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Is Cannabis Use Treatment Also Indicated for Patients with Low to Moderate Polysubstance Use?

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Keywords

Cannabis use disorder · Treatment outcome · Primary and secondary outcomes · Predictors · Polysubstance use · CANDIS

Abstract

Background: Polysubstance use (PSU) is common among patients with cannabis use (CU) and is related to more severe CU problems. However, it is unclear how PSU predicts CU treatment outcomes beyond CU patterns. We examined the frequency, amount, and class of additionally used substances as predictors for primary and secondary outcomes. **Methods:** We conducted crude and adjusted regression analyses for PSU variables as predictors of remission, abstinence, reduction, and secondary outcomes in 166 help-seeking patients from a randomized clinical trial of CANDIS, a cognitive behavioral treatment program. **Results:** Patients with recent illegal PSU experienced more difficulties in reducing their CU ($B = -1.22, p < 0.001$). In contrast, remission rates were slightly higher in patients with a wide variety of last-year-PSU ($RD = 0.04, p < 0.001$). Amphetamine use

predicted poorer outcomes regarding CU-related problems ($B = -4.22, p = 0.019$), and the use of opiates, inhalants, and dissociative substances predicted poorer physical health outcomes ($B = -0.62, p = 0.009$; $B = -0.96, p = 0.039$; $B = -1.18, p = 0.007$). **Conclusions:** CU treatment is also effective for patients with moderate PSU. However, treatment effects may be enhanced by addressing specific PSU characteristics as part of a modularized program.

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Introduction

The number of treatment-seeking patients with problems related to cannabis use (CU) has been steadily rising [1]. Although it has been reported that cannabis is the substance associated with the most problems, approximately 85% of these patients also consume one or more other classes of substances. While effective CU treatment programs are now available [2–5], the additional use of other substances, termed polysubstance use (PSU) according to the 10th revision of the International Statistical

Classification of Diseases and Related Health Problems (ICD-10) [6], may indicate worse responses to treatment, particularly with illegal substance use. The roles of substance class, variety, and frequency of PSU in predicting CU treatment effectiveness have not been elucidated.

Cannabis users often also consume alcohol and nicotine, and a minority of them uses further illegal substances [7, 8]. Although there is considerable variation by country and region, the most frequent types of PSU among more than 70,000 15- to 16-year-old students from 22 European countries were a combination of alcohol and nicotine (type 1, 73%), followed by the combination of alcohol, nicotine, and cannabis (type 2, 20%) and type 2 plus at least one illegal substance (type 3, 3.5%) [9]. There is evidence from longitudinal studies in the general population that previous alcohol and illegal substance use is associated with CU increases or stability [10–12], as well as the onset of a CU disorder (CUD) in adolescents and young adults [13, 14]. A latent class analysis of 1,089 cannabis users from a community sample found that other illegal substance use occurred more often in the group with cannabis-related problems than in the non-problematic users [15]. In a sample of 826 cannabis users referred for treatment, the highest severity of cannabis dependence, comorbid psychopathology, and dysfunctional cannabis cognitions was reported among those who additionally used a wide range of other substances; these other substances most often included amphetamines, and infrequently included tranquilizers and opiates [8]. Therefore, PSU and especially illegal substance use is associated with more severe CU-related problems.

Psychosocial interventions have been shown effective in the treatment of CUD. A series of recent reviews and meta-analyses have demonstrated that cognitive-behavioral therapies (CBT), including elements of motivational enhancement (ME) and problem solving are especially effective in reducing the frequency and severity of CU. Furthermore, these treatments are also effective for improving secondary outcomes such as psychosocial functioning [2–5, 16, 17]. However, research has not yet determined whether PSU predicts CU treatment outcomes beyond the pattern of CU. It has been suggested that patients with PSU are more difficult to treat [9, 18] and may experience fewer benefits from CU treatments.

We examined PSU as a potential predictor (in a non-causal interpretation, see [19]) of primary (remission, abstinence/reduction) and secondary (reduction of CU related problems, health improvements) outcomes in an established and effective CBT treatment program (CANDIS; acronym for CAnnabis DISorders) for ado-

lescents and adults with CUD [2–5, 16, 20, 21]. According to the literature, we hypothesize that patients with PSU of illegal substances experience lower abstinence rates. Whether and how these relations depend on specific PSU features, that is, the variety and frequency of specific illegal substance classes and whether PSU also relates to remission or secondary outcomes has, to our knowledge, not been examined before. These questions will be further explored. As PSU may indicate generally more heavy substance use, we also examined CU characteristics such as frequency, dose, mode of administration, use environment, and age of CU onset. We aimed to determine whether these factors account for relationships between PSU and treatment outcomes. By addressing the complexity of use patterns in the CU population, which often involves multiple substance use, we aim to improve treatment effectiveness for patients who request assistance for reducing negative impacts of cannabis in their lives.

Methods

Design and Sample

CANDIS is a 10-session program comprising fully manualized individual CBT, including ME and problem-solving training [22, 23]. Two randomized controlled trials (RCTs) have demonstrated high efficacy for various treatment outcomes, including achieving abstinence, as well as reducing the frequency of CU, the severity of cannabis dependence, and the number and severity of cannabis-related problems [20, 21].

We used data from an RCT conducted from 2007 to 2010 in 11 German outpatient addiction treatment centers [2–5, 16, 24]. To avoid systematic selection bias, all incoming patients with current and regular CU were invited to participate in the study.

The inclusion criteria were as follows: (1) ≥ 16 years of age, (2) current and regular CU at least twice per week over the course of the past 12 months, (3) motivation to quit or reduce CU, (4) fluency in the German language, (5) written, informed consent concerning study procedures and assessments, as specified by the approval of the ethics board of Technische Universität Dresden (EK313122007).

The exclusion criteria were as follows: (1) ICD-10 dependence on alcohol or any illicit substance other than cannabis in the previous 12 months, (2) current use of opiate substitution or sedative-hypnotic medication, (3) treatment of CU problems within the previous 3 months, (4) a lifetime psychotic disorder, (5) current severe major depression, (6) current severe panic disorder, (7) acute suicidal tendencies, (8) severe learning disability or a pervasive developmental disorder, or (9) indications of severe non-cannabis-related intoxication [21].

The sample consisted of 166 patients who had completed pre- and post-assessment forms and participated in the treatment, either as active or as delayed treatment group starting immediately after being included into the study or with a delay of 3 months respectively. Ages at intake ranged from 16 to 64 years ($M = 27.0$), 87% of patients were men, and CU occurred an average

Table 1. Indicators of PSU and their definitions

1–8: Previous year use-frequency of:			
1	Alcohol, higher doses (i.e., more than 1.5 L of beer, 0.7 L wine, 0.2 L [hard] liqueurs, whiskey etc.)	Monthly average days of use in the previous year, range 1 (“no co-use”) – 8 (“daily use of specific substance”)	
2	Amphetamines (incl. Speed, Ecstasy, Crystal meth)	Transformation:	
3	Tranquilizers	Original scale	Transformed interval scale
4	Opiates (incl. Heroin, Methadone)	0: no use in the previous year	0: no use in the previous year
5	Cocaine (incl. Crack, Coca leaves)	1: <1/month	0.5 days/month
6	Dissociatives (incl. Phencyclidines, e.g., “Angel Dust”)	2: approx. 1/month	1
7	Psychedelics (incl. LSD, Mescaline, Psilocybin mushrooms)	3: 2–3 times/month	2.5
8	Intoxicative inhalants	4: 1/week	4
		5: 2/week	8
		6: 3–4/week	14
		7: 5–6/week	22
		8: daily	28 days/month
9	PSU variety in the previous year	Number of different substance classes used within the previous year, range 0–9 (“use of 9 different substance classes in the previous year”)	
10	PSU frequency in the previous year	Monthly average of use days of substance class consumed most frequent within the previous year, range 0–28 (“daily use of at least one other substance within the previous year”)	
11	Regular PSU in the previous month	Repeated use of illegal substances, nicotine and alcohol in the previous month (4 weeks), range 0–3 (“regular co-use of alcohol, nicotine, and/or regular co-use of any further illegal substances”)	
12	Regular illegal PSU in the previous month	Repeated use of illegal substances in the previous month (4 weeks; yes/no)	
PSU, polysubstance use; LSD, lysergic acid diethylamide.			

of 3.6 days/week. Detailed characteristics of the complete sample that entered treatment ($n = 279$) and descriptions of the methodology are provided in other reports [21, 22, 25].

Instruments and Measures

Control Variables

CU patterns were measured at the start of treatment, and included an ICD-10 last month diagnosis of cannabis dependence [6] measured by the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) [26] as well as age of CU onset (years), days of CU within the last month or within the last week (number), and frequency of use (assessed using a modified version of the Timeline Followback protocol [27]). Additionally, ratings of preference for strong doses, smoking alone (use environment), smoking a joint, pipe, or (gravity) bong were also assessed on a self-developed cannabis questionnaire with a numerical scale ranging from 0 (“never”) to 3 (“most of the time”).

Predictor Variables

Measures of PSU were based on the DIA-X/M-CIDI [26], and included use frequency for 8 substance groups (Table 1) with 2 modifications; alcohol replaced cannabis, and answers ranged from 1 (“less than once/month”) to 8 (“daily or almost daily”) instead of from 1 to 5. Additional measures were daily nicotine use and repeated illegal substance use in the last month (yes/no), as

well as days of alcohol consumption in the last month before treatment start. From this information, 12 different PSU variables were calculated (Table 1).

Treatment Outcomes

The primary outcome measures were abstinence/reductions in CU and remission, and the secondary outcomes were reductions in CU-related problems and improvements in health conditions.

Abstinence was defined as no CU for at least 7 days after treatment, as indicated by both the self-report of abstinence and a negative urine toxicology test result (Drug-Screen-Card Multi-7 by von Minden GmbH, Moers, Germany) for participants with a self-reported abstinence therapy goal ([28], $n = 150$). Remission from ICD-10-dependence (full and partial) [29] and remission from DSM-IV-abuse were defined by a pre-post comparison of a 4 weeks-diagnosis, as measured by the DIA-X/M-CIDI [26], before treatment intake and upon completion of treatment.

Reduction of CU was assessed by a pre-post comparison of CU days in the last 4 weeks before treatment start and upon completion of treatment. Reductions in CU problems were assessed by a pre-post comparison of scores on the Cannabis Use Problem Identification Test (CUPIT), a brief screening instrument with good psychometric properties, which identifies CU problems in users of all ages [30]. The CUPIT includes an “impaired control” subscale with 10 items regarding the amount of use, use patterns, and abil-

Table 2. Regression analyses on pre-treatment PSU as predictors of abstinence and use reduction in (*n* = 166) patients with cannabis use treatment

PSU indicator	Abstinence from cannabis use ^a			Reduction of cannabis use ^c		
	crude model		adjusted model ^b	crude model		adjusted model ^b
	RD (95% CI)	<i>p</i> value		coefficient (95% CI)	<i>p</i> value	coefficient (95% CI)
Previous year variety of use	-0.03 (-0.08 to 0.03)	0.312	-0.04 (-0.09 to 0.01)	-0.17 (-0.32 to -0.01)	0.041	-0.2 (-0.39 to -0.01)
Previous year use frequency, ...all (days/month)	0.01 (-0.002 to 0.03)	0.088	0.01 (-0.01 to 0.021)	-0.01 (-0.06 to 0.05)	0.866	-0.01 (-0.1 to 0.05)
...of specific substances (days/month):						
Alcohol	0.01 (-0.01 to 0.03)	0.230	0.01 (-0.01 to 0.02)	-0.01 (-0.06 to 0.05)	0.863	-0.01 (-0.07 to 0.05)
Amphetamines	-0.02 (-0.07 to 0.03)	0.457	-0.03 (-0.08 to 0.01)	-0.01 (-0.17 to 0.14)	0.892	-0.02 (-0.18 to 0.13)
	atg: -0.04 (-0.05 to -0.03)	<0.001**	atg: -0.05 (-0.06 to -0.04)			
Tranquilizers	0.06 (0.05 to 0.07)	<0.001**	0.06 (0.05 to 0.07)	0.06 (0.26 to 0.38)	0.732 ¹	0.09 (-0.23 to 0.43)
Opiates	0.30 (-1.19 to 0.80)	0.229	0.25 (-0.30 to 0.81)	-2.97 (-4.51 to -1.43)	<0.001**	-3.15 (-4.76 to -1.55)
Cocaine	0.02 (0.02 to 0.02)	<0.001** ²	0.01 (0.01 to 0.02)	0.14 (-0.24 to 0.51)	0.464	0.16 (-0.21 to 0.54)
Dissociatives	0.11 (-0.76 to 0.98)	0.805	-0.24 (-1.21 to 0.72)	-5.86 (-8.84 to -2.88)	<0.001**	-5.88 (-8.98 to -2.79)
Psychodelics	-0.20 (-0.81 to 0.41)	0.524	-0.19 (-0.79 to 0.40)	0.74 (-0.91 to 2.39)	0.374	0.62 (-0.99 to 2.22)
Inhalants	-0.61 (-1.47 to 0.25)	0.167	-0.84 (-1.09 to -0.60)	-6.74 (-9.82 to -3.65)	<0.001**	-6.98 (-10.2 to -3.76)
Last-month PSU						
Regular illegal PSU (yes/no)	-0.22 (-0.46 to 0.02)	0.075	-0.24 (-0.48 to -0.01)	-1.17 (-1.77 to -0.57)	<0.001** ²	-1.22 (-1.86 to -0.59)
Regular PSU (alcohol, nicotine, any illegal substance: 0-3)	atg: -0.34 (0.06 to 0.93)	0.039	atg: -0.33 (-0.60 to -0.07)	-0.42 (-0.72 to -0.11)	0.007 ²	-0.36 (-0.64 to -0.08)
	-0.08 (-0.20 to 0.04)	0.178	atg: -0.13 (-0.27 to -0.03)			

PSU, polysubstance use; ^a risk difference regression model, *n* = 150 with explicit abstinence goal (16 participants with use reduction goal excluded); ^b multivariate regression with predictor, respective cannabis use control variables as well as age and gender; ^c robust linear regression; ¹ only significant in the active treatment group (atg); ² not significant in delayed treatment group; ³ not significant in active treatment group; ** significant when applying Bonferroni correction for seven indicators of illegal PSU with $\alpha = 0.05: 0.05/7 = 0.007$.

ity to control use; it also includes a “problems” scale with 6 items regarding the ability to concentrate and maintain daily routines, as well as regarding personal interests.

Health improvements included mental and physical health improvements, which were measured by pre-post comparisons of self-reported health measures, on a scale from 1 (“very good”) to 4 (“very bad”). Quality-of-life improvements were also assessed and were measured using a shortened version of the World Health Organization Quality of Life Scale [31], which is a widely field-tested, cross-culturally comparable assessment instrument for gauging an individual’s health perceptions.

Statistical Analyses

Identification of Relevant Control Variables of CU Patterns

Combined backward/forward selection was conducted on all CU pattern variables (α for exclusion = 0.05, α for inclusion of a preliminarily excluded covariate = 0.01) for the subsequent regression analysis of a specific outcome. Analyses were conducted separately for each outcome in order to identify its specific control variables. Binary outcome variables were modeled with logistic regression. Dimensional variables were tested for linearity. If linearity was suggested by kdensity analysis or scatter plots, a linear regression model was calculated (model 1). Additionally, a linear regression with robust estimates of standard errors (model 2) and a robust linear regression, which yields point estimates that are robust against outliers, were calculated (model 3) [32]. In cases with similar point estimates, model 2 was given preference. Otherwise, model 3 was preferred. Nonlinear variables were modeled by gamma regressions (generalized linear model for positively skewed outcomes with logarithmic link functions, which allows result interpretations as multiplicative relations).

Identification of PSU Predictors

Each treatment outcome was separately regressed for each indicator. Results on abstinence and remission were modeled with risk difference regression to account for the few baseline rates and occurring empty cells (Tables 2, 3). The outcomes were adjusted for by adding their baseline values to account for regression to the mean (crude model). Age, sex, and relevant CU control variables determined in the previous step were then incorporated into the respective regression model (adjusted model).

Results

One hundred thirty-three patients (80%) completed all sessions. The remaining 20% participated on average in 5 sessions (range 1–9). PSU was not related to retention.

PSU Characteristics

In our sample, 93% of all patients had smoked cigarettes daily for at least 1 month at any point in their life, and 72% had done so in the last month. Additionally, 88% had consumed other substances and/or alcohol in the last year (78% if considering higher doses of alcohol; Fig. 1). Among the illegal substances, amphetamines were the most fre-

Table 3. Risk difference regression analyses on pre-treatment PSU as predictor of remission in ($n = 166$) patients with cannabis use treatment

PSU indicator	Remission ICD-10-dependence ^{a, b}		Remission DSM-IV-abuse ^{a, c}	
	RD (95% CI)	<i>p</i> value	RD (95% CI)	<i>p</i> value
Previous year PSU variety (1–9 substances)	0.04 (0.03 to 0.06)	<0.001	0.07 (0.06 to 0.09)	<0.001
Previous-year use frequency, ...all (days/month)	0.014 (0.01 to 0.018)	<0.001	0.02 (0.01 to 0.02)	<0.001 ¹
...of specific substances (days/month):				
Alcohol	0.014 (0.01 to 0.018)	<0.001 ¹	0.02 (0.01 to 0.02) ¹	<0.001 ¹
Amphetamines	–0.02 (–0.15 to 0.10)	0.735	0.01 (–0.07 to 0.09)	0.771
Tranquilizers	–0.31 (–0.35 to –0.29)	<0.001	0.04 (–0.004 to 0.09)	0.074 ²
	atg: 0.54 (0.25 to 0.83)	<0.001	dtg: 0.88 (0.6 to 1.18)	<0.001
Opiates	0.46 (0.28 to 0.63)	<0.001	0.57 (0.48 to 0.66)	<0.001
Cocaine	0.03 (–0.09 to 0.14)	<0.666	0.11 (0.09 to 0.14)	<0.001
	atg: 0.08 (0.04 to 0.12)	<0.001		
Dissociatives	0.44 (0.28 to 0.62)	<0.001	0.72 (0.54 to 0.90)	<0.001
Psychedelics	0.20 (–0.29 to 0.69)	<0.425	0.75 (0.56 to 0.93)	<0.001
	atg: 0.39 (0.19 to 0.60)	<0.001		
Inhalants	0.44 (0.28 to 0.62)	<0.001	0.73 (0.55 to 0.90)	<0.001
Last-month PSU				
Regular illegal PSU (yes/no)	0.07 (–0.13 to 0.27)	0.519 ²	–0.02 (–0.32 to 0.28)	0.893
	dtg: 0.2 (0.06 to 0.03)	0.006		
Regular PSU (alcohol, nicotine, any illegal substance: 0–3)	0.06 (–0.4 to 0.15)	0.263	0.03 (–0.09 to 0.15)	0.630

PSU, polysubstance use; atg, active treatment group; dtg, delayed treatment group; ^a pre-post-comparison of 4-weeks-diagnosis; sample too small for adjusted models; ^b includes partial and full remission; $n = 90$; ^c $n = 116$; ¹ not significant in the delayed treatment group solely, but in overall sample; ² only significant in delayed treatment group (dtg).

quently used (30%), followed by cocaine (18%). Repeated illegal substance use in the last month before treatment initiation was reported by 10.5% of participants.

Primary Outcomes: Abstinence, Reduction, and Remission

CU days in the last week was a significant predictor of abstinence (OR 0.84 per day of use; 95% CI 0.76–0.94; $p = 0.002$). Cannabis dependence (mean difference; MD = 3.2; 95% CI 0.07–6.24, $p = 0.045$) and days of use in the last month ($b = 0.72$ per day; 95% CI 0.6–0.87, $p < 0.001$) were significant control variables for CU reduction.

Of the 90 patients who met the diagnosis for last month cannabis dependence at treatment intake, 84% achieved at least partial remission (59% full remission). Sixty-nine percent of 109 patients achieved remission from DSM-IV-abuse. Younger age predicted partial remission (OR 0.9; 95% CI 0.84–0.97, $p = 0.007$).

As expected, patients with recent illegal PSU experienced more difficulties in reducing their CU ($b = -1.22$, $p < 0.001$; Table 2). However, this effected abstinence rates only marginally ($b = -0.24$, $p = 0.044$, and not sig-

nificant when applying Bonferroni correction). Concerning remission, a positive relation between most indicators of PSU and treatment outcomes was found, although the estimated risk difference was overall small (Table 3) and was not significant in reference to the previous-month-illegal use.

Secondary Outcomes

Reduction of CU-Related Problems

Improved cannabis-related problems were predicted by dependence at baseline (MD = 6.12; 95% CI 1.55–10.68, $p = 0.01$) and impaired control (CUPIT subscale, $b = 0.46$; 95% CI 0.17–0.75, $p < 0.001$). Use of inhalants and dissociatives predicted improved cannabis-related problems in the robust regression model ($b = 14.48$; 95% CI 1.12–27.85, $p = 0.034$ / $b = 18.23$; 95% CI 10.66–25.81, $p < 0.001$). In contrast, the use of cocaine or amphetamines related to less improvements ($b = -1.77$; 95% CI –3.52 to –0.03, $p = 0.047$ / $b = -2.51$; 95% CI –4.53 to –0.49) but only in the active treatment group. Controlling for dependence and impaired control at baseline, as well as age and gender, relations remain significant for amphet-

Fig. 1. Use of specific substance classes, except cannabis and tobacco ($n = 166$), in the previous year.

amines ($b = -2.56$; 95% CI -4.46 to -0.65 , $p = 0.009$) and dissociatives ($b = 9.59$; 95% CI 0.69 – 18.48 , $p = 0.035$) for both treatment conditions.

Health Improvements

Pre-treatment CU patterns were not significantly related to health improvements. However, patients with regular illegal PSU in the last month before treatment intake showed better improvements in mental health over all treatment groups ($b = 0.39$; 95% CI 0.04 – 0.73 , $p = 0.021$).

Further, use of opiates, inhalants, and dissociatives were related to worse physical health improvements in all treatment groups (opiates: -0.31 , 95% CI -0.53 to -0.09 , $p = 0.007$; Inhalants: $b = -0.48$; 95% CI -0.92 to -0.03 , $p = 0.035$; dissociatives: $b = -0.58$; 95% CI -0.99 to -0.16 , $p = 0.007$). The use of cocaine was related to better physical health improvements, but only in the active treatment group ($n = 95$, $b = 0.11$; 95% CI 0.05 – 0.18 , $p = 0.001$). All reported results remained significant after controlling for age and sex. A preference for high doses of cannabis ($\exp(b) = 0.80$; 95% CI 0.66 – 0.98 , $p = 0.030$), but no PSU indicator predicted perceived quality-of-life improvements.

Discussion

We examined PSU indicators as potential predictors of primary and secondary CU treatment outcomes in an RCT of patients from 11 outpatient treatment centers in

Germany. Patients with PSU, including a wide variety of substances, more often recovered from dependence or abuse. In contrast, they showed less improvement in reducing their CU, especially if they had consumed opiates, inhalants, and dissociatives in the last year. Experiences with these substances were also related to less improvement in physical health, while recent repeated illegal substance use related to better mental health improvements after treatment. These findings were independent of age, sex, and CU patterns.

The unexpected finding of a positive relation between PSU and remission suggests that patients with low to moderate PSU may particularly profit from certain treatment features. For example, problem solving training may be especially beneficial for patients that report a wide range of substance use and demonstrate more difficulties in reducing their CU.

CU days and ICD-10 dependence in the last month at intake were independent predictors of CU and related problem improvements. Patients who initially preferred high doses of cannabis experienced more quality-of-life improvements, which could be interpreted as treatment success. High doses of cannabis can be assumed to impair normal functioning to a greater extent than lower doses; therefore, treatment effects may be more beneficial for those using higher doses by re-establishing daily functioning and quality of life.

Overall, the association between PSU and treatment outcomes was not significantly affected by CU patterns, which supports that PSU does not merely indicate a

heavier substance use behavior; rather, there is an independent role of PSU related to the prognosis for CU treatment outcomes.

Among the 8 substance classes considered, alcohol was used most frequently, followed by amphetamines and cocaine. The rare use frequency of the other substances rather indicates a pattern of experimentation, where future repeated use may not be anticipated. This pattern is consistent with the typical profile of PSU [8]. Nicotine use was the most frequently co-used substance but did not directly relate to any outcome. However, its role may have been difficult to detect in our sample, due to very limited variability for this measure. The high co-occurrence of tobacco and CU can be explained by the habit to smoke both substances in combination, which is common in Germany. Different results may be expected in countries where cannabis is often smoked without tobacco.

In our sample, the alcohol use frequency was lower than that in the general population. However, a substantial amount of patients regularly consumed higher amounts of alcohol (Fig. 1). Our results indicate that alcohol use is no hindrance for the successful completion of the treatment program.

Mixed results have been achieved in regard to illegal substances. In general, illegal substance use was related to less reduction in CU, but better improvements in mental health problems, including remission from abuse and dependence. An exception is the most frequently co-used illegal substance class amphetamines. Respective patients experienced less improvement of cannabis related problems. However, the amphetamines class includes a wide variety of substances and effects and findings may be largely due to specific substances such as Crystal and Ecstasy, but not Speed. It is hence suggested to further differentiate this substance class in future research to better observe possible negative effects of certain amphetamines in the treatment of CU problems.

Regarding intoxicative inhalants, dissociatives, and opiates, there are some noteworthy findings. First, the use of these substances predicted treatment outcomes, although they were consumed by a very small number of patients and at a low frequency (Fig. 1); second, all consumers of these substances with an initial diagnosis of abuse or dependence demonstrated at least partial remission at treatment end. Although the number of observations was too low for further analyses, the results lead to assume that respective clients especially benefit from effects of the treatment. On the other hand, use of these

substances was, in contrast to other patterns of PSU, related to minor physical health improvement. We hypothesize that the use of these substances may have more adverse consequences on one's physical health status even at low consumption frequencies. Their use may also indicate a different socio-economic status of the users [33, 34]. However, given the small sample size, further examinations were not possible and results need to be interpreted very cautiously. While the strength of the paper was to focus in a detailed manner on substance classes, there may still be some inept categorization of substances.

Although the PSU distribution in this sample with high ecological validity appears to represent the typical PSU profile of cannabis users [1, 8, 9, 15], some substances were so rarely used that the analysis relied on few observations with little variance. However, significant relationships with outcomes were observed despite these small rates of use.

Variables including frequency and repeated illegal PSU as sum indicators are sensitive to the use distribution of each individual substance. In this sample, these variables primarily represented use of amphetamines, cocaine, and in parts alcohol. A sample with more frequent PSU in all substance categories would probably produce different results for the sum variables. However, given the ecological validity of the sample, the results likely represent the population of help-seeking cannabis users in outpatient treatment.

Severe cases such as participants with a use disorder for another illegal substance were excluded from participation and are not represented here. However, our results are encouraging that patients with more severe PSU may also benefit from a similar treatment, although factors such as poorer health must be considered.

Two of our three health improvement measures relied on single questions. When replicating the explorative findings on these secondary outcomes with directed hypotheses, future research should use more sophisticated instruments. Measures of primary outcomes were objective (i.e., the urine toxicology test) and relied on established diagnostic instruments (e.g., DIA-X/M-CIDI).

Another strength of our analyses is the consideration of different PSU concepts. This feature allows differentiation of crucial PSU profiles and is methodologically important, since findings also depend on the fit between variable formats for predictors and outcome. Furthermore, all of our results included controls for patterns of CU, sex, and age as important covariates. The present findings are derived from a multicenter study with high

methodological quality, a treatment protocol with demonstrated efficacy, and high ecological validity [2–5, 16, 20, 21].

Conclusions

Patients with CU problems benefit from participation in modular treatment combining ME, CBT, and problem solving, even, and in some cases in particular, if they exhibit low to moderate PSU. Future research should test the robustness of these results and examine more closely the predictor-treatment-interaction. It should be tested how success variables change for patients who do not receive treatment (including control groups and self-instructed quitting attempts in the general population), as well as for patients with more severe PSU.

Overall, our results are encouraging with respect to treating cannabis users with PSU with this effective program [2–5, 16, 20, 21]. However, the special needs of specific PSU characteristics should be considered. For example, patients could be offered more intensive and specific support in reducing CU or achieving abstinence and handling physical health problems. We suggest considering these special PSU characteristics as additional components of a modularized program, in order to further improve existing concepts.

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