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ORIGINAL INVESTIGATION

A prospective observational study of problematic oral cannabinoid use

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Abstract

Background Despite evidence supporting the benefits of cannabinoids for symptom control across a wide range of medical conditions, concerns have been raised regarding the potential misuse and/or problematic use of cannabinoids (CBs).

Objective The first objective of this study was to examine the incidence of problematic prescription cannabinoid use (PPCBU) over a 12-month period among patients initiating cannabinoid therapy. The second objective was to examine the factors associated with PPCBU. A total of 265 patients who were prescribed oral cannabinoid therapy as part of usual medical practice were enrolled into this prospective observational study. Patients first completed a series of baseline questionnaires assessing demographic, clinical, and substance use variables. Three measures designed to assess PPCBU were then administered at 3, 6, and 12 months after initiation of cannabinoid therapy.

Results At each of the follow-up assessment time points, a significantly greater number of patients scored below (vs above) cutoff scores on the three main PPCBU outcomes (all p's < .001). At any follow-up time point, a maximum of roughly 25% of patients demonstrated PPCBU. Heightened odds of PPCBU were observed among patients with a history of psychiatric problems, tobacco smokers, and recreational cannabis users (all p's < .05). Results indicated that past-year substance abuse, assessed using the DAST-20, was the strongest predictor of PPCBU (p < .005).

Conclusion Findings from the present study could have implications for clinicians considering the use of cannabinoids for the management of patients with medical conditions. Although results indicated that the majority of patients included in this study did not reach cutoff scores on the three main PPCBU outcomes, our findings suggest that PPCBU should be routinely assessed and monitored over the course of cannabinoid therapy, particularly among patients with a history of psychiatric or substance use problems.

Keywords Cannabinoids · Problematic cannabinoid use · Incidence · Risk factors

Introduction

Cannabinoids (CBs) are natural or synthetic drugs that bind to cannabinoid receptors or demonstrate endogenous cannabinoid system activity (Aggarwal 2013). Randomized, controlled trials of natural and synthetic CBs are showing efficacy for symptom control across a wide range of conditions, including chronic pain (Narang et al. 2008; Toth et al. 2012; Ware et al. 2010), cancer (Johnson et al. 2010; Portenoy et al. 2012), human immunodeficiency virus (Abrams et al.

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2007; Haney et al. 2005, 2007), and multiple sclerosis (Collin et al. 2010; Notcutt et al. 2012). Consequently, an increasing number of physicians are considering the therapeutic use of cannabinoids for symptom control among patients with these conditions (Carliner et al. 2017; Compton et al. 2017; Corroon et al. 2017; Hasin et al. 2016).

Despite the potential benefits of cannabinoids for symptom control across a wide range of medical conditions, concerns have been raised regarding the potential misuse and/or problematic use of prescription cannabinoids (Kahan and Srivastava 2007; Kalant 2004; Savage et al. 2016). In research and clinical settings, the term "problematic prescription drug use" has been commonly used to describe any problematic drug-related behaviors that arise over the course of therapy (Savage 2008; Smith and Passik 2008). Although problematic prescription drug use may simply take the form of transient "aberrant" drug use behaviors (e.g., hoarding or losing prescription drugs), it may also reflect more serious problems such as prescription drug misuse, addiction, or diversion (Savage 2008; Smith and Passik 2008).

While considerable research has been conducted among recreational cannabis users (Compton et al. 2004; Kalant 2004), research on problematic prescription cannabinoid use (PPCBU) among medical users has considerably lagged behind. To date, the bulk of studies that have been conducted among medical users have focused on potential adverse side effects of herbal cannabis or other prescription cannabinoids, with non-serious side effects such as dizziness, somnolence, and dry mouth being among the most commonly reported (Savage et al. 2016; Ware et al. 2015). A handful of studies have specifically examined the incidence of problematic cannabinoid use (e.g., cannabinoid overuse), but these studies were either short-term (≤ 12 weeks) randomized controlled trials (Collin et al. 2010) or trials in which "high-risk" patients (e.g., those with psychiatric issues or past history of substance use problems) were excluded (Wade et al. 2004; Wade et al. 2006). Longer-term prospective studies conducted with more representative populations of patients are needed to further explore the incidence of problematic prescription cannabinoid use.

Additional research is also needed to further explore the factors that may contribute to problematic prescription cannabinoid use. For instance, in previous studies conducted among patients using other types of prescription drugs, heightened rates of prescription drug misuse have been observed among younger males (Michna et al. 2004; Wasan et al. 2007) as well as among patients with a history of substance use problems (Boscarino et al. 2010; Nielsen et al. 2015; Saunders et al. 2012). Heightened rates of prescription drug misuse have also consistently been observed among patients experiencing high levels of psychological distress such as anxiety (Schieffer et al. 2005; Wasan et al. 2007) or depression (Grattan et al. 2012; Martel et al. 2014). Research has yet to systematically investigate whether these factors also contribute to the problematic use of cannabinoids among patients who are prescribed cannabinoid therapy.

The first objective of this prospective observational study was to examine the incidence of problematic prescription cannabinoid use (PPCBU) over a 12-month period among patients initiating oral cannabinoid therapy. The second objective was to examine the factors associated with PPCBU.

Methods

Study design and participants

A total of 265 patients who were prescribed CBs as part of usual medical practice were enrolled from 12 Canadian outpatient clinics from July 2009 to July 2011 into a prospective, non-interventional, observational, multicenter study. Eligible participants were males or females aged ≥ 18 years, initiating cannabinoid therapy (i.e., having started cannabinoid therapy within the previous 14 days), and prescribed any CB medication during the course of normal clinical practice at a pain, MS, HIV, physical rehabilitation, or other clinic (see Supplementary Table 6). Participants excluded were those who had previously been prescribed CBs, and those with a medical condition or reason that could interfere with study participation or protocol adherence. Substance abuse history alone was not grounds for exclusion.

Procedures and measures

Patients underwent baseline assessment (see Baseline assessment visit) in one of the outpatient clinics and were then followed over a 12-month period during the course of usual care. Each of the clinics had sole discretion for patient assignment to cannabinoid therapy and the subsequent management of patients throughout the study period. In-clinic follow-up assessments were conducted at 3, 6, and 12 months after initiation of cannabinoid therapy (see Follow-up assessment visits). In this study, all data collection procedures were based on a standardized protocol, and one visit at each study (i.e., clinic) site was conducted over the course of the study to monitor data collection and to ensure the quality of study data.

Baseline assessment visit

At baseline, patients were asked to complete a questionnaire assessing demographic and clinical variables. Demographic variables included age, sex, race, marital status, income, and education. Clinical variables included patients' histories of medical and psychiatric problems. Patients' histories of medical and psychiatric problems were assessed based on self-reports. Patients' reports of medical and psychiatric histories

involved any "past" or "current" problems. During the baseline visit, patients were also asked to report on their daily use of alcohol, tobacco, and herbal cannabis, and to complete the Drug Abuse Screening Test (DAST-20; (Skinner 1982)), a self-report questionnaire designed to assess past-year substance abuse problems involving illicit drugs. The DAST was chosen given that it is a well-accepted screening tool that can be easily and rapidly administered in clinic settings in order to screen for past-year substance use problems.

Follow-up assessment visits

At each of the follow-up visits (i.e., 3, 6, and 12 months), three measures designed to assess problematic prescription cannabinoid use were administered. All these measures were originally developed and worded for use in patient populations prescribed opioids, but these measures were adapted for the purposes of the present study by changing the opioid-specific wording to a cannabinoid-specific wording. As can be seen in Supplementary Tables 1, 2, and 3, all scales remained identical to the original versions that were developed and validated, with the exception of the opioid wording. Modified versions of the following measures were administered to patients at baseline:

The Current Opioid Misuse Measure (COMM; (Butler et al. 2007)), a 17-item self-report questionnaire designed to identify patients exhibiting aberrant and/or problematic medication-related behaviors. COMM items are scored on a 5-point scale (0 = *never*, 4 = *very often*) and are designed to assess a variety of behaviors that are indicative of problematic use (e.g., *How often have you taken more medication than prescribed*? *How often have you taken your medications differently from how they were prescribed*?). A cutoff score of ≥ 9 on the COMM is considered indicative of problematic medication use (Butler et al. 2007, 2010).

The Addiction Behavior Checklist (ABC; (Wu et al. 2006)), a 20-item clinician-administered instrument designed to assess problematic medication use. ABC items are rated as "yes" or "no" and focus on observable behaviors exhibited by patients either during or between clinic visits (e.g., *Patient ran out of medications early*; *Patient appears sedated or confused*). A score of ≥ 3 on the ABC is considered indicative of problematic medication use (Wu et al. 2006).

The Chabal Prescription Opioid Abuse Checklist (CPAC; (Chabal et al. 1997)), a 5-item clinician-administered instrument designed to assess problematic medication use. CPAC items are rated as "yes" or "no" and evaluate behaviors such as early refills, dose escalations, and aberrant behaviors such as phone calls or clinic visits to request more medications. A score of ≥ 3 on the CPAC is considered indicative of problematic medication use (Chabal et al. 1997).

During each of the follow-up assessment visits, measures designed to evaluate the severity of patients' medical condition as well as cannabinoid therapy efficacy were also administered. These measures, which were developed and validated to be used with patients with any type of medical condition, included the following:

The Clinical Global Impression (CGI; (Guy 1976)), a standardized instrument designed to be used by clinicians in order to assess the severity of patients' medical condition (CGI-severity range 1 = *normal*; 7 = *extremely ill*). Items on the CGI are also designed to assess clinicians' judgments of treatment efficacy (CGI-efficacy). The CGI is one of the most commonly used measures in pharmacological treatment studies and has been used among patients with a wide range of medical conditions (Spearing et al. 1997).

The Patient Global Impression of Change (PGIC; (Hurst and Bolton 2004)), a single-item self-report measure designed to assess patients' perceptions of changes in condition severity as a result of treatment. The PGIC is rated on a 7-point scale ranging from *very much worse* to *very much improved*.

Data reduction and analysis

In order to examine the incidence of problematic prescription cannabinoid use (PPCBU), we first conducted frequency analyses to determine the number of patients reaching cutoff scores on the three main PPCBU outcomes (i.e., COMM, ABC, CPAC), separately for the 3-, 6-, and 12-month follow-up assessment visits. Frequency distributions for each of the PPCBU outcomes were tabulated as counts and percentages.

In order to examine the factors associated with PPCBU, a series of univariate analyses were first conducted to examine the influence of patient demographics, medication use, psychological/psychiatric characteristics, and substance use history on PPCBU. Analyses were also conducted to examine the influence of patients' condition severity and cannabinoid therapy efficacy on PPBCU. For these analyses, scores on measures of condition severity (PGIC, CGI-severity) and cannabinoid therapy efficacy (CGI-efficacy) were aggregated across follow-up visits. In order to minimize the number of analyses being conducted and the likelihood of family-wise (i.e., type-1) errors, data from each PPCBU outcome (i.e., COMM, ABC, CPAC) were pooled across study visits and used as outcome variables. Outcome variables were coded as "1" if patients scored above the PPCBU cutoff during at least one of the follow-up visits, and coded as "0" if patients scored below the cutoff across all the follow-up visits.

Results

Descriptive statistics

Descriptive statistics on patient demographics are presented in Table 1. Of the 265 enrolled participants, 69.7% were female, 87.9% were Caucasian, and the mean age was 49.2 years (SD = 11.9). As can be seen from Supplementary Table 4, early termination was most frequently due to adverse events (AEs) ($n = 76$; 49.4%), discontinuation of cannabinoid therapy ($n = 51$; 33.1%), and loss to follow-up ($n = 15$; 9.7%). The AEs that were reported by patients over the course of the study are listed in Supplementary Table 5. Cannabinoid therapy discontinuation primarily resulted from lack of efficacy and/or financial considerations. Study completion was not significantly associated with participant age, gender, race, marital status, education, income, or clinical characteristics (all p's > .05).

The most frequent reasons for which cannabinoids were prescribed included pain (93.6%), sleep (18.5%), and spasticity (6%). Other reasons (2.6%) included anxiety and nausea. The specific types of cannabinoid medications that were used by study participants included nabilone (89.7%) and Sativex (9.2%). A small percentage (1.1%) of patients used Sativex in addition to nabilone.

Table 1 Patient demographic characteristics

Variables	*n*	%
Age	49.2	(11.9)
Sex (female)	184	(69.7%)
Racial designation		
White	233	(87.9%)
Black or African American	3	(1.1%)
Asian	10	(3.8%)
Native Hawaiian/other Pacific Islander	1	(0.4%)
North American Indian/Alaska Native	7	(2.6%)
Other	11	(4.2%)
Marital status (% married)	132	(49.8%)
Highest education		
High school	86	(32.5%)
College	64	(24.2%)
University	90	(34.0%)
Other	25	(9.4%)
Income per year		
< $20,000	84	(31.8%)
$20,000–$49,999	68	(25.8%)
$50,000–$69,999	38	(14.4%)
> $70,000	27	(10.2%)
N/A	47	(17.8%)
DAST		
None (0)	104	(39.2%)
Low (1–5)	61	(23.0%)
Intermediate (6–10)	6	(2.3%)
Substantial (11–15)	1	(0.4%)
Psychiatric history		
Depression	88	(51.2%)
Anxiety	41	(23.8%)
Insomnia	20	(11.6%)

Note: Values in parentheses are standard deviation (SD) or frequencies (%). DAST: Drug Abuse Screening Test; DAST categories refer to the severity of past-year substance abuse problems

Incidence of problematic prescription cannabinoid use

As can be seen from Table 2, frequency analyses were conducted to determine the number of patients reaching cutoff scores on the three main PPCBU outcomes (i.e., COMM, ABC, CPAC), separately for the 3-, 6-, and 12-month follow-up assessment visits. At each of the follow-up visits, results from chi-square analyses indicated that a significantly

Table 2 Percentage of patients reaching cutoff scores on main PPCBU outcomes

Follow-up visit	PPCBU outcome	Count	*n*	%	*p*
Month 3	COMM	Yes	48	28.4	<.001
		No	121	71.6	
	ABC	Yes	16	9.2	< .001
		No	157	90.8	
	CPAC	Yes	0	0.0	< .001
		No	174	100	
Month 6	COMM	Yes	27	22.1	< .001
		No	95	77.9	
	ABC	Yes	15	12.3	< .001
		No	107	87.7	
	CPAC	Yes	0	0.0	< .001
		No	125	100	
Month 12	COMM	Yes	46	28.9	< .001
		No	113	71.1	
	ABC	Yes	11	6.8	< .001
		No	150	93.2	
	CPAC	Yes	0	0.0	< .001
		No	163	100	

Yes: Number of patients who scored above the cutoff. No: Number of patients who scored below the cutoff. All percentages were calculated based on each visit's total number of patients with non-missing data. All p values are from chi-square tests

PPCBU problematic prescription cannabinoid use, *COMM* Current Opioid Misuse Measure, *ABC* Addiction Behavior Checklist, *CPAC* Chabal Prescription Abuse Checklist

greater proportion of participants scored below the cutoff threshold (vs cutoff or higher) on all PPCBU measures (i.e., COMM, ABC, CPAC) (all p's < .001). Across all visits, an average of 26.5% of participants reached the COMM cutoff for PPCBU (visits 2, 3, and 4; 28.4, 22.1, and 28.9%, respectively), while an average of 9.4% reached the ABC cutoff (visits 2, 3, and 4; 9.2, 12.3, and 6.8%, respectively). None of the participants met the CPAC cutoff threshold across all follow-up visits.

Subsequent analyses were conducted to examine, for each follow-up visit, the number of "new" patients reaching cutoff scores on PPCBU outcomes. These analyses were done separately for measures of PPCBU derived from the ABC and COMM. Analyses were not conducted based on the CPAC given that none of the participants reached the CPAC cutoff for any of the follow-up visits. Results indicated that 13.3% of patients who scored below the COMM cutoff at the first follow-up (i.e., 3-month) visit reached the COMM cutoff for PPCBU at the 6-month visit. Results also indicated that 15.8% of patients who scored below the COMM cutoff at the second follow-up (i.e., 6-month) visit reached the COMM cutoff for PPCBU at the 12-month visit. For the ABC, results indicated that 4% of patients who scored below the ABC cutoff at the first follow-up (i.e., 3-month) visit reached the ABC cutoff for PPCBU at the 6-month visit. Results also indicated that 1.9% of patients who scored below the ABC cutoff at the second follow-up (i.e., 6-month) visit reached the ABC cutoff for PPCBU at the 12-month visit.

Influence of patients' demographic and psychological characteristics on PPCBU

Analyses were conducted to examine the influence of patients' demographic and clinical characteristics on PPCBU. Results indicated that none of the demographic variables or were significantly associated with the COMM or ABC cutoff (all p's > .05). The use of other prescription drugs in addition to cannabinoids (i.e., opioids, antidepressants, anticonvulsants, or anxiolytics/sedatives) was also not significantly associated with the COMM or ABC cutoff (all p's > .05). Psychiatric history, however, was significantly associated with PPCBU, as a greater proportion of participants with a psychiatric history reached cutoffs on the COMM ($p < .001$) and ABC ($p < .05$) compared to participants without a psychiatric history (see Table 3). In the present study, the most frequent psychiatric problems were depression (51.2%), anxiety (23.8%), and insomnia (11.6%). Post hoc examination of data indicated that the likelihood of reaching cutoff scores on the COMM and ABC was greater among patients with depression than those with other type of psychiatric problems, but these effects did not reach significance (both p's > .05).

Table 3 Percentage of patients reaching cutoff scores on the COMM and ABC as a function of psychiatric history

	Psychiatric history, *n* (%)		*p*
	Yes	No	
COMM	63 (70.0)	27 (30.0)	< .001
ABC	17 (70.8)	7 (29.1)	< .05

Data from the COMM and ABC were pooled across study visits. Patients were categorized as having reached COMM or ABC cutoffs if they reached cutoff scores during at least one of the study visits. Percentages were calculated based on the number of patients with non-missing data across all study visits. All p values are from chi-square tests

COMM Current Opioid Misuse Measure, *ABC* Addiction Behavior Checklist

Influence of substance use on PPCBU

Analyses were conducted to examine whether daily use of alcohol, tobacco, or herbal cannabis, assessed at baseline, was associated with PPCBU. Daily alcohol use was not significantly associated with PPCBU. Results, however, indicated that tobacco use was significantly associated with PPCBU ($p < .05$), as daily tobacco smokers were more likely to reach the ABC cutoff than non-smokers. A significant association between daily herbal cannabis use and PPCBU was also found ($p < .05$), as recreational herbal cannabis users were more likely to reach the ABC cutoff than non-users (see Table 4). Results also indicated that higher DAST-20 scores were associated with a greater likelihood of reaching the ABC cutoff (point-biserial $r = .29$, $p < .001$). In the present sample, 3% of patients had scores on the DAST-20 suggestive of a past-year substance use disorder based on the DAST scoring criteria. A subsequent direct logistic regression analysis indicated that

Table 4 Percentage of patients reaching the ABC cutoff as a function of substance use history

	ABC cutoff, *n* (%)		*p*
	Yes	No	
Tobacco smoking			< .05
Daily smokers	14 (58.3)	47 (32.9)	
Non-smokers	10 (41.7)	96 (67.1)	
Herbal cannabis use			< .05
Users	16 (66.7)	63 (44.1)	
Non-users	8 (33.3)	80 (55.9)	

Data from the ABC were pooled across study visits. Yes: at least one Yes (i.e., cutoff reached) during at least one of the visits, No: cutoff not reached for any of the visits. Percentages were calculated based on the number of patients with non-missing data across all study visits. All p-values are from chi-square tests. "Non-smokers" included patients who do not smoke as well as former smokers

ABC Addiction Behavior Checklist

the DAST-20 was the strongest predictor of PPCBU ($p < .05$). None of the substance use variables were associated with the COMM cutoff (all p's > .05).

Influence of condition severity and cannabinoid therapy efficacy on PPCBU

Analyses were conducted to examine the influence of patients' condition severity and cannabinoid therapy efficacy on PPBCU. Results indicated that patients' reports of condition severity on the PGIC were neither associated with the COMM nor the ABC (both p's > .05). Clinicians' ratings of condition severity (CGI-severity) and cannabinoid therapy efficacy (CGI-efficacy) were also not significantly associated with the COMM or ABC (both p's > .05).

Discussion

The present study examined the incidence of problematic prescription cannabinoid use (PPCBU) over a 12-month period among patients initiating cannabinoid therapy. Overall, results indicated that the majority of patients included in this study did not reach cutoff scores on the three main PPCBU outcomes (i.e., COMM, ABC, CPAC) at the 3-, 6-, and 12-month follow-up assessment visits. Across all the study visits, an average of roughly 25% of participants reached the COMM cutoff, and an average of 9.4% reached the ABC cutoff. None of the patients demonstrated problematic behaviors on the CPAC. On the COMM and ABC, results indicated that the majority of PPCBU behaviors occurred within the first 3 months after initiation of cannabinoid therapy. Incidences of PPCBU behaviors, however, were also observed later over the course of therapy.

Although some of the patients included in the present study may have exhibited behaviors indicative of clinically significant problems associated with cannabinoid use, it is worth noting that PPCBU behaviors are not necessarily indicative of a cannabis use disorder. In recent nationally representative studies examining prevalence rates of cannabis use disorders among adults (Hasin et al. 2015, 2016), the lifetime and 12-month prevalence rates were found to be roughly 6% and 2.5%, respectively. These prevalence estimates were derived based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and DSM-5 criteria for cannabis use disorder. In our study, the incidence of cannabis use disorders was not assessed. However, it is not surprising to find that rates of PPBCU in our study were higher than rates of cannabis use disorders observed among recreational cannabis users. The COMM and ABC, two of the instruments used in our study to assess PPCBU, include items designed to assess "aberrant" drug use behaviors such as having "discussions focused on medication," "expressing worries" about how medications are being handled, and having trouble "thinking clearly." Although some of these behaviors and symptoms may require clinical attention, they are arguably less severe than those characterizing patients with a cannabis use disorder. Additional studies will be needed to assess rates of cannabis use disorders among patients prescribed cannabinoid therapy.

In addition to examining the incidence of problematic prescription cannabinoid use, the present study also examined the factors associated with PPBCU. We found that patients with a history of psychiatric problems, particularly depression, were more likely to exhibit problematic prescription cannabinoid use. This finding is consistent with previous studies that have found heightened rates of prescription drug misuse among patients with psychiatric problems who are prescribed opioids (Boscarino et al. 2010; Edlund et al. 2013; Grattan et al. 2012) or sedatives (Kouyanou et al. 1997; Liebschutz et al. 2010). It has been suggested that these patients might engage in problematic medication use behaviors (e.g., medication overuse) as a way to cope with psychological distress and/or to alleviate (i.e., self-medicate) distressing symptoms (Kirsh et al. 2007; Passik and Lowery 2011). There is also evidence indicating that patients with histories of psychiatric problems tend to self-medicate using cannabis (Corroon et al. 2017; Hasin 2017; Osborn et al. 2015).

Analyses were also conducted to examine the influence of patients substance use history on PPCBU. We found that daily tobacco smokers were more likely to exhibit PPCBU than non-smokers, and a similar pattern of findings was observed for herbal cannabis users. A subsequent regression analysis, however, revealed that past-year substance abuse, assessed using the DAST-20, was the strongest predictor of PPCBU. In previous studies conducted among patients prescribed other types of prescription drugs, heightened rates of prescription drug misuse have been observed among patients with a history of substance use and/or addiction (Edlund et al. 2007; Ives et al. 2006; Michna et al. 2004), similar to what was found here. In our study, it is worth noting that the association between substance use history and PPCBU was not observed based on COMM scores, but only based on the ABC, a clinician-based measure of problematic medication use.

In the present study, we found that the severity of patients' condition, either reported by the patients or evaluated by clinicians, was not associated with PPCBU. The efficacy of cannabinoid therapy, assessed at multiple times across the 12-month period, was also unrelated to PPBCU. Interestingly, this set of findings parallels results from studies among pain patients that failed to find an association between patients' reports of clinical pain severity and problematic opioid use behaviors (Garland et al. 2016; Martel et al. 2014, 2016). It has been argued that some patients, in an attempt to seek symptom relief, may exhibit aberrant and/or problematic medication use behaviors, a phenomenon known as pseudo-addiction (Ballantyne and LaForge 2007; Jamison et al. 2011). Findings from the present study, however, suggest that pseudo-addiction is not likely to

have contributed to problematic cannabinoid use given that patients' condition severity and measures of cannabinoid therapy efficacy were unrelated to PPBCU.

Findings from the present study could have implications for clinicians considering the use of cannabinoids for the management of patients with medical conditions. As noted earlier, rates of problematic cannabinoid use behaviors appear to be relatively low, but our findings nevertheless suggest that PPCBU should be routinely assessed and monitored over the course of cannabinoid therapy. Our findings suggest that monitoring PPCBU among patients with histories of psychiatric and substance use problems might be particularly important. Given that these patients appear to be at heightened risk of PPCBU, the use of a patient risk assessment and stratification approach in CB prescribing should be considered, similar to the current recommended approach for the use of long-term opioid therapy among patients with chronic pain (Chou et al. 2009; Furlan et al. 2010). Opioid-specific tools have been developed and validated for monitoring opioid users (e.g., COMM, ABC), and our findings suggest that these tools could also have some clinical utility for monitoring patients prescribed cannabinoid therapy.

There are limitations to the present study that must be considered when interpreting our findings. First, given that the study sample was restricted to patients prescribed oral cannabinoids, our findings on problematic cannabinoid use cannot be generalized to medical users of inhaled cannabis. Second, our measures of PPCBU were originally developed, validated, and worded for use among patients prescribed opioid analgesics. They were adapted for the purposes of the present study by changing opioid-specific wording to a cannabinoid-specific wording, but none of these measures has been validated in patient populations prescribed cannabinoids. Although tools used in the present study arguably possess high face and content validity by being virtually identical to previously validated opioid tools, further efforts will be needed to support the psychometric properties of the CB-specific tools used in our study. As noted earlier, additional studies relying on structured interviews will also be needed to assess rates of cannabis use disorders among patients prescribed cannabinoid therapy. Finally, as in most longitudinal studies, the possibility that drop-out rates might have influenced study findings must be considered. However, patients lost to follow-up did not differ significantly from patients who completed the study in terms of demographic variables, clinical characteristics, or PPCBU behaviors. This should attenuate potential concerns regarding the influence of attrition bias on the present findings.

In spite of these limitations, findings from the present study provide valuable new insights into the incidence of problematic cannabinoid use among patients prescribed cannabinoid therapy. With previous clinical trials primarily comprised of short-term studies of CB efficacy, issues related to problematic cannabinoid use had not been fully addressed in the literature and contributed to physician reluctance in prescribing CBs (Kahan and Srivastava 2007; Kalant 2004). While a few studies have examined PPCBU associated with smoked or vaporized cannabinoids (Collin et al. 2007, 2010), this is, to our knowledge, the first study to systematically examine PPCBU among patients prescribed oral cannabinoids. Numerous confounding factors prohibit generalization of findings across cannabinoid medications, including THC content, quantity, and pharmacokinetic profiles associated with different routes of administration. Unlike oral administration of CBs containing Δ9-tetrahydrocannabinol (THC) or its analogs, inhaled (e.g., smoked or vaporized) marijuana involves a substantially more rapid pulmonary absorption, plasma distribution, CNS penetration, and mesolimbic cannabinoid receptor binding and activation of THC at CB receptors. Inhalation produces the most rapid onset of therapeutic effects, and the most rapid surge in mesolimbic dopamine release and onset of psychoactivity, a rewarding and reinforcing effect that may, over time, contribute to repeated problematic cannabinoid use or addiction. Theoretically, rates of problematic cannabinoid use associated with orally administered prescribed CBs are thus expected to be lower than those associated with inhaled prescribed marijuana.

In addition to its novelty and clinical relevance, one of the key strengths of this study was to systematically examine the incidence and correlates of PPCBU using a prospective longitudinal study design. Other strengths include multicenter enrolment, the combination of self-report and clinician-based measures of PPCBU, and the inclusion of patients with a past history of substance abuse. Additional studies will be needed to compare rates of PPBCU among patients prescribed different types of cannabinoids. Further efforts are also needed to develop and/or refine risk screening and monitoring tools that could be used among patients prescribed cannabinoids. Advances in this domain would have direct implications for clinicians involved in the management of patients using cannabinoids and might ultimately contribute to preventing problematic prescription cannabinoid use.

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Compliance with ethical standards

Conflict of interest MAW discloses the following relationships: CanniMed, Green Sky Labs (grant to institution), CHI Inc., Zynerba,

and CannaRoyalty (consultant). RJ discloses the following relationships: Astra Zeneca, Knight, Paladin, and Purdue Pharma (speakers' bureau, consultant). MM and JS declare that they have no conflict of interest.

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