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Prevalence of cognitive impairment in patients with substance use disorder

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Abstract

Introduction and Aims. Cognitive impairments in substance use disorder predict treatment outcome and are assumed to differ between substances. They often go undetected, thus the current study focuses on the prevalence of and differences in cognitive functioning across substances by means of a cognitive screen at the early stage of addiction treatment. **Design and Methods.** The Montreal Cognitive Assessment was administered to outpatients seeking treatment for substance use disorder. Patient characteristics (age, years of regular use, polysubstance use, severity of dependence/abuse, depression, anxiety and stress) were also taken into account. **Results.** A total of 656 patients were included (n = 391 used alcohol, n = 123 used cannabis, n = 100 used stimulants and n = 26 used opioids). The prevalence of cognitive impairments was 31%. Patients using alcohol had a lower total- and memory domain score than those using cannabis. Patients using opioids scored lower on visuospatial abilities than those using cannabis or stimulants. Younger patients scored higher than older patients. No effect was found for the other investigated characteristics. **Discussion and Conclusions.** Given the high prevalence of cognitive impairments, standard screening at an early stage of treatment is important to determine the course of treatment and maximise treatment outcome. Caution is needed in interpreting results about opioids due to an underrepresentation of this patient group, and more research is needed on the effect of age on Montreal Cognitive Assessment performance. [Bruijnen CJWH, Dijkstra BAG, Walvoort SJW, Markus W, VanDerNagel JEL, Kessels RPC, De Jong CAJ]. Prevalence of cognitive impairment in patients with substance use disorder. *Drug Alcohol Rev* 2019;38:435–442]

Key words: substance use disorder, cognitive impairment, Montreal cognitive assessment, prevalence.

Introduction

Substance use disorder (SUD) refers to ‘a cluster of cognitive, behavioural and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems’ (p. 483) [1]. Substances like alcohol, cannabis, stimulants and opioids are psychoactive drugs that may change brain function and structure after chronic use,

and result in cognitive and behavioural deficits that remain even after detoxification. The prevalence of cognitive impairments in patients with SUD is still unclear [2] and is estimated between 30% and 80% [3]. This wide range includes, for instance, differences in the mode of action between substances, years and amount of regular use, and effects of gender. As each substance has different effects on brain functioning the

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consequences of prolonged substance use, such as cognitive impairments, will also differ between substances.

Acute alcohol intoxication primarily acts upon cognitive functions associated with the prefrontal cortex, such as planning, verbal fluency, memory and complex motor control [4,5]. The effects of alcohol on cognitive functioning post-detoxification are found to affect all cognitive domains [6]. After 1 to 3 weeks of abstinence, chronic alcohol use is still associated with decrements in memory, visuospatial abilities and inhibition [7]. After six months of abstinence, cognitive recovery generally has occurred [8] but impairments have still been demonstrated in the domains of visuospatial abilities and decision making [9] which may last at least up to 1 year after abstinence [6,7]. There is some evidence that in the long term, the cognitive consequences of alcohol use disorder (AUD) may be fully reversible [10], but cases of persistent cognitive impairments like Korsakoff's syndrome are not uncommon [11].

The acute consequences of cannabis intoxication primarily involve working memory, executive functioning and attention [12]. Post-detoxification effects have been found to impact executive functioning after 17 h until up to 21 days of abstinence [13–15]. In the long term (i.e. after more than one month of abstinence), full cognitive recovery can occur [7,14,16].

Concerning stimulant abuse, including cocaine, amphetamine and ecstasy, cognitive impairments are considered relatively mild [17] and seem to follow an inverted U-shape [18]. Acute intoxication with low doses has mostly enhancing effects on response inhibition, attentiveness, speed and psychomotor performance [19,20]. Cognitive impairments that occur after short-term abstinence in executive functioning, inhibition, (verbal) memory, psychomotor functions and attention disappear again after long-term remission [7,19–24]. After 1 year of complete abstinence cognitive function has been found to be at the level of healthy controls [25,26]. There are case studies, however, that report major cognitive impairments in patients with a history of chronic stimulant use, with dosage being the critical determinant [18,20,27].

Regarding opioid abuse, relatively few studies have assessed the acute cognitive sequelae. There is, however, ample evidence of impairments in the memory domain [28], and impairments are also found after short-term abstinence in executive functioning, such as verbal fluency, inhibition and decision-making. These impairments have been demonstrated after up to 1 year of abstinence [7]. Whether full recovery occurs is largely unknown, although it has been found that at least some recovery is possible after long term abstinence of opioid abuse [29].

Cognitive deficits in chronic substance abuse are clinically relevant, as they affect treatment outcome and predict dropout rates as compared to cognitively intact users [30]. In AUD, cognitive impairments are associated with worse treatment compliance and lower self-efficacy, which in turn result in a drinking outcome with fewer abstinent days and more drinks per drinking day [31,32]. Poorer treatment outcomes, lower treatment retention and less abstinence are also found in cocaine users with mild cognitive impairments [33,34]. Poor executive function performance is associated with worse recognition of problem use and hampers the intention to stop using in both opioid and cocaine users [35,36]. Interventions targeting cognitive functioning, or taking cognitive impairments into account, may lead to a better treatment outcome both regarding the addiction and in everyday functioning [37,38].

Although the literature carefully suggests that full recovery of cognitive impairments may be possible for all substances, the influence of cognitive impairments on treatment outcome shows the importance of detecting these impairments for each individual at an early stage, so that personalised treatment can be implemented. The current study focuses on the prevalence of cognitive impairments and differences in cognitive functioning across substances by means of a cognitive screen [the Montreal Cognitive Assessment (MoCA; 39)] at the early stage of addiction treatment right before interventions are being initiated. The first aim is to determine, at intake, the prevalence of cognitive impairments in patients using different substances. Differences in cognitive performance across substances will be studied per cognitive domain. The second aim is to investigate the effects of age, abstinence (i.e. not having used prior to MoCA assessment classified as <7 days, 7–41 days or ≥ 42 days), abstinence duration (i.e. number of days abstinent prior to MoCA assessment, with a minimum of 7 days), polysubstance use, duration of regular use, severity of dependence/abuse, depression, anxiety and stress on cognitive functioning.

Methods

Design

A cross-sectional study was performed in which a validated cognitive screening instrument was administered as part of the intake procedure that contains items covering all cognitive domains, the MoCA [39]. Data were collected between April 2012 and December 2014 in four addiction treatment centres. The study was approved by the internal review boards of all participating health-care centres and the research board of the Nijmegen Institute for Scientist-Practitioners in Addiction.

Participants

The aim was to include a total of 800 participants seeking treatment for SUD in one of four addiction care centres in the Netherlands (IrisZorg, Novadic-Kentron, Tactus and Vincent van Gogh Institute for Psychiatry). The inclusion criteria were: (i) dependency or abuse of a substance (excluding nicotine) or behaviour; (ii) age 18–75; and (iii) signed informed consent for participation. The only exclusion criterion was an inability to administer the MoCA, due to for instance a neurological (e.g. stroke, dementia, traumatic brain injury) or very instable acute psychiatric disorder, severe lack of motivation or insufficient Dutch language skills. Patients were included regardless of substance use status to comply as much as possible with treatment as usual in all participating institutions and to maximize the generalisability of the sample in relation to the population that is referred to addiction clinics in general.

Materials

Measurements in the addictions for triage and evaluation. The Measurements in the Addictions for Triage and Evaluation (MATE 2.1) [40] consists of an interview and self-report questionnaires for collecting information relevant for treatment purposes. In this study four sections were used. Section 1 ‘Substance use’, is an interview that assesses the use of nine psychoactive substances and behavioural addictions in the past 30 days as well as lifetime. The primary-problem substance is determined by both the patient and the assessor as the substance that causes the most problems. For the current study, a participant was considered a polysubstance user if any substance other than the primary-problem substance, had a lifetime use of 1 year or longer, excluding nicotine and behavioural addictions. Section 3 ‘History of treatment for substance use disorders’, assesses if a patient has ever been in treatment for addiction. Section 4 ‘Substance dependence and abuse’, Section Alcohol & Drugs of the Composite International Diagnostic Interview [41], is an interview questionnaire that helps to diagnose substance abuse or dependence by answering 11 yes or no questions about the primary-problem substance. Nine out of 11 questions are used to determine severity of the addiction, with a maximum score of 9. Finally, section Q2 the Depression, Anxiety and Stress Scale (DASS-21) [42,43], is a self-report questionnaire that measures symptoms of depression, anxiety and stress by answering 21 questions on a four-point scale (anchored with 0 = ‘Did not apply to me at all’ and 3 = ‘Applied to me very much, or most of the time’), and is used to identify psychiatric comorbidity. The sum of all

21 questions multiplied by two, gives the DASS-21 total score, with a maximum of 126.

Montreal cognitive assessment. The MoCA [39] consists of 13 items measuring seven cognitive domains: executive functioning; visuospatial abilities; attention, concentration and working memory (referred to as ‘attention’ from now on); language; abstract reasoning; memory; and orientation. The authorised Dutch translation of MoCA version 7.1 was used in this study (see www.mocatest.org). Administration of the MoCA takes approximately 15 min and scoring can mostly be done during administration. A total score is calculated by summing scores on all items, with a maximum of 30 points, where higher scores represent better cognitive performance. An adjustment for level of education is applied in which participants with a low level of education are awarded two extra points and participants with an average level of education are awarded one extra point, maintaining the maximum score of 30 [44]. In addiction care, an optimal cut-off score of 24 was found to be predictive of substance-induced cognitive impairments, with a sensitivity of 0.56 and a specificity of 0.62, using an extensive neuropsychological assessment as gold standard [45].

Procedure

As part of the intake procedure, the MATE 2.1 was administered to each participant seeking treatment. After the intake, participants were informed about the study. Written informed consent was required for participation and for using information of the administered MATE 2.1. MoCA version 7.1 was administered by professionals (e.g. psychologists, social psychiatric nurses, social workers) immediately or in the following appointment. All professionals were trained in MoCA administration and scoring by the psychologist coordinating this study in accordance with the formal instructions and based on experience of the psychologist for ambiguities that are not clarified in these instructions. Patients provided demographic information, such as sex, age, level of education, marital status and employment. Also, self-reported use of the primary-problem substance in the week before MoCA administration, or abstinence duration (if >7 days) was recorded.

Analyses

For descriptive purposes, differences in patient characteristics between subgroups and between the four addiction treatment centres were explored using χ^2

tests and univariate analyses of variance (ANOVA). Second, the prevalence of cognitive impairments was calculated for the total sample and per primary-problem substance. Third, MoCA total and domain scores for the total sample and differences between primary-problem substances were analysed using univariate and multivariate ANOVAs, respectively. Finally, the effects of age, years of regular use, abstinence duration in days, severity of dependence and/or abuse (Section Alcohol & Drugs of the Composite International Diagnostic Interview), and depression, anxiety and stress (DASS-21) on MoCA total score were examined by Pearson correlations; abstinence (<7 days/7–41 days/≥42 days) [46] with a univariate ANOVA; and the effect of polysubstance use (yes/no) on the MoCA total score was examined with an independent *t* test. Hochberg's GT2 (unequal sample sizes) or Games–Howell post-hoc tests (non-homogeneous population variances) were used as post-hoc analyses in all ANOVA. Alpha was set at 0.05 for all analyses and all data were computed and analysed using IBM SPSS version 25.0.

Results

Patient characteristics

A total of 656 patients was included (77% male). The mean age was 40 years (SD = 13.9). The most prevalent primary-problem substance was alcohol (60%), followed by cannabis (19%), stimulants (15%) and opioids (4%). Only 6 patients primarily used sedatives and another 10 used gamma-hydroxybutyrate as the primary-problem substance (2%). Due to these small numbers, these patients were only included in analyses regarding the total sample. Patient characteristics differed significantly between patients with different primary-problem substances, except for the MATE 2.1 subscales depression and anxiety (Table A1 in Appendix). Between patients from all four health-care centres, there were significant differences for primary-problem substance, marital status, abstinence, depression, stress and DASS-21 total score.

Cognitive impairments

In the current sample, 206 patients (31%) performed below the MoCA cut-off score of 24. Per primary-problem substance, the prevalence was 34% for alcohol, 21% for cannabis, 27% for stimulants and 38% for opioids. Post-hoc tests revealed that only patients using alcohol performed significantly worse on the MoCA total score than those using cannabis

(Table 1). However, taking into consideration the sensitivity and specificity of the MoCA in addiction care [45], a rather high proportion of patients with actual cognitive impairments may remain undetected, while at the same time cognitively intact patients are classified as being cognitively impaired by the MoCA.

Differences between primary-problem substances for cognitive domains

Of all the possible differences that could be found between the primary-problem substances in performance on the MoCA domain scores, only three were significant. Patients using alcohol performed significantly worse on memory than those using cannabis [M diff = 0.44 (SD = 0.14), *P* = 0.01]. Patients using opioids performed significantly worse on visuospatial abilities than those using cannabis [M diff = 0.64 (SD = 0.20), *P* = 0.01] and those using stimulants [M diff = 0.61 (SD = 0.21), *P* = 0.02]. Additionally, patients using opioids performed worse on memory than those using cannabis, which was marginally significant [M diff = 0.96 (SD = 0.35), *P* = 0.05]. A significant main effect was found for executive functioning, with no significant post-hoc differences between substances.

Factors related to cognitive performance

In the total sample, the MoCA total score was negatively correlated with age ($r = -0.28$, $P < 0.01$), with a shared variance of only 9%. None of the other investigated factors (i.e. years of regular use, abstinence duration, severity of dependence and/or abuse, depression, anxiety and stress) were significantly correlated with the MoCA total score. Abstinence and polysubstance use were also not related to the MoCA total score (all *P* values > 0.05). Since age was significantly correlated with MoCA total score in the total sample and there was a significant difference in mean age between substances, the correlation between MoCA total score and age was calculated per primary-problem substance. For alcohol age was negatively correlated with MoCA total score ($P = -0.33$, $P < 0.01$), for cannabis this negative correlation was marginally significant ($P = -0.15$, $P = 0.05$), for stimulants age was positively correlated with MoCA total score ($P = 0.17$, $P = 0.04$), and the correlation between age and MoCA total score for opioids was negative but not significant ($r = -0.20$, $P = 0.17$).

Discussion

To our knowledge this is the first study in addiction care in which a large and heterogeneous group of

Table 1. Mean (SD) Montreal cognitive assessment (MoCA) domain and total scores for the total sample and per primary-problem substance. Post-hoc gives a description of significant differences^a

Cognitive domain (score range)	Total (n = 656)	Alcohol (A) (n = 391)	Cannabis (C) (n = 123)	Stimulants (S) (n = 100)	Opioids (O) (n = 26)	P value	Post-hoc
Executive functioning (0–2)	1.31 (0.67)	1.27 (0.68)	1.45 (0.66)	1.34 (0.66)	1.12 (0.77)	0.04	
Visuospatial abilities (0–4)	2.77 (0.94)	2.73 (0.95)	2.91 (0.90)	2.88 (0.88)	2.27 (1.00)	<0.01	C, S > O
Attention (0–6)	5.40 (0.97)	5.44 (0.95)	5.42 (0.92)	5.40 (0.90)	5.23 (1.31)	0.74	
Language (0–5)	4.46 (0.72)	4.44 (0.76)	4.48 (0.67)	4.51 (0.70)	4.58 (0.64)	0.68	
Abstract reasoning (0–2)	1.52 (0.63)	1.51 (0.64)	1.58 (0.60)	1.51 (0.58)	1.65 (0.63)	0.55	
Memory (0–5)	3.30 (1.49)	3.21 (1.56)	3.65 (1.24)	3.33 (1.33)	2.69 (1.72)	0.01	A < C
Orientation (0–6)	5.75 (0.61)	5.76 (0.62)	5.74 (0.54)	5.79 (0.54)	5.77 (0.65)	0.94	
MoCA total (0–30)	25.52 (3.12)	25.30 (3.23)	26.33 (2.69)	25.86 (2.72)	24.69 (3.88)	<0.01	A < C
n (%) scoring below cut-off	206 (31)	134 (34)	26 (21)	27 (27)	10 (38)	0.03	A > C

^aPatients with sedatives or gamma-hydroxybutyrate as the primary-problem substance are only included in the total sample and not separately described.

patients with SUD are assessed on cognitive impairments. The current study found a prevalence of cognitive impairments of 31% in the total sample, ranging from 21% for cannabis to 39% for opioids. Patients using alcohol had a significantly lower MoCA total score than those using cannabis and it was found that in the total sample younger patients scored significantly higher than older patients. Years of regular use, abstinence (duration), severity of dependence and/or abuse, polysubstance use, depression, anxiety and stress were not related to MoCA outcomes.

Previous research shows a prevalence of cognitive impairments in patients with SUD ranging from 30% to 80% [3]. The prevalence in our study falls at the bottom of this range, yet is still remarkable as cognitive impairments are found to affect treatment outcomes. Differences between primary-problem substances on MoCA performance were not as profound as expected. Patients using alcohol had lower outcomes than those using cannabis, both on the MoCA total score and on the domain memory, and patients using opioids had lower outcomes on visuospatial abilities in comparison to those using cannabis and stimulants. The lack of significant differences could be influenced by the high percentage of polysubstance users in our sample and the relatively small number of patients using opioids (see Table A1). There was a significant difference in age between substance types, and age was found to have an effect on MoCA performance in this study. The finding that age is negatively correlated to MoCA scores is in line with findings in a sample of patients with AUD aged >18 [47] and also in a sample of healthy controls aged 25–91 [48]. It is, however, striking that the directionality of the correlation between age and MoCA total score was different for stimulants than for the other substances. This may be a consequence of the primarily enhancing effects of stimulant

intoxication at low doses [19,20], although abstinence was no significant factor on MoCA performance in the total sample. Substance type and age are thus factors that should be taken into account when interpreting the MoCA total score.

SUD patients may experience more psychological complaints than healthy people, and they are not always abstinent at intake. In our sample, none of the variables (abstinence, abstinence duration, polysubstance use, years of regular use, severity of dependence and/or abuse, depression, anxiety and stress) were related to MoCA outcome. The lack of relations between MoCA total score and depression, anxiety and stress is in line with recent findings in a sample of polysubstance users where the MoCA total score was not related to results on a (psychiatric) symptom checklist [49]. As for abstinence and abstinence duration, our findings are not in line with the literature, as a review by Walvoort *et al.* [46] points to a minimum period of 6 weeks abstinence before an extensive (neuro)psychological assessment can be carried out validly.

In clinical practice, cognitive impairments often remain undetected at the start of or during treatment. Early detection of cognitive impairments is essential to increase the chance of a favourable outcome of treatments and the MoCA is a relatively quick and easy tool to assess cognitive functioning at intake. When cognitive impairments are indeed present, adequate interventions, such as cognitive training [50] or errorless learning [51] may help to increase treatment compliance, self-efficacy and cognitive performance. As our results show, screenings for cognitive impairment can be validly interpreted in every patient applying for addiction treatment, independent of possibly relevant characteristics. When interpreting findings obtained with the MoCA one should, however, take into

account that older adults with SUD may perform lower than younger adults with SUD (except for stimulants, where the opposite effect of age was found).

Some strengths to our study are in the design, which was kept as close to clinical practice as possible, by only adding a MoCA assessment to the intake procedure as usual. Also, patients were only excluded if administration of the MoCA was impossible. Consequently, a large number of patients using different substances, whether or not abstinent and with a variety of psychological complaints, could be included. Therefore, results are representative of clinical practice. There are some limitations to the current study. First, it was impossible to perfectly balance the number of patients for each primary-problem substance. Users of cocaine, amphetamines and ecstasy were therefore combined into 'stimulants' and the relatively small number of patients using opioids lowered the power of the analyses that included this group. The small number of patients using sedatives and gamma-hydroxybutyrate were not included in the comparisons making it impossible to conclude about consequences on cognitive functioning for these substances. Finally, the rather low sensitivity and specificity of the MoCA for use in addiction care [45] may have influenced our results and therefore the actual prevalence of cognitive impairments may well be different than that currently found.

In conclusion, a prevalence of 31% for cognitive impairments was found in addiction care and, therefore, detection of cognitive impairments at an early stage of treatment is important to determine the course of treatment and maximise treatment outcome. Significant differences in MoCA performance were only found between patients using alcohol and cannabis, but not between other substances. Because of the underrepresentation of patients using opioids in our sample, differences between this group and the other substance groups cannot be excluded. More research is needed on how to adjust for the effect of age on MoCA performance in individuals without SUD. Finally, we emphasise the fact that the MoCA is not intended as a diagnostic instrument and that a full neuropsychological assessment is always preferred. We therefore recommend to use the MoCA as a first screen in the triage for subsequent more expensive and time-consuming (extensive neuropsychological) assessments.

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Conflict of Interest

The authors have no conflicts of interest.

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Appendix

Table A1 Patient characteristics in the total sample and per primary-problem substance^a

	Total (n = 656)	Alcohol (A) (n = 391)	Cannabis (C) (n = 123)	Stimulants (S) (n = 100)	Opioids (O) (n = 26)	P value	Post-hoc
Mean age in years (SD)	40.4 (13.9)	46.6 (12.6)	28.9 (8.9)	30.2 (8.8)	43.0 (9.9)	<0.01	A,O>C,S
Sex (%)						<0.01	
Male	505 (77)	285 (73)	105 (85)	80 (80)	25 (96)		
Female	151 (33)	106 (27)	18 (15)	20 (20)	1 (4)		
Health-care centre (%)						<0.01	
IrisZorg	178 (27)	102 (26)	32 (26)	21 (21)	21 (81)		
Novadic-Kentron	166 (25)	96 (25)	30 (24)	29 (29)	3 (12)		
Tactus	141 (22)	97 (25)	20 (16)	20 (20)	1 (4)		
Vincent van Gogh	171 (26)	96 (25)	41 (33)	30 (30)	1 (4)		
Level of education (%)						<0.01	
Low	126 (19)	64 (16)	30 (24)	18 (18)	11 (42)		
Average	421 (64)	242 (62)	78 (63)	76 (76)	14 (54)		
High	109 (17)	85 (23)	15 (12)	6 (6)	1 (4)		
Employment (%)						<0.01	
Employed (full-/part-time)	253 (39)	148 (38)	47 (38)	44 (44)	8 (31)		
Unemployed	229 (35)	112 (29)	51 (42)	45 (45)	14 (54)		
Incapacitated	139 (21)	96 (25)	25 (20)	11 (11)	4 (15)		
Retired	35 (5)	35 (9)	0 (0)	0 (0)	0 (0)		
Marital status (%)						<0.01	
Single	269 (41)	118 (30)	76 (62)	54 (54)	14 (54)		
With partner	256 (39)	168 (43)	37 (30)	35 (35)	7 (27)		
Separated/divorced	119 (18)	95 (24)	10 (8)	10 (10)	4 (15)		
Widowed	12 (2)	10 (3)	0 (0)	1 (1)	1 (4)		
Years of regular use ^b	(n = 381)	(n = 229)	(n = 65)	(n = 60)	(n = 17)		
Mean no. years (SD)	14.01 (11.54)	15.78 (12.93)	13.26 (8.33)	8.90 (6.43)	14.29 (12.25)	<0.01	A,C>S
Polysubstance use ^b (%)	(n = 432)	(n = 247)	(n = 71)	(n = 76)	(n = 23)	<0.01	
No	133 (31)	125 (51)	5 (7)	1 (1)	0 (0)		
Yes	299 (69)	122 (49)	66 (93)	75 (99)	23 (100)		
Abstinence ^c (%)						<0.01	
No (<7 days)	474 (72)	275 (70)	107 (87)	56 (56)	25 (96)		
Yes (7–41 days)	128 (20)	83 (21)	8 (7)	35 (35)	0 (0)		
Yes (≥42 days)	54 (8)	33 (8)	8 (7)	9 (9)	1 (4)		
Abstinence duration ^b	(n = 182)	(n = 116)	(n = 16)	(n = 44)	(n = 1)		
Mean no. days (SD)	42.85 (57.50)	36.84 (42.80)	66.44 (88.52)	46.00 (68.84)	270.00 (–)	<0.01	
History of treatment ^b (%)	(n = 650)	(n = 387)	(n = 122)	(n = 100)	(n = 25)	<0.01	
No	357 (55)	210 (54)	86 (71)	48 (48)	5 (20)		
Yes	293 (45)	177 (46)	36 (30)	52 (52)	20 (80)		
CIDI-SAD ^b (SD)	(n = 470)	(n = 287)	(n = 81)	(n = 69)	(n = 20)		
Dependence	4.79 (1.75)	4.71 (1.77)	4.68 (1.77)	5.42 (1.34)	4.30 (2.03)	<0.01	A,C<S
Abuse	2.09 (1.11)	2.05 (1.11)	1.94 (1.04)	2.48 (1.02)	1.80 (1.36)	<0.01	A,C<S
Severity	6.11 (2.21)	6.00 (2.20)	6.00 (2.34)	6.99 (1.74)	5.40 (2.80)	<0.01	A,C<S
DASS-21 ^b (SD)	(n = 581)	(n = 353)	(n = 107)	(n = 83)	(n = 24)		
Depression	13.89 (11.29)	13.47 (11.40)	15.87 (10.89)	14.00 (11.50)	10.42 (10.04)	0.11	
Anxiety	9.52 (8.43)	8.96 (7.87)	11.03 (9.43)	9.78 (8.88)	8.25 (8.43)	0.13	
Stress	15.61 (10.27)	14.14 (9.63)	18.92 (9.96)	18.07 (11.24)	12.08 (11.18)	<0.01	A,O<C; A<S
DASS-21 total	39.05 (26.53)	36.57 (25.78)	45.81 (26.29)	42.10 (27.45)	30.75 (26.45)	<0.01	A<C

^aPost-hoc gives a description of significant differences. Patients with sedatives or gamma-hydroxybutyrate as the primary-problem substance are only included in the total sample and not separately described. ^bDue to missing data the *n* included is mentioned separately. ^cAbstinence was only assessed for the primary-problem substance. CIDI-SAD, Section Alcohol & Drugs of the Composite International Diagnostic Interview; DASS-21, Depression Anxiety Stress Scales.