Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study

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Summary

Background Although cannabis use after a first episode of psychosis has been associated with relapse, little is known about the determinants of this most preventable risk factor for relapse of psychosis. Here we aimed to study whether the effects on outcome vary depending on the type of cannabis consumed and usage pattern.

Methods In this observational study, we prospectively recruited and followed up patients aged 18–65 years who presented with their first episode of psychosis to psychiatric services in south London, London, UK. Relapse of psychosis within 2 years after onset of psychosis was defined as risk of subsequent admission to hospital. We classified patients into different patterns of cannabis use based on continuity of use after onset of psychosis, potency of cannabis consumed, and frequency of use after the onset of their illness. We used multiple regression analyses (logistic or binominal) to compare the different cannabis use groups and propensity score analysis to validate the results.

Findings Between April 12, 2002, and July 26, 2013, 256 patients presented with a first episode of psychosis. We did follow-up assessments for these patients until September, 2015. Simple analyses showed that former regular users of cannabis who stopped after the onset of psychosis had the most favourable illness course with regards to relapse. In multiple analysis, continued high-frequency users (ie, daily use in all 24 months) of high-potency (skunk-like) cannabis had the worst outcome, indexed as an increased risk for a subsequent relapse (odds ratio [OR] 3·28; 95% CI 1·22–9·18), more relapses (incidence rate ratio 1·77; 95% CI 0·96–3·25), fewer months until a relapse occurred (*b* –0·22; 95% CI –0·40 to –0·04), and more intense psychiatric care (OR 3·16; 95% CI 1·26–8·09) after the onset of psychosis.

Interpretation Adverse effects associated with continued use of cannabis after the onset of a first episode of psychosis depend on the specific patterns of use. Possible interventions could focus on persuading cannabis-using patients with psychosis to reduce use or shift to less potent forms of cannabis.

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Introduction

In the past 30 years, findings of studies have shown that cannabis use is a contributory cause of psychotic disorders, especially if used often and initiated at an early age.[1,2] Cannabis remains the most commonly used illicit drug in patients with established psychosis[3] and use is especially high in young people presenting with their first episode of psychosis.[4] Only a few patients with established psychosis start using cannabis after onset of psychosis,[5] but a major concern is the substantial proportion who continue using the drug.[6] Findings of a recent meta-analysis suggest that continued cannabis use after the onset of psychosis predicts poor disease outcome as shown by a high number of relapses, admittance to hospital, and more severe positive symptomatology.[7] These findings are consistent with evidence that experimental administration of the key psychoactive ingredient in cannabis is associated with transient psychotic symptoms and cognitive impairments in healthy individuals and exacerbation of symptoms in patients with a pre-existing psychotic disorder.[8,9]

However, whether the association between cannabis use and worse outcome in pre-existing psychosis is causal has remained inconclusive[7] because prospective evidence so far has not always established that cannabis use actually preceded and was in reasonable temporal proximity to the outcome of interest (ie, relapse of psychosis). More importantly, how parameters of cannabis use, such as type and potency of cannabis used and frequency of use, affect outcome has remained unclear. This gap in the scientific literature is especially important in view of findings that dose, type, and pattern[10] of cannabis use are important determinants of its effect on onset of psychosis. In particular, for such evidence to be translated into real world meaningful solutions in the clinical setting, it is important to develop a more nuanced understanding of the association between one of the most potentially

Research in context

Evidence before this study

In January, 2016, we published a meta-analysis in *The Lancet Psychiatry*, wherein we studied the effect of continued cannabis use on the risk of relapse in patients with psychosis. In this meta-analysis, we searched MEDLINE for articles published in any language until April, 2015, using a combination of search terms for describing the exposure (cannabis use), the outcome of interest (relapse of psychosis), and the study population (patients with psychosis). Data were pooled together from 24 studies (16 565 participants) to compare relapse outcomes in the following groups: continued cannabis users, discontinued cannabis users, and non-users. Continued cannabis users had more relapses and longer stays in hospital compared with non-users. These adverse effects were not recorded in patients who discontinued cannabis use after the onset of psychosis. An update of the search (April 11, 2016, 129 included studies) identified two additional studies (appendix p 4), which confirmed an increased risk for relapse related to cannabis use in first episode psychosis and hospital admissions in patients with established schizophrenia.

Added value of this study

Our findings add to the evidence on cannabis use and relapse in psychosis. For the first time, we used a detailed assessment of distinct cannabis use profiles in a large sample of first episode psychosis patients and showed that the effect on outcome varies depending on the type of cannabis consumed as well as usage pattern, after controlling for a range of important confounders previously not generally considered (eg, medication adherence or other illicit drug use). The results were validated for covariate adjustment (by using propensity score matching) and consistency (by using different measures of relapse, including risk and number of relapses, length of relapse, time until relapse, severity of relapse), and point towards potential targets for intervention.

Implications of all the available evidence

Continued cannabis use (at least monthly use) after the onset of psychosis, especially use of high-potency cannabis, is associated with a significantly worse outcome in individuals with first episode psychosis. In our study, outcomes were better in those who used cannabis in smaller doses (reduced frequency, lower potency, and shorter duration of continuation) after onset, which suggests that interventions should aim to reduce frequency of use or shift to less potent forms of cannabis when complete cessation of cannabis use might not be a realistic goal.

preventable risk factors of psychosis—ie, cannabis use and its determinants and the risk of relapse in psychosis.

Understanding the role of cannabis in relapse of psychosis is important not just because prevention of relapse is crucial for improved long-term outcome in psychosis,[11] but also because of the substantial financial implications associated with need for hospital care in those who relapse;[12] up to 50% of first-episode psychosis patients experience a relapse that results in hospital admission within the first 2 years of illness, with the risk increasing to more than 80% by the eighth year.[13]

Here we investigate the effects of continued cannabis use on risk of relapse as indexed by hospital admission over the first 2 years after the onset of psychosis.

Methods

Participants

We recruited patients with first-episode non-organic (non-affective [ICD10 codes F20–F29]) or affective [F30–F33]) psychosis,[14] aged 18–65 years who had been admitted to psychiatric services in South London, London, UK. Participants were assessed twice, first close to the onset of their illness using face-to-face interviews and subsequently for follow up, using either a face-to-face or a telephone interview (if the individual was unable to attend interviews in person). Data from clinical records regarding hospital admissions were collected for participants who refused to take part in the follow-up interview (n=133) during the 2 years after psychosis onset. The study was approved by South London and Maudsley NHS Foundation Trust and Institute of Psychiatry Local Research Ethics Committee. All participants included in the study gave written informed consent.

See Online for appendix

Outcomes

We assessed cannabis use with a modified version of the Cannabis Experience Questionnaire (CEQ_{mv}),[10] and collected data for premorbid cannabis use, and use in the first 2 years after onset of psychosis. Cannabis users were classified into different cannabis use profiles based on their pattern of use depending on continuity and frequency of cannabis use after onset of psychosis. Type of cannabis (hash-like *vs* skunk-like) used was assessed by asking participants to describe their preferred type of cannabis. Based on this information, grouping was done in the same way as reported previously,[10] Information about service use, number, duration and legal status (voluntary or involuntary) of inpatient admissions, referral to crisis intervention team or standard treatment by a community mental health team was obtained from electronic patient records using established methods (appendix). Relapse was defined as admission to a psychiatric inpatient unit because of exacerbation of psychotic symptoms within 2 years of first presentation to psychiatric services and diagnosis of psychosis. If the patient was admitted to hospital upon first presentation to psychiatric services with a diagnosis of psychosis, this

was not considered as a relapse event. Alcohol use, other illicit drug use, and cigarette use, care intensity at onset (as a proxy measure of illness severity based on a rating of intensity of service use for each subject at onset; appendix p 7), and medication adherence were assessed and included in the analysis as potential confounders based on previous scientific literature. The appendix describes estimated measurements of cannabis use, relapse, and confounders.

Statistical analysis

Data analysis was done with R. We modelled follow-up data for 2 years after the onset of psychosis for every participant. The cannabis profile variable was coded as an ordered categorical variable, with the former (regular) user group acting as the reference group (appendix). First, exploratory simple analyses, including χ^2 test for categorical variables and Kruskal-Wallis test and Mann-Whitney *U* (two-sided) test for continuous outcomes were used to compare the different cannabis use groups. Following common practice,[2] we generated Kaplan-Meier curves and compared the different cannabis use groups using log-rank tests. Pairwise comparisons were adjusted with Bonferroni correction to account for multiple testing. Multiple logistic regression analyses were employed to compute the odds ratio (OR) and 95% CIs, using binary logistic regression for binary outcomes (risk of relapse) and ordinal logistic regression analysis for ordered categorical outcome (care intensity at follow up). We used multiple negative binominal regression models for continuous outcomes (number of relapses, length of relapse, time to relapse; appendix). Sensitivity analysis was done by calculating propensity scores to validate the results and to address the limitations by confounding adjustment in regression analysis (appendix).[15] We included antipsychotic medication adherence in a separate regression model because these data were available for only a subset of cases, considering that antipsychotic medications were not prescribed for all participans after the onset of illness.

Role of the funding source

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have approved the final version of the paper.

For **R software** see http://www.R-project.org/

Results

Between April 12, 2002, and July 26, 2013, we recruited 256 first episode psychosis patients and did follow-up assessments until September, 2015. The two groups (completers and refusers) did not differ significantly in their risk of relapse (36% *vs* 38% relapsed, χ^2= 0·15; p=0·70) and baseline characteristics (appendix p 6). Most patients (200 [78%]) were admitted to hospital around the onset of illness; more than half of those (119 [60%]) experienced involuntary admission. Within the first 2 years after onset of psychosis, 93 (36%) patients experienced a relapse leading to hospital admission. The highest number of relapses recorded was three, and the longest hospital stay recorded was 14·8 months within

	All participants	Former (regular) cannabis user	Never (regular) cannabis user	Intermittent cannabis user	Continued cannabis user	p value*
Number of participants	256 (100%)	54 (21%)	103 (40%)	35 (14%)	64 (25%)	..
Age of onset	28·06 (8·03)	28·05 (7·65)	29·74 (8·96)	27·95 (8·21)	25·43 (5·83)	0·02
Men	156 (61%)	37 (69%)	44 (43%)	24 (69%)	51 (80%)	<0·0001
Non-white ethnic origin	170 (66%)	23 (43%)	78 (76%)	22 (63%)	47 (73%)	0·0002
Care intensity at onset						0·71
Referral to community team only	39 (15%)	12 (22%)	15 (15%)	4 (11%)	8 (13%)	..
Required contact with crisis team	17 (7%)	5 (9%)	6 (6%)	2 (6%)	4 (6%)	..
Required hospital admission (non-compulsory)	81 (32%)	13 (24%)	38 (37%)	12 (34%)	18 (28%)	..
Required hospital admission (compulsory)	119 (47)	24 (44%)	44 (43%)	17 (49%)	34 (53%)	..
Months stayed in hospital at onset	1·72 (3·37)	2·10 (6·28)	1·57 (2·09)	1·31 (1·20)	1·88 (2·16)	0·57
Employment status at onset (n in employment)†	83 (33%)	21 (40%)	38 (37%)	9 (26%)	15 (24%)	0·15
Family history of mental illness (yes)	96 (49%)	20 (44%)	40 (55%)	11 (42%)	25 (48%)	0·61
Onset diagnosis (non-affective)	211 (82%)	47 (87%)	82 (80%)	30 (86%)	52 (81%)	0·64
Medication prescribed at onset (yes)	240 (94%)	52 (96%)	96 (93%)	33 (94%)	59 (92%)	0·82
Type of medication at onset						0·46
Second-generation antipsychotic	236 (98%)	52 (100%)	94 (98%)	33 (100%)	57 (97%)	..
First-generation antipsychotic	4 (2%)	0	2 (2%)	0	2 (3%)	..

Data are n (%) or mean (SD). *p value estimates from Kruskal-Wallis test for means and χ^2 tests for independence for percentages to compare all cannabis groups. †Missing data for three participants.

Table 1: **Baseline characteristics**

	Relapse (yes)*	Number of relapses†	Length of relapses†‡	Time to relapse†‡	Care intensity at follow up*			
					0	1	2	3
Former (regular) user	13 (24%)	0·35 (0·73)	0·59 (1·74)	20·86 (6·55)	40 (74%)	1 (2%)	9 (17%)	4 (7%)
Never (regular) user	31 (30%)	0·43 (0·74)	0·66 (1·46)	20·24 (6·57)	59 (57%)	13 (13%)	16 (16%)	15 (15%)
Intermittent user	14 (40%)	0·51 (0·70)	1·66 (3·53)	18·75 (6·88)	16 (46%)	5 (14%)	4 (11%)	10 (29%)
Continued user (hash-like)	4 (44%)	0·67 (1·00)	1·11 (2·07)	21·23 (5·22)	5 (56%)	0	1 (11%)	3 (33%)
Continued user (skunk-like/low frequency)	13 (54%)	0·62 (0·65)	1·69 (3·34)	20·27 (4·67)	11 (46%)	0	4 (17%)	9 (38%)
Continued user (skunk-like/high frequency)	18 (58%)	0·87 (0·92)	1·71 (2·85)	16·03 (8·21)	12 (39%)	1 (3%)	9 (29%)	9 (29%)

Data are n (%) or mean (SD). *χ^2 test for independence to compare all groups for risk of relapse (p=0·009, χ^2=15·33) and care intensity at follow up (p=0·004, χ^2=33·49) †Kruskal-Wallis test to compare all groups in number of relapses (p=0·01), length (months) of relapses (p=0·009), time (months) to relapse (p=0·02). ‡Median and IQR are reported in the appendix (p 17). Care intensity at follow up: 0=required only community treatment without crisis intervention; 1=required crisis intervention without hospital admission; 2=required hospital admission without compulsory admission; 3=required compulsory hospital admission.

Table 2: **Cannabis use pattern and relapse outcome**

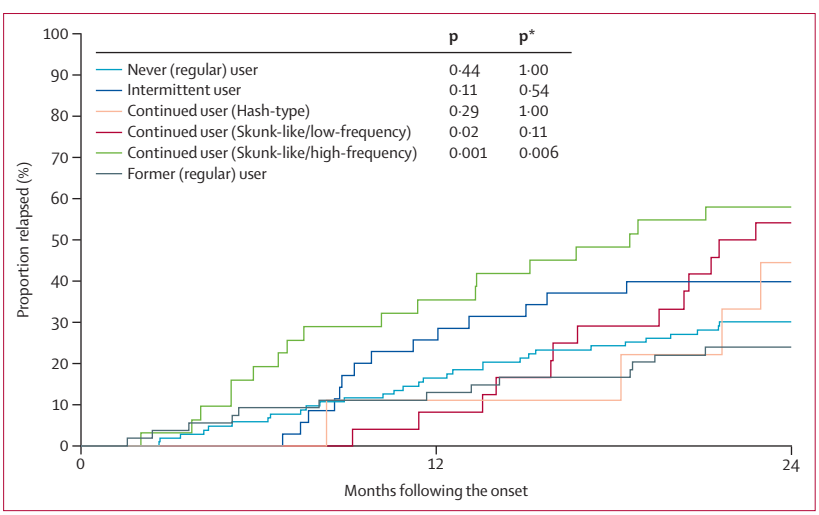

Figure: **Kaplan-Meier curves of cannabis use pattern and time to relapse**
p values are estimated from the log-rank tests to compare the different groups (reference group is the former [regular] user group). *Bonferroni-corrected significance level.

2 years. Out of participants with pre-onset or post-onset cannabis use, only two (1%) of 153 participants started using cannabis after the onset, and most (97 [63%]) of these had used cannabis regularly before the onset of illness (appendix). The different subgroups based on pattern of cannabis use (table 1) differed in the age of onset of their psychosis (Kruskal-Wallis test p=0·02) and in ethnic origin (χ^2=25·98; p<0·0001) and sex (χ^2=19·34; p=0·0002) distribution. Of those baseline characteristics assessed, only non-white ethnic origin was associated with risk of relapse (χ^2=6·46, p=0·01; appendix).

Risk of relapse differed across all groups (χ^2=15·33; p=0·009). The greatest risk was recorded in continued high-frequency users of high-potency cannabis (skunk-like), and the lowest was in former cannabis users currently abstaining (18 [58%] *vs* 13 [24%], respectively). Former cannabis users had the highest rate of community treatment only, requiring no referral for crisis intervention or inpatient care (table 1). By contrast, low-frequency and high-frequency users of high-potency (skunk-like) cannabis were more likely to experience compulsory admissions than former cannabis users (29% and 38% *vs* 7%). We noted an effect of pattern of cannabis use on number of relapses (p=0·01), length of relapses (p=0·009), time to relapse (p=0·02), and care intensity (p=0·005; table 2). Kaplan-Meier curves suggested that the different groups significantly differed with regard to their time to relapse (Kaplan-Meier p=0·007). High-frequency and skunk-like users were more likely to have an earlier relapse than the former (regular) user group (Kaplan-Meier with Bonferroni correction p=0·006; figure).

In multiple logistic regression analysis, continued high-frequency use of high-potency cannabis (indexed as at least daily use throughout the follow up) remained a significant predictor for relapse (OR 3·28; 95% CI 1·22–9·18) when compared with former users (table 3). The effect remained significant when medication non-adherence was included in the model (OR 2·73; 95% CI 1·02–7·56), although this effect was reduced in magnitude when compared with the odds from simple logistic regression analysis (OR_{simple} 4·37; 95% CI 1·72–11·85). None of the other cannabis groups were different in their risk of relapse when compared with former users. In those risk models, only three other predictors remained significant, including non-white ethnic origin, care intensity at onset, and antipsychotic medication non-adherence (table 3). The results from the other multiple regression analyses confirmed that the adverse effects of continued high-frequency skunk-like use were also evident on the number of relapses, time to relapse, and a higher care intensity at follow up, while controlling for the above confounders. Including medication adherence into the model did not substantially change the results, although high-frequency skunk-like use remained a significant predictor only for length of relapse in this model (table 3). In propensity score-matched analyses

	Risk of relapse			Number of relapses			Length of relapses			Time to relapse			Care intensity at follow-up		
	OR†	95% CI	p value	IRR‡	95% CI	p value	*b*§	95% CI	p value	*b*§	95% CI	p value	OR¶	95% CI	p value
Model 1* (n=256)															
Never (regular) user	1·24	0·53 to 3·03	0·63	1·27	0·70 to 2·29	0·43	−0·01	−0·81 to 0·79	0·99	−0·01	−0·15 to 0·13	0·92	2.01	0·91 to 4·60	0·09
Intermittent user	1·76	0·67 to 4·64	0·25	1·22	0·64 to 2·34	0·54	0·78	−0·09 to 1·66	0·07	−0·06	−0·23 to 0·10	0·46	2.78	1·14 to 6·91	0·03
Continued user (hash-like)	1·82	0·36 to 8·76	0·45	1·13	0·43 to 2·97	0·80	−0·33	−1·84 to 1·25	0·65	0·07	−0·20 to 0·35	0·60	2.40	0·51 to 10·44	0·25
Continued user (skunk-like/low frequency)	2·42	0·80 to 7·52	0·12	1·11	0·54 to 2·31	0·77	0·41	−0·64 to 1·49	0·41	0·05	−0·14 to 0·25	0·60	3.12	1·09 to 9·08	0·03
Continued user (skunk-like/high frequency)	3·28	1·22 to 9·18	0·02	1·77	0·96 to 3·25	0·07	0·61	−0·31 to 1·55	0·17	−0·22	−0·40 to −0·04	0·02	3.16	1·26 to 8·09	0·01
Ethnic origin (non-white)	2·36	1·23 to 4·69	0·01	1·82	1·16 to 2·85	0·01	0·97	0·35 to 1·59	0·002	−0·12	−0·23 to −0·01	0·03	1.94	1·08 to 3·54	0·03
Women	1·42	0·78 to 2·60	0·26	1·20	0·82 to 1·74	0·35	−0·27	−0·83 to 0·30	0·33	−0·04	−0·14 to 0·06	0·44	1.51	0·88 to 2·61	0·13
Other illicit drug	1·79	0·68 to 4·76	0·24	1·79	1·05 to 3·04	0·03	0·70	−0·17 to 1·60	0·10	−0·11	−0·28 to 0·07	0·23	1.43	0·60 to 3·41	0·42
Cigarette use	1·49	0·78 to 2·83	0·23	1·73	1·12 to 2·67	0·01	0·37	−0·17 to 0·92	0·20	−0·07	−0·18 to 0·04	0·24	1.66	0·92 to 3·02	0·09
Age of onset	1·01	0·97 to 1·04	0·78	1·00	0·97 to 1·02	0·82	−0·02	−0·05 to 0·01	0·30	0·00	−0·01 to 0·00	0·42	0.99	0·96 to 1·03	0·71
Alcohol use	1·72	0·75 to 3·94	0·20	1·14	0·69 to 1·88	0·60	−0·09	−0·85 to 0·69	0·81	−0·01	−0·15 to 0·14	0·90	1.96	0·95 to 4·08	0·07
Care intensity at onset	1·37	1·05 to 1·84	0·03	1·32	1·08 to 1·60	0·01	0·59	0·32 to 0·87	<0·001	−0·03	−0·07 to 0·02	0·22	1.33	1·03 to 1·73	0·03
Model 2|| (n=236)															
Never (regular) user	1·28	0·58 to 2·88	0·55	1·13	0·65 to 1·98	0·65	0·20	−0·55 to 0·94	0·59	−0·01	−0·15 to 0·12	0·83	1·80	0·88 to 3·86	0·12
Intermittent user	1·57	0·58 to 4·29	0·37	1·22	0·62 to 2·42	0·56	0·78	−0·14 to 1·74	0·09	−0·06	−0·23 to 0·12	0·53	2·47	1·00 to 6·20	0·05
Continued user (hash-like)	2·54	0·50 to 12·98	0·25	1·74	0·67 to 4·52	0·25	0·57	−0·80 to 2·23	0·45	0·04	−0·25 to 0·33	0·80	3·30	0·70 to 14·76	0·12
Continued user (skunk-like/low frequency)	2·63	0·91 to 7·91	0·08	1·34	0·66 to 2·7	0·42	0·89	−0·06 to 1·91	0·08	0·03	−0·16 to 0·23	0·74	3·23	1·17 to 9·07	0·02
Continued user (skunk-like/high frequency)	2·73	1·02 to 7·56	0·05	1·74	0·94 to 3·24	0·08	0·98	0·09 to 1·90	0·04	−0·20	−0·38 to −0·01	0·03	2·93	1·17 to 7·47	0·02
Medication non-adherence	3·25	1·79 to 6·09	<0·001	2·29	1·46 to 3·57	<0·001	0·57	−0·01 to 1·15	0·05	−0·15	−0·25 to −0·05	0·01	3·36	1·93 to 6·00	<0·001

Reference group refers to former (regular) users. OR=odds ratio. IRR=incidence rate ratio. *Medication non-adherence not included as a covariate. †Estimated from multiple logistic regression analysis. ‡Estimated from negative binomial regression. §Coefficient estimate from negative binomial regression. ¶Estimated from multiple ordinal regression analysis. ||Only medication non-adherence included as a covariate.

Table 3: **Multiple regression analyses of cannabis use pattern and relapse outcome**

considering all covariates (appendix), the effect of high-frequency skunk-like use was reduced in its magnitude but remained a significant predictor for risk of relapse and care intensity at follow up.

Several other predictors were significantly linked to relapse in the multiple regression analyses (table 3). Ethnic origin and medication non-adherence remained significant predictors in all models, including risk of relapse, number and length of relapses, time to relapse, and care intensity at follow up. Number of relapses was predicted by cigarette use and other illicit drug use. Finally, higher care intensity at onset was associated with risk of relapse, an increase in number of relapses and increase of length of relapse, as well as a higher care intensity throughout the 2 years following the onset of illness.

Further analyses using the continued user group (skunk-like/high-frequency) as the reference group showed that this group relapsed earlier than did the continued user (hash-like; b=0·29; 95% CI 0·01–0·58) and continued user (skunk-like/low frequency; b=0·27, 95% CI 0·06–0·48) and never (regular) user groups (b=0·21, 95% CI 0·04–0·39; appendix).

Discussion

For the first time, this study of outcome in patients after their first episode of psychosis investigated the effect of different patterns of cannabis use on risk of relapse by incorporating information about continuation, frequency, and type of cannabis used. Our results suggest that effects of cannabis use on outcome vary, depending on specific

cannabis use profile. Whereas former regular cannabis users who stopped using the substance regularly after the onset of psychosis had the lowest risk of relapse, those who continued to use at least on a monthly basis were most likely to experience a relapse. More specifically, continued users of high-potency (skunk-like) cannabis who were using on a daily basis had the highest risk of relapse of psychosis when compared to former cannabis users. This effect was independent of other putative risk factors for poor outcome, including ethnic origin, sex, age of onset, alcohol, cigarette and illicit drug use, and care intensity at onset (appendix). Furthermore, high-frequency skunk-like users had more relapses, longer durations of hospital stay, shorter times to relapse, and more severe (as indexed by care intensity at follow up) relapses, when compared with former users. More rigorous adjustment for confounders using propensity score matching showed similar results, with high-frequency users having a 1·9 times higher risk of relapse of psychosis. This effect is similar in its magnitude, albeit in the opposite direction, to the effect of antipsychotic medication treatment on risk of relapse in psychosis (eg, 2·4 times higher risk for placebo *vs* drug-treated patients[16]).

High-frequency skunk-like users also relapsed earlier than hash-like and low-frequency skunk-like continued cannabis users and never (regular) users. Together, these results extend previous observational[2,17] and experimental evidence[9] of dose–response effects of cannabis in patients with psychosis to demonstrate that the effects of cannabis use on outcome in psychosis depend on the type of cannabis consumed as well as frequency of use. This finding is consistent with similar evidence on the onset of psychosis.[10] High-potency cannabis has become dominant in the UK.[18] It has higher levels of delta-9-tetrahydrocannabiniol (THC), the main psychotogenic ingredient in cannabis, which modulates the neural substrates implicated in psychosis.[8,19] Furthermore, high-potency cannabis has minimal concentrations of cannabidiol (CBD),[18] which ameliorates some of the effects of THC[20] and might have antipsychotic properties.[21] High relapse rates and short time to relapse in high-frequency skunk users might be the result of a failure to respond to antipsychotic treatment[4] either on its own or in combination with an increase in the severity of psychotic symptoms in those frequently exposed to a higher dose of THC,[9] which were not investigated in the present study. This result might explain why some previous studies that did not differentiate between the type of cannabis did not report an association between cannabis use and relapse.[22] It might also explain why the risk estimate noted in our study for the high-dose group (high-frequency/skunk-like) was substantially higher compared with the pooled odds from previous studies that investigated the risk of cannabis on relapse (OR_{simple} 4·37 *vs* OR_{simple} 1·97).[7] The finding of no difference in outcome between cannabis users who remained abstinent after the onset of psychosis and the non-user group suggests that the effects of previous cannabis use on outcome in psychosis are not irreversible[7] and that investigations need to move beyond the effects of lifetime cannabis use or cannabis use assessed at onset only.[23] Future investigations should focus on changes in pattern of use and type of cannabis used after psychosis onset because these might be the key factors driving adverse outcomes associated with cannabis use in patients with psychosis.

Our data suggest that high-frequency use of potent forms of cannabis will adversely affect outcome even in treatment-adherent patients, perhaps by reducing the effectiveness of antipsychotics.[3] Together, these results are opposed to non-causal explanations for the association between frequent (daily) use of high-potency skunk-like cannabis and outcome, such as reverse causation or confounding, and suggest that change in cannabis use after the onset of psychosis is an important determinant for outcome in psychosis. In view of the lack of effective psychological[24] or pharmacological[25] treatments for comorbid cannabis users with psychosis, our results suggest that reducing frequency of use or shifting to less potent forms might be useful intervention strategies in psychotic patients who are otherwise unable to stop using cannabis.

This study has certain limitations, such as comprising a selective subset of inner city, first episode of psychosis patients more likely to engage with community mental health services and having less severe psychopathology, bias from refusal to take part in the study, use of retrospective self-report measures of cannabis and other substance use leading to under-reporting, modest sized (n=8) continued hash-like (resin) user group, and not controlling for the effect of migrant status, or the effect of type and dose of antipsychotic medication on relapse. However, as discussed in greater detail in the appendix, these factors are unlikely to have affected the direction of our results.

Nevertheless, this is the first study that suggests that those who continue to use high-potency cannabis even after the onset of their psychosis are at the greatest risk of relapse of their illness and of experiencing more frequent and earlier relapses that require more intensive psychiatric care than those who do not continue cannabis use.

Contributors

SB and TS had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. SB designed the study and supervised the data collection and analysis, TS analysed the data and wrote the first draft with SB. All other authors provided data, reviewed the results, and contributed to the final draft of the report.

Declaration of interests

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