



A retrospective study of the role of long-acting injectable antipsychotics in preventing rehospitalization in early psychosis with cannabis use



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ABSTRACT

Background: Despite compelling evidence that cannabis use is associated with neurocognitive deficits, loss of cerebral gray matter, relapse and rehospitalization, a substantial number of individuals with early psychosis continue to use recreational or medicinal marijuana. One identified pathway to relapse is non-adherence. Recurrent relapses modify the trajectory of illness and culminate in long-term disability. Long-acting antipsychotic medications are superior to oral equivalents in preventing relapse.

Purpose: The current paper sought to examine the role of long-acting antipsychotics in preventing relapse in cannabis using early psychosis patients.

Methods: The present retrospective study, which was based in an early psychosis program in mid-Michigan, examined the association between patient perceptions of antipsychotic medication and subsequent rehospitalization, among cannabis users (n = 24) and non-users (n = 27). Patient perceptions of antipsychotic medications were assessed using a single question from the NAVIGATE Patient Self-Rating Form: "Between now and your next visit, do you think we should keep your medication the same, or consider changing the medication?"

Results: Cannabis users were substantially more likely to report dissatisfaction with antipsychotic medication (Pearson Chi-square 9.67, df = 1.0, p < 0.002), and more likely to experience rehospitalization (Pearson Chi-square 4.40, df = 1.0, p = 0.036). Those maintained on long-acting injectable antipsychotic medications were rehospitalized less frequently when compared to others maintained on oral formulations (Pearson Chi-square 4.61, df = 1.0, p = 0.032).

Conclusions: Dissatisfaction with antipsychotics may predict non-adherence and subsequent rehospitalization in early psychosis patients who use cannabis. Long-acting antipsychotics may prevent rehospitalization.

1. Introduction

In patients with first episode psychosis cannabis use is associated with neurocognitive deficits and loss of cerebral gray matter (Nunez et al., 2016; Rais et al., 2008). Continued cannabis use after first episode psychosis is associated with a dose-dependent increase in the risk, frequency and severity of relapse (Schoeler et al., 2017). It is estimated that a third of all patients with schizophrenia (Starr, Bermak, Mao, Rodriguez, & Alphs, 2018), and two thirds of patients who have experienced a first psychotic episode (Hahn, 2018) use cannabis. For many, cannabis-induced psychosis represents a step in the overall progression towards schizophrenia. Nearly 50% of patients who experience a first episode of cannabis-induced psychosis convert to schizophrenia over the ensuing 2–4 years (Starzer, Nordentoft, & Hjorthoj,

2018). Unfortunately, individuals who have experienced a first episode of psychosis, and those who are at extremely high risk for developing psychosis, have a proclivity for cannabis abuse (Shrivastava, Johnston, Terpstra, & Bureau, 2015).

The RAISE-ETP (Early Treatment Program) study, which enrolled patients between the ages of 15 and 40, who had experienced a single episode of schizophrenia and related disorders, established that early detection and coordinated specialty care of first episode psychosis can modify the trajectory of illness, enabling patients to achieve a better quality of life, minimizing overall symptom burden (Kane, Robinson, & Schooler, 2016). Relapse during the first few years after first psychotic episode predicts long term disability. Relapse occurs twice as commonly among those who continue to smoke marijuana as compared to those that stop smoking (Schoeler et al., 2017). The UK Schizophrenia

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Commission (Schizophrenia Commission, 2012) identified cannabis use as the “single most preventable risk factor in the development of a psychotic disorder.”

It is estimated that 30% of adverse outcomes associated with cannabis use in schizophrenia are related to medication non-adherence (Schoeler et al., 2017). It follows, therefore, that interventions directed at enhancing medication adherence may prevent relapse. Long-acting injectable antipsychotics are superior to oral equivalents in preventing relapse in patients with early psychosis (Kishi, Oya, & Iwata, 2016), and in dually diagnosed patients with psychosis and comorbid substance use disorder (Starr et al., 2018; Viala et al., 2007). We are unaware of any study that examined the role of long-acting antipsychotics in preventing relapse in patients with early psychosis and concurrent cannabis use disorder.

2. Objective

The purpose of this study was to examine the role of long-acting injectable antipsychotics in preventing relapse in a cohort of early psychosis patients with concurrent cannabis use disorder. Our hypothesis was that long-acting antipsychotics would prove to be superior to oral formulations in this population.

3. Methods

We completed a retrospective chart review of all patients diagnosed with early psychosis at the Early Treatment & Cognitive Health (ETCH) Program in East Lansing, over 12 consecutive calendar months (2017). At ETCH, a treatment program that specializes in the management of early psychosis, we employ the NAVIGATE ETP model of Coordinated Specialty Care. For the purpose of our study “early psychosis” was defined as having experienced a duration of psychosis of 18 months or less. The Institutional Review Board at Michigan State University was apprised of the study, and considered it exempt. Sources of data included the NAVIGATE Patient Self-Rating Form, the Practice Fusion web-based electronic medical record platform, and the ETCH program’s hospitalization log. Item 36 on the NAVIGATE Patient Self-Rating Form inquires: “Since your last visit have you used any marijuana?” Patients who had at least a single positive answer on this item, during calendar year 2017, were considered as cannabis users. Patients who had negative responses on this item but were reported to be users by their therapists at ETCH were also categorized as cannabis users. Urine drug screening was not used. The prescriber’s role in the NAVIGATE ETP treatment model is based on Shared Decision Making. Hence, Item 38 on the NAVIGATE Patient Self-Rating Form asks: “Between now and your next visit, do you think we should keep your medication the same, or consider changing the medication?” A request to change the medication was considered to represent dissatisfaction with the prescribed regimen. Antipsychotic prescription information was gleaned from the Practice Fusion electronic medical record. All data were abstracted anonymously and entered into the MYSTAT statistical software program for analysis. Differences in the mean values of relapse (defined as re-hospitalization) between patients maintained on long acting injectable antipsychotics were compared to others maintained on oral antipsychotics or those not taking any recommended antipsychotic.

4. Results

Fifty-one patients, ages 17–31 years, were included in the study. These included 39 men and 12 women. Twenty-seven (53%) were cannabis non-users. Twenty-four (47%) were cannabis users. Twenty-two (56%) of the men, but only two (17%) of the women were cannabis users; Pearson Chi-square 5.81, $df = 1.0$, $p = 0.016$. The study did not address socioeconomic status or level of education. Users and non-users did not differ in severity of illness, measured using Clinical Global Impression (Severity) rating completed at every visit (Table 1). Long-

Table 1

Demographic and clinical characteristics of patient sample (n = 51).

	Non-users (n = 27)	Users (n = 24)	Statistical significance
Age	23.0 (SD = 3.3) years	21.9 (SD = 2.5) years	Two sample t-test = 1.3, $df = 49$, $p = 0.194$
Gender	10 women, 17 men	2 women, 22 men	Pearson Chi square 5.818, $df = 1$, $p = 0.016$
CGI (S)	3.3 (SD + 1.0)	3.2 (SD = 1.0)	Two sample t-test = 0.5, $df = 48$, $p = 0.637$

acting antipsychotics used included aripiprazole extended-release injection, haloperidol decanoate, paliperidone palmitate (1-month and 3-month formulations). Overall, 17 patients were maintained on long-acting injectable antipsychotics. Eight patients received long-acting injectable aripiprazole (1-month formulation). Six patients received long-acting paliperidone palmitate (1-month formulation). Three received long-acting paliperidone palmitate (3-month formulation). Oral antipsychotics included haloperidol, aripiprazole, ziprasidone, lurasidone, risperidone, olanzapine, quetiapine and clozapine. The cannabis users were more likely to express dissatisfaction with antipsychotics and request a medication change when compared to non-users. Sixteen (59%) of the users requested a change. Only four (16%) of the non-users requested a change; Pearson Chi-square 9.67, $df = 1.0$, $p < 0.002$. Eleven (46%) of the cannabis users were hospitalized during the calendar year. Only 5 (21%) of the non-users were hospitalized. Differences in rates of rehospitalization were statistically significant: Pearson Chi-square 4.40, $df = 1.0$, $p = 0.036$ (Table 2). Of the 10 cannabis users who were maintained on long-acting injectable antipsychotics, only 2 (20%) were hospitalized. Six patients were maintained on long-acting injectable aripiprazole (1-month formulation), 3 were maintained on long-acting paliperidone palmitate (1-month formulation), and 1 was maintained on paliperidone palmitate (3-month formulation). By comparison, 9 (64%) of 14 cannabis users on either oral or no antipsychotics were hospitalized. Differences in relapse rates were significant: Pearson Chi-square = 4.61, $df = 1.0$, $p = 0.032$ (Table 3).

5. Discussion

Worldwide, frequent use of high potency cannabis during adolescence is the single most important preventable cause of schizophrenia (The Health and Social Effects of Non-Medical Cannabis, 2016). High potency cannabis is more likely to induce enduring psychosis than other abused substances (Starzer et al., 2018). The pathogenic mechanisms implicated are unique, and not exclusively related to a perturbation of the dopamine circuits typically associated with psychosis (D’Souza, Sewell, & Ranganathan, 2009). Cannabinoid-1 receptors play a modulatory role in the delicate neuroplastic sculpting of the adolescent brain. Long-term use of exogenous cannabinoids such as tetrahydrocannabinol (THC) derail this delicate process, producing persistent impairments of cognitive and executive function (Atkinson & Abbott, 2018). The endogenous cannabinoid (anandamide) is a

Table 2

Effect of cannabis use on rates of re-hospitalization in early psychosis patients (n = 51).

	Non-users	Users	Total
Not hospitalized	22	11	35
Hospitalized	5	11	16
Total	27	24	51

Eleven (46%) of the cannabis users were hospitalized vs only 5 (21%) of the non-users.

Pearson Chi-square 4.40, $df = 1.0$, $p = 0.036$.

Table 3

Influence of antipsychotic formulation on re-hospitalization rates in cannabis users (n = 24).

	Not-hospitalized	Hospitalized	Total
Oral antipsychotics	5	9	14
Long-acting antipsychotics	8	2	10
Total	13	11	24

Only 2 (20%) of cannabis users maintained on long-acting injectable antipsychotics were hospitalized compared to 9 (64%) of 14 cannabis users on either oral or no antipsychotics were hospitalized.

Pearson Chi-square = 4.61, df = 1.0, p = 0.032.

retrograde “stress responsive” neurotransmitter. Released “on-demand” from post-synaptic neurons it modulates the activity of pre-synaptic neurons. It is thought to serve the purpose of erasing unnecessary and undesirable memories (e.g. traumatic events). In contrast, exogenous cannabinoids (e.g. THC) induce global memory deficits, loss of hippocampal gray matter volume and enduring down-regulation of cannabinoid-1 receptors in the hippocampus (Atkinson & Abbott, 2018). Additionally, disruption of balance between the dentate gyrus and CA3 areas of the hippocampus increases generation of associations (creativity) and decreased error-checking, leading to false beliefs (delusions) (Atkinson & Abbott, 2018).

In patients with schizophrenia cannabis use is associated with symptom exacerbation, relapse and rehospitalization. A third of the adverse outcomes is attributed to medication non-adherence (Schoeler et al., 2017).

In the present study cannabis users were more likely to express dissatisfaction with antipsychotic medication. They were also more likely to experience rehospitalization than non-users. Cannabis users who were maintained on long-acting injectable antipsychotic agents were less likely to be rehospitalized than those maintained on oral compounds. Conversely, it is conceivable that the more serious cannabis users were more likely to decline injectable long-acting antipsychotics, and express a preference for oral formulations, which enabled non-adherence, resulting in subsequent rehospitalization. There are few studies that suggest effective strategies for managing patients with early psychosis and concurrent cannabis use disorder (Bosanac, Lusicic, & Castle, 2018). Psychosocial interventions that combine motivational interviewing and cognitive behavior therapy are more effective than treatment as usual (Bosanac et al., 2018; Cooper, Chatters, Kaltenhaler, & Wong, 2015). Randomized controlled trials of cannabinoid receptor agonists (e.g. dronabinol), the opioid ν receptor antagonist (naltrexone) and antidepressants (e.g. bupropion) have proven inconclusive. Gabapentin and N-acetylcysteine have modest effects on curbing the use of cannabis. Among antipsychotics, second generation compounds as a group, and clozapine in particular, provide a modest advantage over first generation antipsychotics, in decreasing cannabis use in patients with schizophrenia and concurrent cannabis use disorder (Bosanac et al., 2018). Long-acting injectable antipsychotics are superior to oral equivalents in preventing relapse in dually diagnosed patients with psychosis and comorbid substance use disorder (Starr et al., 2018; Viala et al., 2007).

Long-acting antipsychotic medications are generally reserved for patients who are non-adherent with recommended oral preparations. A naturalistic study reflected that the difference in efficacy between long-acting antipsychotics and oral compounds was equivalent to the difference in efficacy between oral antipsychotics and placebo (Tiihonen, Mittendorf-Rutz, & Majak, 2017). A recent real-world prospective study of patients with schizophrenia and concurrent substance use disorders, who were recently released from prison, demonstrated that long-acting antipsychotics reduced rates of rehospitalization when compared to oral equivalent compounds (Starr et al., 2018).

The present study suggests that long-acting injectable antipsychotics may play a critical role in preventing rehospitalization in cannabis

using early psychosis patients.

The limitations of this study include the small (n = 51) sample size, the retrospective rather than prospective nature, and the single rather than multiple site design. It was assumed that a participant’s expressed desire for “a change in medication” implied “dissatisfaction” with prescribed medication. It is plausible that an individual’s desire for a change did not necessarily represent a desire to decrease or stop the antipsychotic medication. Rather, it may have represented a desire for an increase in dosage of the antipsychotic for better symptom control, or the addition of an antidepressant or anti-anxiety agent. Additionally, the subsample of cannabis users was identified using a single question on the NAVIGATE Self-Rating Form. Routine toxicology urine drug screening may have provided a more reliable measure of cannabis use. All participants were attending an early psychosis treatment program in a university town located in the US Mid-West. This may not be representative of the general population. The proportion of females to males was low, and the proportion of female cannabis users was even less. Therefore, it would be necessary to replicate this study with a larger, more diverse sample.

6. Conclusion

The present study affirms that cannabis use is common in patients with early psychosis. Cannabis use is associated with dissatisfaction with antipsychotic medication, discontinuation of recommended treatment and subsequent rehospitalization. Cannabis using patients who were maintained on long-acting antipsychotics were rehospitalized less frequently as compared to those maintained on oral compounds.

Future prospective studies of long-acting antipsychotic medications in this vulnerable population may shed further light on the growing enigma of cannabis use in early psychosis. Finally, among cannabis using early psychosis patients, expression of dissatisfaction with antipsychotic medication may be an early warning sign of impending non-adherence and subsequent relapse.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.abrep.2019.100221>.

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