Research Article

Cognitive Impairments in Patients with GHB Use Disorder Predict Relapse in GHB Use

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Abstract

Background: The recreational use of gamma hydroxybutyrate (GHB) is associated with frequent overdoses, coma and the risk of developing GHB use disorder (GUD). Several studies suggest negative effects of GHB use or related comas on cognition. Since relapse rates are high in GUD and cognitive impairment has been associated with relapse in other substance use disorders, we aimed to (1) investigate the prevalence of cognitive impairment before and after detoxification, (2) analyse the relationship between GHB use, comas, and cognitive impairment, and (3) explore the association between cognitive impairment and relapse after detoxification in GUD patients. *Methods:* In these secondary analyses of a prospective cohort study, a consecutive series of patients with GUD (*n* = 103) admitted for detoxification were recruited at six addiction care facilities in the Netherlands. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairments before and after detoxification. The follow-up duration for the assessment of relapse in GHB use was 3 months. *Results:* A substantial number of patients with GUD screened positive for cognitive impairment before (56.3%) and after (30.6%) detoxification. Impairment on the MoCA memory domain was most frequent (58.8%). Cognitive impairment was not related to the severity of GUD or number of GHB-induced comas. Logistic regression analysis showed that only the memory score independently predicted relapse. *Discussion:* Cognitive impairment seems highly prevalent among patients with GUD, possibly related to the risk of relapse. The absence of a relationship between the severity of GUD, level of GHB use, the number of GHB-induced comas, and cognitive impairment suggest that other factors may also contribute to the observed cognitive impairment.

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Background

Gamma hydroxybutyrate (GHB) is a GHB and GABA-B receptor agonist and an increasingly popular party drug, mainly due to its euphoric, sociability, and sexually stimulating effects [1–4]. However, GHB use is also associated with frequent overdoses, comas [5], hospital ad-

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missions [6], and a risk of physical dependence [7]. In line with DSM-5 criteria for substance use disorder (SUD) [8], physical GHB dependence is commonly part of GHB use disorder (GUD), with a pattern of continued use despite negative consequences, craving for GHB and loss of control over GHB intake [5].

Patients with GUD generally show high drop-out and relapse rates, up to 50–60% within 3 months after detoxification [9, 10]. It is therefore common that patients go through multiple detoxifications as a part of their recovery [5, 11] and the reenrolment rate of patients with GUD is twice as high as seen in patients with alcohol or cannabis use disorder [10]. It is unknown why relapse rates are higher among patients with GUD compared to other SUD. Several reasons for this have been suggested, such as the prosocial effects of GHB with few noticeable downsides could play a part in the high relapse rates [2, 5]. Other suggested explanations are the high levels of anxiety in patients with GUD [5], similar to, for example, patients with alcohol use disorder [12].

One aspect that might be particularly relevant in the context of relapse in patients with GUD, cognitive impairment, has not been studied yet for this population. In general, cognitive impairments in patients with SUD have a negative impact on the patients' ability to engage in therapeutic programmes [13]. This can prohibit patients from acquiring effective strategies in coping with their SUD [14]. Patients with cognitive impairments are also showing poorer treatment compliance [15] and cognitive impairment has been associated with relapse in several SUDs, e.g., alcohol [16], cocaine [17] and opioids [18]. While research on cognitive impairment in GUD is limited, several studies suggest negative effects of GHB on cognition. For instance, a double blind, placebo controlled study with healthy volunteers showed that GHB intoxication temporarily impaired working- and episodic memory, in a dose dependent manner [19]. Recent studies also suggest that repeated GHB-induced comas are associated with (verbal) memory impairments, impulsivity, anxiety, depression, and stress in patients with GUD [20–24], all of which are predictors of relapse in patients with SUD [25]. Moreover, in this cross-sectional study repeated GHB-induced comas were also associated with alterations in long-term memory networks and lower hippocampus/lingual gyrus activity while performing memory tasks [21]. GHB-induced comas are common in patients with GUD, with 84% having experienced GHB-induced comas at least once and often even on a daily basis [5, 6]. Therefore, cognitive impairment might result from repeated comas due to excessive GHB use and can potentially be an important factor in the high relapse rates observed in patients with GUD.

To our knowledge no studies on the relationship between cognitive impairment and relapse in patients with GUD have been published to date. Based on both the literature and clinical observations that GHB use [19] and repeated GHB-induced coma's [20, 21] seem associated with cognitive impairments a new study was proposed. As memory problems were also frequently observed by the nursing staff in patients with GUD who applied for detoxification, we included patients referred to these clinics. Detoxification for patients with GUD often takes place in an inpatient setting, due to the potential fulminant course of GHB withdrawal [26]. During their stay patients' withdrawal is closely monitored while they are gradually tapered off with pharmaceutical GHB according to the Dutch GHB guideline [6, 7, 27]. Patients stay about 3 weeks for detoxification in the clinic, after which they continue with outpatient treatment for GUD based on cognitive behavioural therapy (CBT) and Community Reinforcement Approach (CRA). Cognitive screening was taken before and after detoxification. This prospective cohort study in patients with GUD aimed to (1) investigate the prevalence of cognitive impairment before and after detoxification. (2) analyse the relationship between cognitive impairment, GHB use and comas, and (3) explore the association between cognitive impairment and relapse after detoxification in GUD patients. We expect that cognitive impairment will improve after detoxification due to the sedating effects of GHB prior to detoxification [19]. Furthermore, we expect that a higher dose of GHB use and/or more GHB-induced coma's are associated with more cognitive impairment. Finally, in our exploratory analyses we anticipate cognitive impairment to be associated with relapse since this has also been demonstrated in other substances of abuse [16–18].

Methods

Design

This study is a secondary analysis of data collected in an exploratory prospective, observational, multicentre cohort study, with two measurements of cognitive screening of patients with GUD before and after detoxification. Due to the observational design, the study was exempted from medical ethical review by the Medical Ethical Committee of the Medical Spectrum Twente. Part of the data of this study has already been published as a naturalistic cohort study with baclofen as part of treatment after detoxification [9].

Participants

A consecutive series of patients with GUD (according to DSM-IV criteria of substance dependence, DSM-5 was not yet applied) who were admitted for detoxification at one of six participating addiction care facilities in the Netherlands (IrisZorg, Mondriaan, Novadic-Kentron, Tactus Verslavingszorg, Victas, and Verslavingszorg Noord-Nederland) were recruited as part of a larger monitoring study on GHB detoxification. Inclusion criteria were 18–65 years old, an indication for inpatient GHB detoxification, and comprehension of the Dutch language. Exclusion criteria were the presence of acute psychiatric problems interfering with study participation, such as mania or acute psychosis. A physician screened patients on these criteria before detoxification. All patients signed informed consent before they were included in the monitoring study. For the current study on cognitive deficits, only patients that completed at least one Montreal Cognitive Assessment (MoCA) questionnaire were included; this was 103 out of 137 patients.

Measurements

Demographic Data

Demographic data (sex, date of birth, ethnicity, housing situation, source of income, and level of education) were collected through self-report.

Measurements of Addictions for Triage and Evaluation (MATE)

The MATE is a structured clinical interview that measures the history, frequency, and consequences of drug use, including medical, social, and psychological problems [28], based on the Composite International Diagnostic Interview (CIDI) [29]. For this study "Module 1: Drug Use" was used to assess GHB and other substance use patterns. During this structured interview patients were asked about their drug use over the past 30 days (number of days and amount used) and lifetime (total years of use of at least 3 days per week). The MATE has a good inter-rater reliability, ranging between 0.75 and 0.92 and is part of standard clinical assessment in Dutch addiction care [28].

GHB Questionnaire

In addition to the questions on GHB use in the MATE, the GHB questionnaire was included to obtain more detailed information on GHB use patterns [6]. The original questionnaire has 28 questions regarding motivation for GHB use, first introduction to GHB, location of use, frequency of use, dose, duration of use, comas, hospital admissions, and experienced withdrawal symptoms. For this study, we included only the five questions on the frequency of GHB use, the dose of GHB used (in millilitres), the duration of GHB use (in months), the duration of daily GHB use (in months), and how often participants experienced a coma due to GHB use in their lifetime.

Montreal Cognitive Assessment

The MoCA [30, 31] was used to screen for cognitive impairment. It consists of 12 items measuring: executive functioning; visuospatial abilities; attention, concentration, and working memory (referred to as "attention" from now on); language; abstract reasoning; memory; and orientation. For this study, the Dutch MoCA versions 7.1 and 7.2 were used to minimize learning effects, with version 7.1 administered at T1 and 7.2 at T2. The administration of the MoCA takes approximately 15 min. A higher score represents better cognitive performance. An adjustment for level of education is applied. Participants with a low level of education receive two extra points, and participants with an average level of education receive one extra point to their total score, while maintaining a maximum score of 30 points [30]. In line with previous studies, a cut-off score of 25 or lower was used as an indicator of cognitive impairment [20]. The MoCA is widely used in clinical practice for the screening on cognitive impairment in various populations and has a moderate to excellent inter-rater reliability ($k = 0.46 - k = 0.94$) [32].

Treatment Outcome

Three months after detoxification, all patients were contacted either in person (when the patient was still in treatment) or by phone when patients were no longer in treatment. During this interview, patients were asked about their GHB use in the past 3 months and whether they had relapsed in GHB use. In Dutch practice, lapse and relapse are commonly distinguished. Lapse is generally not considered problematic as patients are still quite in control over their substance use [33]. We considered fewer than 5 times GHB use (one dose) in the past 3 months as GHB lapse since, in clinical practice, full relapse in GHB use is mostly characterized by daily use of GHB at intervals of just a couple of hours indicating loss of control over GHB use [5, 34]. Therefore, lapse was classified as non-relapse in this study. Abstinence was not confirmed using systematic urine or blood tests due to the narrow timeframe in which GHB can be detected as a result of its short half-life [35].

When patients could not be reached, a predetermined close contact of the patient was approached about treatment outcome. In cases where nobody was available, patient records were examined for treatment outcome. The last clinical observation was carried forward in this case.

Procedure

Patients were informed about the study before admission to the clinic (before detoxification). After informed consent forms were signed, the demographic data, the MATE, and the MoCA 7.1 were collected by a trained nurse or psychologist prior to detoxification (T1). After detoxification and during recovery phase, on average 20.1 days after the first day of detoxification, the MoCA 7.2 was administered (T2). Three months after detoxification patients were contacted to assess relapse into GHB use (T3). Data collection occurred between January 2014 and May 2015.

Analysis

The patient characteristics for age, sex, substance use, and MoCA scores (total, domain, and cut-off) were summarized using descriptive statistics for both T1 and T2. Differences between the MoCA scores T1 and T2 were analysed exploratory using repeated measures ANOVAs for all domain scores and the total score, and χ^2 test for categorical variables. Only patients with data available for both timepoints were included in these analyses.

For each patient, a total GHB exposure score was calculated by taking "the average daily dose of GHB" times "the number of days GHB was used in the past 30 days" times "the months of daily GHB use." To study the relationship between MoCA scores (total and domain scores), the number of comas and GHB use (dose per day, months of use, months of daily use, and GHB exposure score), Pearson and Spearman correlations were used where appropriate, separately for T1 and T2.

Table 1. MoCA scores on T1 and T2

	T1 (n = 39)		T2 (n = 39)	
	mean (SD)	%	mean (SD)	%
Executive functioning & visuospatial abilities (0–6)	4.36 (1.20)	72.7	4.74 (1.17)	79.0
Attention (0–6)	5.00 (1.07)	83.3	5.13 (1.08)	85.5
Language (0–5)	4.40 (1.05)	88.0	4.66 (0.63)	92.2
Abstract reasoning (0–2)	1.63 (0.62)	81.5	1.81 (0.44)	90.5
Memory (0–5)	2.94 (1.58)	58.8	3.52 (1.54)	70.4
Orientation (0–6)	5.84 (0.48)	97.3	5.79 (0.48)	96.5
Total (0–30)	24.16 (3.01)	80.1	25.65 (2.78)	85.5
Below cut-off,* %	56.3		30.6	

% comprises the mean percentage of points obtained on the Montreal Cognitive Assessment. * $p < 0.005$.

The difference on MoCA scores (total score and domain scores) between relapsed and non-relapsed patients at the 3-month follow-up was analysed using an explorative MANOVA separably for T1 and T2; only patients with a MoCA score on both timepoints were included in this analysis. In order to assess the predictive value of the MoCA, a backward logistic regression was performed with relapse as the dependent variable and MoCA scores as the independent variables. p values <0.05 (two-sided) were considered statistically significant. Data were analysed with SPSS Statistics 26.

Results

Patient Characteristics

Data of 103 patients were analysed in this study, including 80 MoCA measurements at T1 and 62 at T2. In total 39 patients had completed MoCA measurements at both T1 and T2, a flowchart of the study can be found in online supplementary material II (for all online suppl. material, see www.karger.com/doi/10.1159/000525507). These 39 patients did not differ from patients with a MoCA on either T1 or T2 for sex, age, GHB dose, length of daily GHB use, number of comas, and MoCA scores. Their mean age was 28.5 years (SD: 6.47 range 19–45) and 68% were men. The mean duration of daily GHB use was 31.3 months (SD: 32.61), with a mean of 89.9 mL GHB per day (SD: 52.60). GHB-induced comas were common, with 41.4% reporting five or less GHB comas, 18.4% between six and nineteen times, 19.5% between twenty and fifty times, and 20.7% reported to have experienced more than fifty comas in their lifetime. Comorbid substance use in the past 30 days was the highest for nicotine (83.7%), followed by stimulants (amphetamines/MDMA) (50%), alcohol (43.5%), cannabis (33.7%), and cocaine (33.7%). All but 3 patients accounted for at the follow-up, these

three left against treatment advice and were presumed relapsed based on last-observation carried forward. This was confirmed after the study, when they reapplied for treatment.

Scores on MoCA

Patients with both time measurements scored on average 24.2 points on the MoCA (SD: 3.01) at T1 and 25.7 points (SD: 2.78) at T2. The effect of time (difference between T1 and T2) showed a trend towards significance on total scores (Wilks' Lambda = 0.903, $F(1, 38) = 4.076$, $p = 0.051$). Fewer patients scored below the cut-off score on T2 than on T1 ($\chi^2(1) = 5.214$, $p = 0.022$), see Table 1. In total 27 patients improved their scores between T1 and T2, five had the same score and seven had a lower score. On domain level, patients performed lowest on Memory and highest on Orientation on both T1 and T2. No significant differences were observed on domain level between T1 and T2.

Relationship between GHB Coma, GHB Use, and Cognitive Impairment

For the total group, MoCA total scores did not correlate with number of comas, GHB dose, total length of GHB use, length of daily GHB use, and GHB exposure score on both T1 and T2, see online supplementary Table 1.

Relationship between Relapse and Cognitive Impairment

Two MANOVAs with treatment outcome (relapse/non-relapse) as between-subject variable and MoCA scale- and total scores as dependent variables were performed for T1 and T2. The MANOVA for T1 showed a trend towards significance for the multivariate effect

Table 2. Treatment outcome and MoCA scores

	T1			T2		
	non-relapse (*n* = 28) mean score (SD)	relapse (*n* = 52) mean score (SD)	*p* value	non-relapse (*n* = 29) mean score (SD)	relapse (*n* = 33) mean score (SD)	*p* value
Executive function & visuospatial abilities	4.42 (1.14)	4.33 (1.24)	0.721	4.80 (1.08)	4.69 (1.26)	0.750
Attention	5.32 (0.86)	4.83 (1.13)	0.047*	5.27 (1.07)	5.00 (1.09)	0.319
Language	4.46 (1.04)	4.37 (1.07)	0.691	4.72 (0.59)	4.61 (0.66)	0.463
Abstract reasoning	1.57 (0.69)	1.65 (0.59)	0.576	1.72 (0.53)	1.89 (0.33)	0.167
Memory	3.61 (1.42)	2.58 (1.55)	0.005*	3.83 (1.47)	3.24 (1.58)	0.138
Orientation	5.82 (0.39)	5.85 (0.45)	0.810	5.83 (0.47)	5.76 (0.50)	0.574
Total*	25.21 (2.91)	23.60 (2.94)	0.021*	26.17 (2.24)	25.21 (2.91)	0.163
Below cut-off, %	56.6	76.9	0.030*	27.6	42.4	0.171

* *p* < 0.05.

(Wilks' Lambda = 0.859, $F(6, 73)$ = 1.993, p = 0.078). Univariate analysis showed that patients who remained abstinent at follow-up scored higher on Attention, Memory and total score at T1 in comparison with patients who relapsed in GHB use between detoxification and follow-up. More patients who did not relapse scored above the cut-off score of 25 on the MoCA at T1 ($\chi^2(1)$ = 4.619, $p <$ 0.030), compared to patients who relapsed. No relationship was found between treatment outcome and MoCA scores on T2 (Wilks' Lambda = 0.951, $F(6, 55)$ = 0.856, p = 0.553). The results are shown in Table 2. Assumptions for equal variance were met despite unequal group sizes. A repeated measures MANOVA including only 39 patients with a MoCA on both timepoints found no effect for group (relapse/non-relapse) (Wilks' Lambda = 0.719, $F(6, 32)$ = 2.084, p = 0.083) or group time interaction (Wilks' Lambda = 0.924, $F(6, 32)$ = 0.438, p = 0.848).

Given that only the MoCA scores on T1 were related to treatment outcome, only these scores were used in the backward logistic regression analyses to explore the predictive value of the MoCA for relapse. The logistic regression model was statistically significant, $\chi^2(1)$ = 8.617, $p <$ 0.003, with only memory as a significant predictor in the final model. The model explained between 10.2% and 14.1% (Nagelkerke R^2) of the variance in relapse and correctly classified 68.8% of the cases. Each point scored on the subscale T1 memory increases the odds of abstinence with 1.64.

Discussion

This study explored cognitive impairment in patients with GUD, and its relationship with (1) GHB use patterns and (2) relapse in GHB use after detoxification. Using the MoCA, a substantial number of patients with GUD screened positive for cognitive impairment before detoxification (56.3%). Cognitive functioning improved after detoxification with still about one third screening positive for impairment (30.6%). The cognitive domain showing the strongest impairment was memory. No correlation was found between cognitive impairment and the number of comas, GHB use patterns, or severity of GUD. Cognitive impairment before detoxification, particularly on the subscale memory, was associated with relapse.

In the current sample, more than half of the patients had an indication for cognitive impairment during admittance, with a total average score on the MoCA of about 24. A recent study observed similar to slightly better MoCA scores in patients admitted with alcohol, cannabis, stimulant, and opioids use disorders (scores: 25, 26, 26, and 25, respectively) [36]. Though no direct comparison between these samples can be made, this does raise the question whether the observed cognitive impairments in patients with GUD are specific for excessive GHB use or related to (indirect) negative effects of substances of abuse on cognitive performance in general. Furthermore, it is important to note that most patients with primary GUD have poly substance use problems, often stimulants [5, 6], making it difficult to differentiate between effects of GHB and other substances.

Patients showed a trend towards improvement in total scores and a significant decrease in scoring below cut-off score between T1 and T2, indicating that cognitive functioning partially recovered during detoxification. This is in line with studies in SUD patients using other sedatives, including alcohol [37] and benzodiazepines [38], who also show improvement of cognitive functioning during abstinence. It is important to note that patients in the cur-

rent study were only abstinent of GHB for several days when T2 was administered. Therefore, further improvement with prolonged abstinence cannot be ruled out and is to be expected. Literature on alcohol has for instance shown that cognitive function can improve up to after 6 weeks to over a year of abstinence [39]. Future studies should further investigate recovery of cognitive impairment in patients with GUD with long-term abstinence.

Patients with GUD scored particularly low on the sub-domain Memory, also when compared to studies in patients with other SUDs [36]. Since GHB receptors are predominantly expressed in the hippocampus, this observation might reflect the direct effects of GHB in the brain [19, 40, 41]. GHB-induced comas have also been suggested to affect hippocampal activity, both in humans [21] and animals [42], which could also contribute to the observed memory problems. Since memory is a broad concept [43], with various sub domains (e.g., working memory, long-term memory, declarative memory, etc), future studies should explore which specific memory domains are most affected in patients with GUD.

Despite several studies suggest that cognitive impairment in patients with GUD might be caused by repeated GHB-induced comas [20, 21] the current study did not observe a relationship between the number of self-reported GHB-induced comas and cognitive impairment. Several methodological limitations hamper strong conclusions concerning the (causal) relationship between repeated GHB-induced coma and cognitive impairment. First, studies, including ours, commonly rely on self-reported comas. A detailed and reliable account of the total number of GHB-induced comas is hard to obtain due to its frequency (usually on a daily basis) [5], amnesia (as this might be an aspect of GHB-induced coma itself) [4], and the observed memory impairment in patients with GUD. Second, as seen in other samples, patients with GUD often also use other substances. These might also contribute to cognitive impairment in these patients. Finally, it may also be that it is not the number of GHB-induced comas or substance use levels that contribute to cognitive impairment. Similar to patients with other SUDs our data did not find a relationship between MoCA scores and years of regular use (GHB) dose, severity of dependence and coma's [36]. This suggests that other factors might be involved, for instance lack of sleep, malnutrition, other psychiatric or somatic comorbidities, or medication use, e.g., baclofen. Future studies should explore mechanisms contributing to cognitive impairment in patients with GUD and other SUDs.

The current study shows that MoCA scores, in particular performance on the memory domain, were associated with the risk of relapse. This is in line with studies in other SUD, such as alcohol [16], cocaine [17], and opioids [18], where cognitive impairment is associated with the risk of relapse and poor treatment retention. Cognitive functions are crucial to direct behaviour and obtain control over impulses and emotions [44], including substance use. Cognitive impairment in patients with SUD (including GUD) might thus interfere with taking control of substance use, to change behaviour, and reach treatment goals [44, 45]. SUD patients with cognitive impairment might require treatment adaptations focussing on cognitive enhancement [46, 47]. Indeed, several studies have shown that such personalized treatment approaches can be efficacious in patients with SUD and cognitive impairment [34]. To what extent this might also benefit patients with GUD remains to be studied. It should be noted that we only found results on the cognitive screener before detoxification, and not after detoxification to predict relapse. This finding seems counter-intuitive since it is expected that especially those with persisting cognitive deficits are most likely to relapse [16, 17]. However, the number of participants who screened positive for cognitive impairment declined from 56% at baseline to 30% after detoxification. The lower baseline MoCA scores might indicate another factor than cognitive performance per se that relates to relapse risk. For instance, low baseline MoCA scores might represent a more severe level of SUD or intoxication on admittance, increased stress levels prior to detoxification, or for instance more severe insomnia that all can interfere with MoCA performance. These conditions are likely to improve over detoxification, but might still relate to the risk of relapse after detoxification. Future studies should therefore further explore which factors, including cognitive performance, are most predictive of relapse into GHB use after detoxification in GUD patients.

The results of this study should be viewed in the light of several limitations. First, the MoCA is not a diagnostic tool for cognitive impairment. While the MoCA has been shown to be a valid screening instrument in patients with SUD [30, 36], no extensive neuropsychological assessments were used in the current study. Therefore, future studies should confirm the current findings, using more detailed neuropsychological assessments across different cognitive domains. Second, post hoc power analysis showed that the study was underpowered for the prediction analysis on the relationship between MoCA scores and relapse. Furthermore, repeated measure ANOVAs

were used for comparing MoCA scores between T1 and T2, but only participants of which the two measurements were available could be included. We did not correct for multiple testing because of the exploratory nature of the study and the potential for an increase in type II errors. Given the low sample size in some of the analyses, results should be interpreted with caution. Another limitation is that most patients with primary GUD have poly substance use, often stimulants [5, 6, 48]. It is therefore impossible to disentangle GHB effects on cognitive impairment from the effects of other substances. In addition, the observed persistent cognitive impairments could have been present before the use of GHB (or other substances) started.

In conclusion, in the current study, about half of patients with GUD had an indication for cognitive impairment before detoxification, decreasing to about one third after detoxification. Cognitive impairment before detoxification, particularly memory problems, was associated with a higher relapse risk after detoxification. Current findings warrant clinical attention for cognitive impairment in patients with GUD, for instance by screening for cognitive impairment using the MoCA, and full neuropsychological assessment during a sufficient period of abstinence after detoxification when appropriate. Results should be interpreted with caution due to low sample size. Future studies should confirm these findings and explore whether GUD patients with cognitive impairment require specific treatment adaptations.

Statement of Ethics

All participating patients have given verbal and written consent for participation in the current study. Due to its observational design, he study was exempted from medical ethical review by the Medical Ethical Committee of the Medical Spectrum Twente. The research was conducted in accordance with World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

A.F.A. Schellekens is an Editorial Board Member of European Addiction Research. The rest of the authors have no interest to declare.

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Author Contributions

Harmen Beurmanjer and Carolien Bruijnen managed the data collection. Boukje Dijkstra and Harmen Beurmanjer conducted most of the analysis and wrote the first draft of the manuscript. Peter Greeven, Arnt Schellekens, and Cor de Jong were involved in the data interpretation and supervision of the project. All the authors critically revised the manuscript and gave final approval of the version to be submitted.

Date Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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