) = 0 cigarettes/day, Light/Moderate (LM) = 1-19 cigarettes/day, and Heavy ≥ 20 cigarettes/day. SES, socioeconomic status; DUP, duration of untreated psychosis; CPZeq, chlorpromazine equivalents; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; HARS, Hamilton Anxiety Rating Scale; SCLFS, Strauss Carpenter Level of Functioning Scale.

[a]Hollingshead index scores range from 1 to 5, and higher scores correspond with lower SES.

[b]DUP required a logarithmic transformation to achieve normal distribution.

[c]Age at program entry and frequency of cannabis use were entered as covariates for these analyses.

[d]Type of neurocognitive battery and frequency of cannabis use were entered as covariates for this analysis.

Table 4. Secondary substance dependence and abuse diagnoses (past and current) at baseline for participants ($N$ = 140) according to their smoking status.

| | Non-Smokers ($n$ = 66) | Light/Moderate ($n$ = 47) | Heavy ($n$ = 27) |
|---|---|---|---|
| Alcohol | | | |
| Dependence | 0 | 0 | 2 |
| Abuse | 6 | 7 | 7 |
| Cannabis | | | |
| Dependence | 8 | 12 | 13 |
| Abuse | 9 | 19 | 7 |
| Cocaine | | | |
| Dependence | 0 | 1 | 1 |
| Abuse | 1 | 4 | 0 |
| Amphetamine | | | |
| Dependence | 0 | 1 | 3 |
| Abuse | 2 | 1 | 2 |
| Hallucinogen | | | |
| Dependence | 0 | 0 | 0 |
| Abuse | 0 | 2 | 1 |
| Other Substance | | | |
| Dependence | 0 | 0 | 1 |
| Abuse | 0 | 0 | 0 |
| Polysubstance | | | |
| Dependence | 0 | 3 | 6 |
| Abuse | 2 | 0 | 1 |

*Note:* Frequencies refer to past and current diagnoses based on the Structured Clinical Interview for DSM-IV. Diagnoses are not mutually exclusive, and participants may be represented in multiple cells if they met criteria for more than one substance dependence and/or abuse diagnosis in the past and/or at present.

## Conflicts of Interest

Dr. Malla is supported by the Canada Research Chairs Program funded by the Federal Government of Canada. In addition, Dr. Malla has received research funding and honoraria for conference presentations and participation in advisory boards for the following pharmaceutical industries in the past five years: Otsuka, Lundbeck, Roche, Janssen-Ortho, and Bristol-Myers Squibb.

Dr. Joober is supported by the Fonds de recherche du Québec – Santé. In addition, Dr. Joober sits on the advisory boards and speakers' bureaus of Pfizer Canada, Janssen Ortho Canada, BMS and Sunovian, Myelin Canada, Otsuka Canada and Perdue Pharmaceuticals; he has received grant funding from AstraZeneca and Lundbeck Canada. He has received honoraria from Janssen Ortho Canada, Shire and from Pfizer Canada for CME presentations and royalties from Henry Stewart talks.

Dr. Iyer is supported by the Fonds de recherche du Québec – Santé, and reports no biomedical financial interests or potential conflicts of interest.

Mr. Grossman, Dr. Bowie, and Dr. Lepage report no conflicts of interest.

## Contributors

The first and senior authors (Mr. Grossman, Dr. Joober, and Dr. Iyer) conceptualized and designed the study. Mr. Grossman conducted the literature search, undertook the statistical analyses, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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