

A typology of cannabis-related problems among individuals with repeated illegal drug use in the first three decades of life: Evidence for heterogeneity and different treatment needs

Hans-Ulrich Wittchen^{a,c,1}, Silke Behrendt^{a,*,1}, Michael Höfler^a, Axel Perkonig^a, Jürgen Rehm^{a,d}, Roselind Lieb^{b,c}, Katja Beesdo^a

a Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Chemnitz Str. 46, D-01187 Dresden, Germany

b Institute of Psychology, University of Basel, Birmannsgasse 8, CH-4009 Basel, Switzerland

c Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, D-80804 Munich, Germany

d Centre for Addiction and Mental Health, University of Toronto, Canada

Abstract

Background: Cannabis use (CU) and disorders (CUD) are highly prevalent among adolescents and young adults. We aim to identify clinically meaningful latent classes of users of cannabis and other illegal substances with distinct problem profiles.

Methods: N= 3021 community subjects aged 14–24 at baseline were followed-up over a period ranging up to 10 years. Substance use (SU) and disorders (SUD) were assessed with the DSM-IV/M-CIDI. Latent class analysis (LCA) was conducted with a subset of N= 1089 subjects with repeated illegal SU. The variables entered in the LCA were CU-related problems, CUD, other SUD, and other mental disorders.

Results: Four latent classes were identified: “Unproblematic CU” (class 1: 59.2%), “Primary alcohol use disorders” (class 2: 14.4%), “Delinquent cannabis/alcohol DSM-IV-abuse” (class 3: 17.9%), “CUD with multiple problems” (class 4: 8.5%). Range and level of CU-related problems were highest in classes 3 and 4. Comorbidity with other mental disorders was highest in classes 2 and 4. The probability of alcohol disorders and unmet treatment needs was considerable in classes 2–4.

Conclusion: While the majority of subjects with repeated illegal SU did not experience notable problems over the 10-year period, a large minority (40.8%) experienced problematic outcomes, distinguished by clinically meaningful profiles. The data underline the need for specifically tailored interventions for adolescents with problematic CU and highlight the potentially important role of alcohol and other mental disorders.

Keywords: Latent class analysis, Cannabis, Epidemiology, Problem profile, Adolescence

1. Introduction

Cannabis use (CU) and cannabis use disorders (CUD; DSM-IV-abuse and -dependence) are highly prevalent in western countries (Boden et al., 2006; Coffey et al., 2002; Compton et al., 2004; Perkonig et al., 2008) and associated with a range of CU-related problems in adolescents and young adults as outlined below. Due to a wide range of investigated factors and different study designs it has been difficult to translate these findings into clinically meaningful guidance for prevention and intervention because of the heterogeneity among cannabis users. It has also been difficult to demonstrate to what degree the range and level of CU-related problems is associated with CU patterns and CUD. Also, it has been difficult to

derive a clearer picture of the cannabis-specific clusters of problems that develop during the high-incidence phase of CU and CUD in adolescence. This difficulty may partially be the result of earlier conceptions of CU as a typically transient phenomenon unrelated to a cannabis-specific dependence syndrome unless other problematic substance use (SU) or substance use disorder (SUD) occurs. Currently, there is little consensus of whether there is a group among subjects with repeated illegal SU that has predominant CUD but no further illegal SU/SUD and how large this group may be. Using community data we aim to derive clinically meaningful classes of individuals with repeated (at least 5 times) use of illegal substances by taking into account CU-related somatic and mental health problems, interpersonal problems, violence and delinquency, and occupational/financial problems in the first three decades of life.

The high-incidence phase for CU and CUD is in the second decade of life (Behrendt et al., 2009; Monshouwer et al., 2005; Patton et al., 2002; Vega et al., 2002; Wagner and Anthony, 2002). There is evidence that CU and CUD frequently persist into adulthood (Perkonig et al., 2008; Robertson et al., 1996).

CU in adolescence is associated with a broad range of somatic and mental health issues such as affective and anxiety symptoms and disorders, antisocial behaviour, legal and illegal SU and alcohol disorders (Degenhardt et al., 2002; Höfler et al., 1999; Patton et al., 2002, 2005; Rey et al., 2002; von Sydow et al., 2001; Wittchen et al., 2007; Zimmermann et al., 2005). The proportion of users experiencing CU-related problems is considerable but seems to vary with CU-frequency and DSM-IV-cannabis abuse or dependence (Caldeira et al., 2007; Nocon et al., 2006). The risk of CUD is higher among subjects with early onset of CU (Chen et al., 2005).

CU and CUD are predicted by and associated with nicotine dependence (Wittchen et al., 2007). Also, frequent CU predicts smoking (Patton et al., 2005). Conduct problems/disorders predict CU and CUD (Wittchen et al., 2007; Boyle et al., 1992; King et al., 2004; Pedersen et al., 2001). Also, anxiety, and depression may occur primary (Wittchen et al., 2007) and/or secondary to CU (Hayatbakhsh et al., 2007) or CUD (Wittchen et al., 2007). CU and CU-frequency were further associated with subsequent psychotic symptoms (Henquet et al., 2005) and related to poorer educational outcome (Brook et al., 1999; Fergusson et al., 2003; Georgiades and Boyle, 2007).

Help-seeking rates of subjects with CU-related problems increased in Germany and other European countries until 2005 (European Monitoring Centre for Drugs and Drug Addiction, 2007; Pfeiffer-Gerschel et al., 2007). At the same time drug services confronted with growing numbers of patients struggle with the choice of appropriate interventions and the lack of established interventions designed for cannabis-problems. Further, the mere scale of the problem in numbers of help-seeking subjects makes it unlikely that treatment offers can be allocated to all subjects asking for help. In this situation, data clarifying the question, whether subjects with CUD are a homogenous group or whether there are subgroups with distinct profiles requiring different interventions might provide some initial guidance. This question has also important implications for the development of CUD-specific treatments (Copeland et al., 2001; Dennis et al., 2004; Hoch et al., 2007; Stephens et al., 2002) that have recently become available from treatment research.

Adult cannabis users differ by CUD symptoms (Grant et al., 2006) and adults with CUD differ by concomitant illegal SUD² (Agrawal et al., 2006). However, the subject remains understudied for the high-risk phase for onset of CU and CUD in adolescence and young adulthood. We aim to identify subgroups with specific problem profiles in a community sample of adolescents and young adults. In this regard we aim to take into account all CU-related problems and CUD that occurred in the high-risk phase of SU and SUD in this sample. Therefore, we considered all CU-related problems and CUD cases that occurred at any assessment of the study in order to derive a complete picture of all problems reported in this sample in a time period of over up to 10 years that covered the core incidence phase of SU and SUD in adolescence.

We aim to

- (1) identify latent classes of subjects with repeated illegal SU by CU-related problems, alcohol disorders, other mental disorders and antisocial behaviours;
- (2) further characterize these classes in terms of sex, nicotine dependence, treatment seeking, and age at first SU.

2. Methods

2.1. Sample and overall design

Data were collected as part of the EDSP study (Early Developmental Stages of Psychopathology Study) a prospective-longitudinal study on the prevalence, course and risk-factors of SU, SUD and other mental disorders. Detailed descriptions of the sample, the study design and objective have been presented elsewhere (Lieb et al., 2000; Wittchen et al., 1998b). The sample is a community-based sample of N= 3021 subjects aged 14–24 at baseline. The study emphasizes early developmental stages of psychopathology. Therefore, individuals aged 14–15 years were sampled at twice the probability of those aged 16–21 years and individuals aged 22–24 years were sampled at half the probability of those aged 16–21. The baseline sample was drawn randomly from metropolitan Munich, Germany government registries in 1994 and followed-up over a 10-year period with up to three follow-up assessments. The baseline assessment took place in 1995 (T0, N= 3021, response rate 71%). The follow-up assessments were carried out 1.6 years (T1, median interval since baseline, only for the younger cohort of N= 1228 subjects aged 14–17 at baseline), 3.5 years (T2) and 8.2 years (T3) later. Conditional response rates (based on T0 participants) were 84.3% (N= 2548) at T2 and 73.2% (N= 2210) at T3. At T3, the age range was 21–34 years. The latent class analysis was conducted with the subset of N= 1089 subjects who reported repeated use (5 times or more) of at least one illegal substance at at least one assessment.

We assessed whether repeated CU or repeated other illegal SU at T0 predicted a lower rate of maintaining in the sample. In the younger cohort, repeated other illegal SU at baseline predicted drop-out at T3 (OR: 0.36, 95% CI: 0.1–0.9, $p = 0.031$).

2.2. Diagnostic assessment

Participants were assessed with the baseline or respective follow-up interval computer-assisted versions of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen et al., 1998a; Wittchen and Pfister, 1997), an updated version of the World Health Organisation (WHO) CIDI (Wittchen and Semmler, 1990). The DIA-X/M-CIDI is a

² In the following text, the terms other illegal SU and other illegal SUD will refer to illegal SU or illegal SUD related to illegal drugs except cannabis

fully standardized diagnostic interview designed for epidemiological research (Wittchen et al., 1998a). With the DIA-X/M-CIDI, it is possible to assess symptoms, syndromes and diagnoses (based on the computerized M-CIDI/DSM-IV algorithms) of 48 mental disorders along with information about onset, course, and impairment. The validity and reliability of DIA-X/M-CIDI diagnoses have been established: Validity was good for SUD (kappa 0.86) and reliability was satisfactory to good for any drug disorder (kappa 0.64) (Lachner et al., 1998; Reed et al., 1998).

SU and SUD were assessed with the three DIA-X/M-CIDI-sections for nicotine, alcohol, and medication and illegal substances, which have been described elsewhere in detail (Behrendt et al., 2009; Perkonigg et al., 2008). Diagnostic criteria for SUD were assessed if criteria for minimal SU of the respective substance were met. Criteria were (a) daily tobacco use over 4 weeks and (b) illegal SU at 5 times (for other illegal SUD and CUD; for CU-related problems). Alcohol dependence was assessed in case the individual reported alcohol use at least 3 times a week in a longer period or more than three standard drinks per drinking day during the last 12 months. DSM-IV-alcohol abuse was assessed in case of alcohol use on at least 13 occasions in at least 1 year during lifetime. Subjects who did not meet these criteria were coded as zero in the SUD-variables. All modes of CU (e.g. joints, bongs) were considered. Unfortunately, data did not permit differentiating between CU with and without simultaneous tobacco use. Criteria for cannabis dependence included withdrawal but endorsement of physical dependence symptoms was no prerequisite for a dependence diagnosis. Four substance categories were considered: alcohol, nicotine, cannabis and illegal drugs other than cannabis. The following use levels were considered: no use, any use, repeated use, DSM-IV-abuse, DSM-IV-dependence (DSM-IV-dependence and -abuse diagnoses were non-hierarchical; participants could be given both lifetime diagnoses).

2.3. Statistical analysis

Data were weighted to account for different sampling probabilities at baseline, and response rates at baseline varying over age, sex, and geographic location. With the exception of the latent class analysis (LCA), the Stata Software package 10.0 (StataCorp., 2007) was used for analyses and computing robust variances, confidence intervals, and p-values (by applying the Huber–White sandwich matrix) required when performing analyses with weighted data (Royall, 1986). Multiple linear regression and multi-nominal logistic regression analyses were used to examine associations between latent classes and other variables.

2.3.1. Latent class analysis

LCA (Skrondal and Rabe-Hesketh, 2004) was used to empirically identify the typologies of cannabis and other illegal drug users. LCA is a probabilistic method to identify latent groups of individuals so that, given group status, the manifest variables entered into the analysis are as independent as possible from one another within the latent classes (“local independence”). Therefore, LCA seems promising to reduce the probably complex structure of dependencies between variables to a single multi-categorical variable. LCA models were calculated using the statistical package Mplus, version 5.0 (Muthén and Muthén, 1998–2006).

1000 random sets of starting values were generated in the initial and 30 optimizations were carried out in the final stage; calculations were repeated to ensure that the found solution was the global maximum of the likelihood function. We fitted models with three to seven classes. Model fit was assessed with the Bayesian information criterion (BIC), the sample size adjusted BIC (ABIC), and Akaike's information criterion (AIC), the most common indices

which reveal a compromise between model fit and model parsimony (low number of parameters). Lower BIC, ABIC and AIC values indicate a better model fit. In addition, model fit was assessed with the Lo Mendell Rubin Adjusted Likelihood Ratio Test (LMR) comparing the actual model with one class less. Class membership was estimated using maximum posterior probabilities.

2.3.1.1. Variables in the LCA. Variables in the LCA were coded as 1 if a problem occurred at any wave, regardless of later remission or drop-out. Findings were combined across assessment waves. The variables on CU-related problems were composed of problem items from the SUD-section of the DIA-X/M-CIDI. CU-problems had to occur in relation with CU, not in relation with other SU. This ensures that problems reported by users of illegal substances were related to cannabis. Whether a problem was due to CU was decided by the participants. CU-related problems were defined as:

- (1) CU-related mental health problems: CU-related psychological problems.
- (2) CU-related somatic health problems: Injuries and somatic health problems because of CU.
- (3) CU-related interpersonal problems: Termination of a close relationship; reproach by close persons because of CU.
- (4) CU-related violence and delinquency (subsequently referred to as “legal problems”): CU-related legal problems; CU in a physically dangerous situation; committed physical assault.
- (5) CU-related occupational and financial problems (subsequently referred to as “occupational problems”): Financial problems; failure to fulfil role obligations at home, in school or at work; giving up important social, occupational or recreational activities.
- (6) Two or more mental disorders other than SUD: The following disorders were considered: major depression, dysthymia, bipolar disorder I and II, social phobia, any specific phobia, panic disorder, agoraphobia without a history of panic disorder, generalized anxiety disorder, posttraumatic stress disorder, obsessive–compulsive disorder, pain disorder, hypochondriasis, SSI4/6 (four somatoform symptoms endorsed by males, six somatoform symptoms endorsed by females), anorexia nervosa, bulimia nervosa, any psychotic disorder.
- (7) Other variables used in the LCA: Antisocial behaviour,³ DSM-IV-alcohol abuse, alcohol dependence, DSM-IV-cannabis abuse, cannabis dependence, other illegal drug abuse and other illegal drug dependence (DSM-IV-abuse and dependence were non-hierarchical).

2.3.1.2. Latent class characterization. To further characterize the latent classes, firstly a dimensional measure of the number of lifetime occasions of CU and of other illegal SU was transformed into a dichotomous variable and used in the logistic regressions analysis. Reports were gathered from the 794 individuals who provided information on the number of lifetime experiences of illegal SU at T2 and/or T3 (this information was not available from other waves), for other subjects it had to be coded as missing and those coded as missing were omitted from the analysis. In case that an individual reported different numbers of occasions of illegal SU at T2 and T3, the higher number of occasions reported was taken into account. Three dichotomous variables were created based on the dimensional measure: (1) other illegal SU on <10 occasions vs. ≥ 10 occasion, (2) other illegal SU on ≤ 100 occasions vs. on >100 occasions, and (3) CU on ≤ 200 vs. on >200 occasions.

³ Antisocial behavior was assessed with questionnaires at first (parental information on conduct disorder) and second follow-up (participant information on conduct disorder and anti-social personality disorder). For the present analysis, both diagnoses were collapsed into one category labelled “Antisocial behavior”, using information from subjects who had participated at first and/or second follow-up.

3. Results

3.1. *The LCA solution*

Table 1 shows the fit indices for three to seven latent classes. According to the LMR only the three class solution was better than the two class solution. The BIC was smallest for four latent classes. The AIC and the ABIC were smallest for seven latent classes. This seven class solution, however, included three very similar classes. Using tetrachorical correlations we found dependencies of the class indicators within classes for all solutions (results available upon request). We then tested whether the solutions could be replicated when adjusting the classification for sex and age at last assessment. If LCA adjusted for socio-demographic variables yields different patterns this would indicate that the local independence assumption is violated resulting in a potentially wrong solution (results available on request). Only the four class solution remained stable. Therefore, we chose the four class solution.

3.2. *Class characteristics*

Class 1 (“Unproblematic CU”; 59.21%): In the largest of the four classes, individuals had very low estimated probabilities for CUD, CU-related somatic health, mental health, legal, and occupational problems and other illegal SUD (0.0–1.9%). Probabilities of CU related interpersonal problems, alcohol disorders, burden of mental disorders, and antisocial behaviour were comparable to those in the entire sample or lower (see Table 2).

Class 2 (“Primary alcohol use disorders”; 14.36%): In this class, no one fulfilled criteria for DSM-IV-cannabis abuse and estimated probabilities of cannabis dependence were comparable to those in the entire sample (4.2%). However, rates were considerable for CU-related interpersonal and mental health problems (23.0% and 27.5%), elevated for occupational (6.6%) and somatic health problems (13.3%) in comparison to class 1, but only 1.3% for legal problems. Compared to class 1, this class had high relative frequencies of DSM-IV-alcohol use disorders (61.0–79.0%) and elevated relative frequencies of antisocial behaviour, other illegal SUD and having \geq two mental disorders (43.9%).

Class 3 (Delinquent cannabis/alcohol DSM-IV-abuse; 17.90%): All class members fulfilled criteria for DSM-IV-cannabis abuse (100%) and many met DSM-IV-alcohol abuse criteria (60.9%). Rates for all CU-related problems were elevated, especially for legal (85.3%) and interpersonal problems (51.3%).

Class 4 (“CUD with multiple problems”; 8.53%): This class had high rates for DSM-IV-cannabis abuse (92.7%) and dependence (82.7%). It also had the most distinct CU-related problem profile, with high frequencies for the entire problem-range (62.0–91.5%). Class 4 had the highest rate of having two or more mental disorders other than SUD (59.0%). The frequencies of antisocial behaviours and alcohol disorders were strongly elevated in comparison to class 1. Probabilities for other illegal drug dependence were elevated in comparison to class 1 but comparable to those in class 2.

3.3. *Further class characteristics*

We assessed whether the four derived classes allowed to distinguish between variables not entered in the LCA. For the description of rates and for multiple logistic and linear regression analyses, we chose class 1 (“Unproblematic CU”) as a comparison group (for rates see Table

3, for results of the multiple logistic regression analysis see Table 4; results of the multiple linear regression analysis are given in the text).

Age: Multiple linear regression revealed that subjects in classes 3 and 4 had a lower baseline age (Mean difference (MD) = -1.20, 95% CI: -1.7 to -0.6; MD = -1.00, 95% CI: -1.8 to -0.2; respectively) and a lower maximum age over assessments (MD = -1.53; 95% CI: -2.2 to -0.9; MD = -1.20; 95% CI: -2.1 to -0.3; table available upon request).

Sex: The rate of being female was highest in classes 1 (50.3%). Multiple logistic regression showed that females were less likely to fall into classes 2–4.

Frequency of illegal SU: Multiple logistic regression revealed that the risk of CU at more than 200 occasions and the risk of other illegal SU on ten or more occasions was elevated in classes 2–4.

Nicotine dependence: The rate of lifetime nicotine dependence was higher in classes 2–4.

Treatment: A large proportion (45.9–69.9%) of subjects in classes 2–4 did not receive any treatment. Any treatment seeking was more likely in class 4. Also having contacted a psychotherapist was more likely in class 4. However, the rate of untreated cases in this class was 45.9%.

Age at first SU: The relation between age-of-onset of SU (outcome) and classes (independent variable) was assessed with multiple linear regression analyses. Subjects in class 2 had an average 0.71 years earlier onset of alcohol use (95% CI: 0.2–1.2). This was also found for classes 3 and 4 (0.85, 95% CI: 0.4–1.3 and 0.70, 95% CI: 0.07–1.3). First nicotine use occurred earlier in classes 2 and 4 (0.60, 95% CI: 0.03–1.2 and 0.49, 95% CI: 0.01–1.0). First use of cannabis occurred earlier in classes 2–4 (class 2: 1.11, 95% CI: 0.6–1.6; class 3: 1.18, 95% CI: 0.8–1.5; class 4: 1.86, 95% CI: 1.3–2.4) (table available upon request).

4. Discussion

This study aimed to identify subgroups of cannabis users in adolescence and young adulthood by taking into account various problems that occurred in the period covering the high-risk phase of incident SU and SUD. The main findings are:

(1) A large proportion (59.2%) was classified as “non-problematic”, while 40.8% were classified as problematic users, (2) classes with elevated problem probabilities differed by problem profiles possibly indicating different treatment needs, (3) the “problematic” classes (2–4) differed from the “unproblematic CU” class by SU onset, nicotine dependence and SU frequency, (4) classes with problematic CU had elevated probabilities of alcohol disorders. Some had high probabilities of other mental disorders.

4.1. Methodological aspects

Before discussing the results in detail, methodological aspects should be addressed. We found some violations of local independence when examining the correlation structure within all classes in all LCA solutions. However, the 4 class solution presented here was stable when covariates were added indicating robustness against the violated local independence assumption. However, the six class solution appeared to be very interesting. In comparison to the four class solution, it offered a differentiation between problem profiles characterized by

either CUD alone or CUD with other illegal SUD. This may be regarded as an evidence of further possible differentiations between subgroups of adolescents with CU. In larger and more heterogeneous datasets, it may be possible to observe these additional subgroups.

4.2. Subgroup proportions and profiles

We found that the majority of subjects with repeated illegal SU did not report many CU-related problems, while a considerable 40.8% developed a problematic profile. Information on age indicates that the “Unproblematic CU” class does not simply consist of subjects who have not developed the problems yet. In conclusion, not all subjects with repeated illegal SU do necessarily develop problems. By taking into account other salient and public-health relevant problems we showed that the non-problematic group had low probabilities for all investigated problem areas. Females were more likely to be in the “non-problematic” class which is in agreement with LCAs conducted with adult data (Agrawal et al., 2006; Grant et al., 2006) and the greater risk of CUD in males (Compton et al., 2004; von Sydow et al., 2001; Wagner and Anthony, 2007). One may speculate that the different problem profiles may reflect a continuum of clinical severity for repeated illegal SU. However, the high rates of alcohol use disorders combined with low rates of cannabis use disorders in class 2 may also indicate that for some subjects not cannabis but alcohol is the substance of choice. Thus, class 2 would not represent a lower degree of CU-problem severity but a subgroup with primarily alcohol-related problems. In comparison to the “Unproblematic CU”-class, all “problematic” classes had a lower average age of onset of CU. This may support the conceptualization of early SU as a general indicator of adolescent problem behaviours (McGue and Iacono, 2008).

In all “problematic” classes, frequencies of alcohol disorders were elevated. Subjects seeking drug treatment for cannabis were more likely to report problems with a second substance, most likely alcohol (Urbanoski et al., 2005). Also, alcohol dependence predicts stability of CU (Perkonig et al., 2008). Thus, alcohol disorders should merit careful attention in CUD treatment. However, this issue is not explicitly addressed in the design of new CUD interventions (Copeland et al., 2001; Dennis et al., 2004; Hoch et al., 2007; The Marijuana Treatment Project Research Group, 2004). Also, the probabilities for nicotine dependence were elevated in all “problematic” classes. Among cannabis users, nicotine users had higher odds of cannabis dependence and CU-related problems (Caldeira et al., 2007). Thus nicotine use and dependence should be targeted in interventions for CUD. Nicotine and cannabis may be used simultaneously, but this information was not available in the dataset. Following the assumption that nicotine as an addictive substance may serve as a strong reinforcer for CU if the two substances are used simultaneously, this issue deserves further follow-up.

In class 2 (“Primary alcohol use disorders”) subjects had low rates of CUD but elevated rates for CU-related problems. Comparable results have been reported (Caldeira et al., 2007; Degenhardt et al., 2002). Thus, CU-related problems may occur in the absence of CUD and the respective subjects may profit from interventions as harm reduction strategies (Degenhardt et al., 2002; Toumbourou et al., 2007). We covered the entire high-risk-phase for CU and CUD in this sample (Behrendt et al., 2009). Thus, subjects in this class may not represent early stages of CU-problem development but a less severe, possibly stable form of CU-related problems as found for subclinical alcohol disorders (Bucholz et al., 2000). However, the elevated probability of mental disorders may put this group at risk for later CUD (von Sydow et al., 2002; Wittchen et al., 2007) or further mental health complications. With regard to the high rates of alcohol use disorders in this subgroup, it may also be the case that this class represents a group which is severely affected by SUD but for whom alcohol, not cannabis is the drug of choice.

The most severely affected group was class 4. Interestingly, this class was characterized by especially high probabilities for CUD and all CU-related problems. Also, the high probabilities for alcohol use disorders are notable. Probabilities of other illegal SUD were elevated, especially for DSM-IV-abuse (29.2%). However, differences between probabilities of CUD and other illegal SUD seem to indicate that a substantial proportion in this group did not make a further transition from CUD to other illegal SUD in the high incidence phase of other illegal SUD (Wittchen et al., 2008) in spite of early CU-onset and high CU-frequencies. This is somewhat surprising, since CU, early CU onset and CU-frequency have been linked to other illegal SU (Fergusson et al., 2006; Lynskey et al., 2006; Zimmermann et al., 2005). The profile of this group indicates considerable treatment need, but actual treatment rates did not exceed 54%, indicating unmet needs. This is surprising since SU-related problems are associated with treatment seeking and consideration to change (Annaheim et al., 2007; Wu et al., 2003).

Class 4 was characterized by a lower age at first CU and more frequent CU. Subjects with these features may profit from interventions supporting the decision process towards change (Miller and Rollnick, 2002). Notably, the burden of other mental disorders in this group is high. Other mental disorders are highly prevalent in subjects seeking CUD treatment (Dennis et al., 2004) and associated with treatment seeking (Perkonig et al., 2006). Also, the considerable probability of alcohol disorders in this group deserves attention as does the probability of other illegal SUD. For example, alcohol abuse was related to more negative CU-consequences in treatment-seeking adults (Stephens et al., 1993). Treatments for CU/CUD are effective without explicitly focusing on other mental disorders (Copeland et al., 2001), but approaches addressing problems besides CU may be more successful (The Marijuana Treatment Project Research Group, 2004), especially with regard to long-term outcomes (Dennis et al., 2004).

4.3. Future research

This study served as a first exploratory investigation of global subtypes of cannabis and other illegal substance users in adolescence and young adulthood. In future research it would be of interest to investigate possible further subgroups of subjects with multiple CU-related problems and high CUD-probabilities with regard to further (illegal) SU involvement. In this regard, it would be of interest to investigate cognitive control processes (Bühner et al., 2008) in CU-problem profiles and CUD. The role of alcohol disorders for CU and CUD should be investigated. Research should address how nicotine and alcohol disorders can be targeted in CUD-treatment. Future research should identify specific mental disorders in subgroups of cannabis users. In keeping with DSM-IV nomenclature DSM-IV-abuse and -dependence are investigated separately and categorically. However, there is evidence that the two disorders are part of a latent continuum of substance use severity (Saha et al., 2007). The high probabilities for both CUD in class 4 may support this assumption. Also, the high probabilities of CU related problems in the class with highest probabilities of CUD may indicate the possible meaningfulness of an additional dimensional approach for CUD diagnoses to address the issue of severity.

4.4. Limitations

Several limitations should be noted. First, the results do not provide information on subgroup development over time and the sequence of problem incidence. Also, we did not take into account differences in the chronicity of mental disorders. Second, data were derived from

metropolitan Munich, a relatively wealthy region in Germany. In this region, attitudes towards alcohol and nicotine use are relatively liberal but illegal drug use is prohibited. Thus, our findings cannot necessarily be generalized to other regions (e.g. regions with more restrictive SU policies). Third, we did not focus on specific mental disorders such as anxiety or mood disorders.

In summary, we could identify clinically meaningful subgroups of subjects with repeated illegal SU indicating different treatment needs and the necessity of considering comorbid mental disorders in treatment for CUD.

Table 1
Model fit results for the LCA^a.

# Classes	Loglikelihood	# Free parameters	AIC ^b	BIC ^c	ABIC ^d	Entropy	Lo Mendel-Rubin Adjusted LRT ^e	
							Test statistic	p-Value
3	-5145.354	41	10,372.707	10,577.421	10,447.196	0.956	337.489	0.0059
4	-5058.04	55	10,226.080	10,500.696	10,326.004	0.828	172.862	0.3203
5	-5010.299	69	10,158.598	10,503.116	10,283.957	0.850	94.516	0.7858
6	-4967.584	83	10,101.168	10,515.588	10,251.962	0.870	84.566	0.5459
7	-4935.577	97	10,065.153	10,549.476	10,241.383	0.905	63.367	0.9728

^a The parametric bootstrapped likelihood ratio test was not applied because of the use of weighted data.

^b Akaike's information criterion.

^c Bayesian information criterion.

^d Sample size adjusted Bayesian information criterion.

^e Lo Mendel-Rubin Adjusted Likelihood Ratio Test.

Table 2
The four class solution of the LCA^a.

	Total no.					
	Reference: total sample ^b , N= 3021	Analysis sample ^b , N= 1089	Class no. 1 ^{a,c} , N= 619	Class no. 2 ^{a,c} , N= 151	Class no. 3 ^{a,c} , N= 217	Class no. 4 ^{a,c} , N= 102
Variables entered in LCA						
CU related problems						
CU-related mental health problems	5.09	14.51	1.87	27.49	13.28	83.02
CU-related somatic health problems	3.07	8.76	0.85	13.25	6.48	61.96
CU-related interpersonal problems	8.13	23.18	6.09	23.04	51.28	83.02
CU-related violence and delinquency	7.44	21.19	0.00	1.33	85.29	69.38
CU-related occupational and financial problems	4.18	11.91	0.25	6.55	16.85	91.53
Diagnoses						
2+ mental disorders ^d	24.42	32.38	27.29	43.88	27.34	58.98
DSM-IV-cannabis abuse ^e	9.13	25.81	0.00	0.00	100.00	92.69
Cannabis dependence	3.14	8.94	0.28	4.24	6.21	82.70
DSM-IV-alcohol abuse ^e	24.72	41.55	22.97	78.80	60.93	67.16
Alcohol dependence	10.98	21.83	5.50	60.89	29.36	53.62
DSM-IV-other illegal drug abuse ^e	3.07	8.54	1.14	17.54	15.95	29.22
Other illegal drug dependence	1.67	4.76	0.48	12.64	8.47	13.42
Antisocial behaviour ^f	14.35	24.93	12.40	47.16	35.33	52.89

^a Estimated class probabilities (weighted) for classes 1–4.

^b Cumulative incidence rates (weighted percentages) as observed up to T3.

^c Class 1: unproblematic CU, class 2: primary alcohol use disorders, class 3: delinquent cannabis/alcohol DSM-IV-abuse, class 4: CUD with multiple problems.

^d Other than substance use disorders.

^e Diagnostic hierarchy not applied.

^f Conduct disorder or antisocial personality disorder; assessed at T1/T2; refers to reduced sample size of N=985.

Table 3
Further characterization of classes^a.

Total no.	Reference: total sample, N= 3021	Class no. 1 ^b , N= 619	Class no. 2 ^b , N= 151	Class no. 3 ^b , N= 217	Class no. 4 ^b , N= 102
Proportion ^c		59.21	14.36	17.90	8.53
Gender (female) ^d	50.60	50.30	35.73	22.13	27.84
CU> 200 times ^{d,e}	7.96	5.03	17.72	54.29	70.97
Other illegal drug use ≥ 10 times ^{d,e}	4.94	5.83	21.85	21.65	31.14
Other illegal drug use > 100 times ^{d,e}	1.34	0.55	6.97	6.01	13.56
Nicotine dependence ^{d,f}	28.50	38.49	59.09	60.90	77.39
Any treatment ^{d,f}	24.31	30.97	35.37	30.11	54.15
Contacted a psychotherapist ^{d,f,g}	14.16	19.77	18.62	15.13	30.40

^a Weighted percentages.

^b Class 1: unproblematic CU, class 2: primary alcohol use disorders, class 3: delinquent cannabis/alcohol DSM-IV-abuse, class 4: CUD with multiple problems.

^c Row percentages (weighted).

^d Column percentages (weighted).

^e Assessed at T2 and/or T3; N=794.

^f Cumulative life-period incidence rates (dichotomous variables).

^g Psychologist or physician with professional training in psychotherapy; any other psychotherapist.

Table 4
Further characterization of classes

	Class 1 ^{a,b}		Class 2 ^c		RRR ^d	95% CI		p	Class 3 ^e		RRR	95% CI		p	Class 4 ^f		RRR	95% CI		p
	Yes	No ^g	Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No	
Gender (female)	308	311	55	96	0.54	0.3–0.8	0.004	48	169	0.27	0.1–0.4	<0.001	29	73	0.37	0.2–0.6	<0.001	29	73	<0.001
CUD > 200 times	28	420	21	91	3.66	1.8–7.3	<0.001	86	71	17.73	9.9–30.2	<0.001	57	20	39.47	19.5–79.6	<0.001	57	20	<0.001
Other illegal drug use ≥ 10 times	26	422	22	90	4.35	2.2–8.5	<0.001	31	126	4.05	2.1–7.6	<0.001	26	51	6.73	3.4–13.3	<0.001	26	51	<0.001
Other illegal drug use > 100 times	3	445	7	105	na ^h			7	150	na			10	67	na			10	67	<0.001
Nicotine dependence	228	391	89	62	2.44	1.6–3.7	<0.001	128	89	2.84	1.9–4.1	<0.001	76	26	6.10	3.5–10.6	<0.001	76	26	<0.001
Any treatment seeking	183	436	53	98	1.48	0.9–2.3	0.079	64	153	1.42	0.9–2.1	0.078	56	46	3.84	2.3–6.4	<0.001	56	46	<0.001
Contacted a psychotherapist ^f	106	513	28	123	1.14	0.6–2.0	0.632	32	185	1.19	0.7–2.0	0.491	33	69	2.80	1.5–5.0	0.001	33	69	0.001

^a Reference group.

^b Class 1: unproblematic CUD, class 2: primary alcohol use disorders, class 3: delinquent/criminal alcohol DSM-IV-abuse, class 4: CUD with multiple problems.

^c Total numbers (for the number of drug use experiences, information was only available from N= 794 subjects).

^d Weighted relative risk ratio, controlled for maximum age up to T3 and sex.

^e Not applicable.

^f Psychologist or physician with professional training in psychotherapy; any other psychotherapist.

References

- Agrawal, A., Lynskey, M.T., Madden, P.A.F., Bucholz, K.K., Heath, A.C., 2006. A latent class analysis of illegal drug abuse/dependence: results from the National Epidemiological Survey on alcohol and related conditions. *Addiction* 102, 94–104.

- Annaheim, B., Rehm, J., Neuenschwander, M., Gmel, G., 2007. Quitting hash. The readiness for behaviour change among cannabis users in Switzerland. *Int. J. Public Health* 52, 233–241.
- Behrendt, S., Wittchen, H.-U., Höfler, M., Lieb, R., Beesdo, K., 2009. Transitions from first substance use to substance use disorders in adolescence: is early onset associated with a rapid escalation? *Drug Alcohol Depend.* 99, 68–78.
- Boden, J.M., Fergusson, D.M., Horwood, L.J., 2006. Illegal drug use and dependence in a New Zealand birth cohort. *Aust. N. Z. J. Psychiatry* 40, 156–163.
- Boyle, M.H., Offord, D.R., Racine, Y.A., Szatmari, P., Fleming, J.E., Links, P.S., 1992. Predicting substance use in late adolescence: results from the Ontario Health Study follow-up. *Am. J. Psychiatry* 149, 761–767.
- Brook, J.S., Balka, E.B., Whiteman, M., 1999. The risks for late adolescence of early adolescent Marijuana use. *Am. J. Public Health* 89, 1549–1554.
- Bucholz, K.K., Heath, A.C., Madden, P.A.F., 2000. Transitions in drinking in adolescent females: evidence from the Missouri adolescent female twin study. *Alcohol Clin. Exp. Res.* 24, 914–923.
- Bühlinger, G., Wittchen, H.-U., Gottlebe, K., Kufeld, C., Goschke, T., 2008. Why people change? The role of cognitive-control processes in the onset and cessation of substance abuse disorders. *Int. J. Methods Psychiatr. Res.* 17, 4–15.
- Caldeira, K.M., Arria, A.M., O’Grady, K.E., Vincent, K.B., Wish, E.D., 2007. The occurrence of cannabis use disorders and other cannabis-related problems among first-year college students. *Addict Behav.* 33, 397–411.
- Chen, C.-Y., O’Brien, M.S., Anthony, J.C., 2005. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. *Drug Alcohol Depend.* 79, 11–22.
- Coffey, C., Carlin, J.B., Degenhardt, L., Lynskey, M., Sanci, L., Patton, G.C., 2002. Cannabis dependence in young adults: an Australian population study. *Addiction* 97, 187–194.
- Compton, W.M., Grant, B.F., Colliver, J.D., Glantz, M.D., Stinson, F.S., 2004. Prevalence of Marijuana use disorders in the United States: 1991–1992 and 2001–2002. *JAMA* 291, 2114–2121.
- Copeland, J., Swift, W., Roffman, R., Stephens, R., 2001. A randomized controlled trial of brief cognitive-behavioral interventions for cannabis use disorder. *J. Subs. Abuse Treat.* 21, 55–64.
- Degenhardt, L., Lynskey, M., Coffey, C., Patton, G., 2002. “Diagnostic orphans” among young adult cannabis users: persons who report dependence symptoms but do not meet diagnostic criteria. *Drug Alcohol Depend.* 67, 205–212.
- Dennis, M., Godley, S.H., Diamond, G., Tims, F.M., Babor, T., Donaldson, J., Liddle, H., Titus, J.C., Kaminer, Y., Webb, C., Hamilton, N., Funk, R., 2004. The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. *J. Subs. Abuse Treat.* 27, 197–213.
- European Monitoring Centre for Drugs and Drug Addiction, 2007. Annual report on the state of the drugs problem in Europe. European Monitoring Centre for Drugs and Drug Addiction.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2006. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* 101, 556–569.
- Fergusson, D.M., Horwood, L.J., Beautrais, A.L., 2003. Cannabis and educational achievement. *Addiction* 98, 1681–1692.
- Georgiades, K., Boyle, M.H., 2007. Adolescent tobacco and cannabis use: young adult outcomes from the Ontario Child Health Study. *J. Child Psychol. Psychiatry* 48, 724–731.
- Grant, J.D., Scherrer, J.F., Neumann, R.J., Todorov, A.A., Price, R.K., Bucholz, K.K., 2006. A comparison of the latent class structure of cannabis problems among adult men and women who have used cannabis repeatedly. *Addiction* 101, 1133–1142.
- Hayatbakhsh, M.R., Najman, J.M., Jamrozik, K., Mamun, A.A., Alati, R., Bor, W., 2007. Cannabis and anxiety and depression in young adults: a large prospective study. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 408–417.

- Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C.D., Lieb, R., Wittchen, H.-U., van Os, J., 2005. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *Br. Med. J.* 330, 11–14.
- Hoch, E., Noack, R., Pixa, A., Rohrbacher, H., Henker, J., Dittmer, K., Bühringer, G., Wittchen, H.-U., 2007. Behandlung von Cannabisstörungen – Eine Aufgabe für Psychotherapeuten in Deutschland. *Psychotherapeutenjournal* 4, 362–367.
- Höfler, M., Lieb, R., Perkonig, A., Schuster, P., Sonntag, H., Wittchen, H.-U., 1999. Covariates of cannabis use progression in a representative population sample of adolescents: a prospective examination of vulnerability and risk factors. *Addiction* 94, 1679–1694.
- King, S.M., Iacono, W.G., McGue, M., 2004. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction* 99, 1548–1559.
- Lachner, G., Wittchen, H.-U., Perkonig, A., Holly, A., Schuster, P., Wunderlich, U., Türk, D., Garczynski, E., Pfister, H., 1998. Structure, content and reliability of the Munich Composite International Diagnostic Interview (M-CIDI). Substance use sections. *Eur. Addict Res.* 4, 28–41.
- Lieb, R., Isensee, B., von Sydow, K., Wittchen, H.-U., 2000. The early developmental stages of psychopathology study (EDSP): a methodological update. *Eur. Addict Res.* 6, 170–182.
- Lynskey, M.T., Vink, J.M., Boomsma, D.I., 2006. Early onset Cannabis use and progression to other drug use in a sample of Dutch twins. *Behav. Genet.* 36, 195–200.
- McGue, M., Iacono, W.G., 2008. The adolescent origins of substance use disorders. *Int. J. Methods Psychiatr. Res.* 17, 30–38.
- Miller, W.R., Rollnick, S., 2002. *Motivational Interviewing: Preparing People to Change Addictive Behaviours*. Guilford Press, New York.
- Monshouwer, K., Smit, F., de Graaf, R., van Os, J., Vollebergh, W., 2005. First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on substance use. *Addiction* 100, 963–970.
- Muthén, L., Muthén, B. (Eds.), 1998–2006. *Mplus User's Guide*. Muthén & Muthén, Los Angeles, CA.
- Nocon, A., Wittchen, H.-U., Pfister, H., Zimmermann, P., Lieb, R., 2006. Dependence symptoms in young cannabis users? A prospective epidemiological study. *J. Psychiatr. Res.* 40, 394–403.
- Patton, G.C., Coffey, C., Carlin, J.B., Degenhardt, L., Lynskey, M., Hall, W., 2002. Cannabis use and mental health in young people: cohort study. *Br. Med. J.* 325, 1195–1198.
- Patton, G.C., Coffey, C., Carlin, J.B., Sawyer, S.M., Lynskey, M., 2005. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. *Addiction* 100, 1518–1525.
- Pedersen, W., Mastekaasa, A., Wichstrøm, L., 2001. Conduct problems and early cannabis initiation: a longitudinal study of sex differences. *Addiction* 96, 415–431.
- Perkonig, A., Goodwin, R.D., Fiedler, A., Behrendt, S., Beesdo, K., Lieb, R., Wittchen, H.-U., 2008. The natural course of cannabis use, abuse and dependence during the first decades of life. *Addiction* 103, 439–449.
- Perkonig, A., Settele, A., Pfister, H., Höfler, M., Fröhlich, C., Zimmermann, P., Lieb, R., Wittchen, H.-U., 2006. Where have they been? Service use of regular substance users with and without abuse and dependence. *Soc. Psychiatry Psychiatr. Epidemiol.* 41, 470–479.
- Pfeiffer-Gerschel, T., Kipke, I., David-Spickermann, M., Bartsch, G., 2007. 2007 National Report to the EMCDDA by the REITOX National Focal Point Germany. New Developments, Trends and In-Depth Information on Selected Issues. *Drug Situation 2006/2007*. DBDD.
- Reed, V., Gander, F., Pfister, H., Steiger, A., Sonntag, H., Trenkwalder, C., Sonntag, A., Hundt, W., Wittchen, H.-U., 1998. To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *Int. J. Methods Psychiatr. Res.* 7, 142–155.
- Rey, J.M., Sawyer, M.G., Raphael, B., Patton, G.C., Lynskey, M., 2002. Mental health of teenagers who use cannabis. Results of an Australian Survey. *Br. J. Psychiatry* 180, 216–221.
- Robertson, J.R., Miller, P., Anderson, R., 1996. Cannabis use in the community. *Br. J. Gen. Pract.* 46, 671–674.

- Royall, R.M., 1986. Model robust confidence intervals using maximum likelihood estimators. *Stat. Rev.* 54, 221–226.
- Saha, T.D., Stinson, F.S., Grant, B.F., 2007. The role of alcohol consumption in future classifications of alcohol use disorders. *Drug Alcohol Depend.* 89, 82–92.
- Skrondal, A., Rabe-Hesketh, S. (Eds.), 2004. *Generalized Latent Variable Modeling*. Chapman & Hall/CRC, Washington, DC.
- Stephens, R.S., Roffman, R.A., Simpson, E.E., 1993. Adult Marijuana users seeking treatment. *J. Consult. Clin. Psychol.* 61, 1100–1104.
- Stephens, R.S., Babor, T.F., Kadden, R., Miller, M., 2002. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction* 97 (Suppl.1), 109–124.
- The Marijuana Treatment Project Research Group, 2004. Brief treatments for Cannabis dependence: findings from a randomized multisite trial. *J. Consult. Clin. Psychol.* 72, 455–466.
- Toumbourou, J.W., Stockwell, T., Neighbors, C., Marlatt, G.A., Sturge, J., Rehm, J., 2007. Interventions to reduce harm associated with adolescent substance use. *Lancet* 369, 1391–1401.
- Urbanoski, K.A., Strike, C.J., Rush, B.R., 2005. Individuals seeking treatment for cannabis-related problems in Ontario: demographic and treatment profile. *Eur. Addict Res.* 11, 115–123.
- Vega, W.A., Aguilar-Gaxiola, S., Andrade, L., Bijl, R., Borges, G., 2002. Prevalence and age of onset for drug use in seven international sites: results from the international consortium of psychiatric epidemiology. *Drug Alcohol Depend.* 68, 285–297.
- von Sydow, K., Lieb, R., Pfister, H., Höfler, M., Sonntag, H., Wittchen, H.-U., 2001. The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study in adolescents and young adults. *Drug Alcohol Depend.* 64, 347–361.
- von Sydow, K., Lieb, R., Pfister, H., Höfler, M., Wittchen, H.-U., 2002. What predicts incident use of cannabis and progression to abuse or dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug Alcohol Depend.*, 49–64.
- Wagner, F., Anthony, J., 2002. From first drug use to drug dependence: developmental periods of risk for dependence upon Marijuana, Cocaine, and alcohol. *Neuropsychopharmacology* 26, 479–488.
- Wagner, F.A., Anthony, J.C., 2007. Male-female differences in the risk of progression from first use to dependence upon cannabis, cocaine and alcohol. *Drug Alcohol Depend.* 86, 191–198.
- Wittchen, H.-U., Behrendt, S., Höfler, M., Perkonig, A., Lieb, R., Bühringer, G., Beesdo, K., 2008. What are the high risk periods for incident substance use and transitions to abuse and dependence? implications for early intervention and prevention. *Int. J. Methods Psychiatr. Res.* 17, 16–29.
- Wittchen, H.-U., Fröhlich, C., Behrendt, S., Günther, A., Lieb, R., Perkonig, A., Rehm, J., Zimmermann, P., 2007. Cannabis use and Cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal study in adolescents. *Drug Alcohol Depend.* 88, 60–70.
- Wittchen, H.-U., Lachner, G., Wunderlich, U., Pfister, H., 1998a. Test–retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Soc. Psychiatry Psychiatr. Epidemiol.* 33, 568–578.
- Wittchen, H.-U., Perkonig, A., Lachner, G., Nelson, C.B., 1998b. Early Developmental Stages of Psychopathology Study (EDSP): objectives and design. *Eur. Addict Res.* 4, 18–27.
- Wittchen, H.-U., Pfister, H., 1997. DIA-X Interview. Instruktionsmanual zur Durchführung von DIA-X-Interviews (Instruction manual for the DIA-X-Interview). Swets & Zeitlinger, Frankfurt.
- Wittchen, H.-U., Semmler, G., 1990. Composite International Diagnostic Interview (CIDI). Beltz, Weinheim.

- Wu, P., Hoven, C.W., Fuller, C.J., 2003. Factors associated with adolescents receiving drug treatment: findings from the National Household Survey on drug abuse. *J. Behav. Health Serv. Res.* 30, 190–201.
- Zimmermann, P., Wittchen, H.-U., Waszak, F., Nocon, A., Höfler, M., Lieb, R., 2005. Pathways into ecstasy use: the role of prior cannabis use and ecstasy availability. *Drug Alcohol Depend.* 79, 331–341.