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Full length article

Detoxification with titration and tapering in gamma-hydroxybutyrate (GHB) dependent patients: The Dutch GHB monitor project

Boukje A.G. Dijkstra^{a,b,*}, Rama Kamal^{a,b}, Martijn S. van Noorden^c, Hein de Haan^{a,d},
Anton J.M. Loonen^e, Cor A.J. De Jong^{a,f}

^a Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA), Radboud University Nijmegen, 6525 ED Nijmegen, the Netherlands

^b Novadic-Kentron, Network for Addiction Treatment Services, PO Box 243, 5260 AE Vught, the Netherlands

^c Department of Psychiatry, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands

^d Tactus Addiction Treatment, PO Box 154, 7400 AD Deventer, the Netherlands

^e Pharmacotherapy of Psychiatric Patients, Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, the Netherlands

^f Department of Clinical Psychology, Radboud University Nijmegen, 6525 HR Nijmegen, the Netherlands

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ABSTRACT

Background and aims: Gamma-hydroxybutyrate (GHB) detoxification procedures have been insufficiently studied for effectiveness and safety. Based on case reports, benzodiazepines are generally regarded as first-choice agents in GHB detoxification. Detoxification by titration and tapering (DeTiTap) with pharmaceutical GHB in an open-label consecutive case series of 23 GHB-dependent patients showed to be feasible, effective and safe. This study further explored the feasibility, effectiveness and safety of this detoxification procedure in a large group of patients.

Method: A large observational multicenter study was carried out in six addiction treatment centers in the Netherlands. GHB-dependent inpatients (229 unique patients, 274 admissions) were titrated on and tapered off with pharmaceutical GHB.

Results: Successful detoxification was achieved in 85% of cases. Detoxification was carried out in 12.5 days in most patients. The DeTiTap procedure proved to be feasible and significantly reduced the experienced withdrawal symptoms and craving ($p \leq 0.001$). Several symptoms were found to influence the course of subjective withdrawal symptoms. During detoxification, psychological symptoms such as depression, anxiety, and stress decreased ($p \leq 0.05$). The main complications were hypertension and anxiety. Six patients were sent to the general hospital for observation, but all six were able to continue detoxification in the addiction treatment centers. Most patients (69%) relapsed within three months after detoxification.

Conclusions: The DeTiTap procedure using pharmaceutical GHB seems a safe alternative to benzodiazepines as a GHB detoxification procedure. However, the high relapse rates warrant further investigation.

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1. Introduction

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that naturally occurs in the human brain and acts as a neuromodulator and neurotransmitter (Snead and Gibson, 2005). Since the mid-nineties, GHB has become popular as a recreational drug, mainly used in a liquid oral form (Degenhardt et al., 2002; Kam and Yoong, 1998; Nicholson and Balster, 2001). It has relaxing, euphoric, and sexually stimulating effects at low doses (Sumnall

et al., 2008). In the Netherlands, concentrations of illicit 'street' GHB varied between 384.7 mg/ml (delivered by consumers for personal reasons; Van Laar and Van Ooyen-Houben, 2015) and 650 mg/ml (delivered by GHB dependent patients before GHB detoxification). GHB is produced using gamma-butyrolactone (GBL). GBL has a different pharmacokinetic profile (Brunt et al., 2014) and when used in pure form it is rapidly converted to GHB in the body.

Withdrawal symptoms may occur when GHB is used more than four times daily for two to four weeks at doses of over 18 g per day (Brunt et al., 2014). Case reports, mainly from the United States, described relatively mild symptoms like insomnia, tremors, and anxiety following cessation of daily GHB use. The symptoms appeared to resemble those of alcohol withdrawal syndrome, but with a much more sudden onset. The duration of withdrawal symp-

* Corresponding author.

E-mail addresses: boukje.dijkstra@gmail.com, boukje.dijkstra@gmail.com (B.A.G. Dijkstra).

toms in these cases varied from five to 12 days (Craig et al., 2000; Galloway et al., 1994, 1997; Tunnicliff, 1997). Some case studies showed successful treatment of GHB withdrawal symptoms with low doses of benzodiazepines (Addolorato et al., 1999; Price, 2000). In contrast, other patients developed severe GHB withdrawal symptoms upon cessation, including delirium, psychosis, autonomic instability, rhabdomyolysis, seizures, and agitation, despite high-dose benzodiazepine treatment and/or additional pentobarbital (Chin, 2001; Craig et al., 2000; Dyer et al., 2001; Schneir et al., 2001; Sivilotti et al., 2001; van Noorden et al., 2015). Nevertheless, benzodiazepines are still considered first choice agents in GHB withdrawal, according to reviews and case reports (Schep et al., 2012).

Already in 2001, Miotto and Roth concluded that GHB detoxification procedures had been insufficiently studied for effectiveness and safety. We developed a Detoxification procedure by Titration and Tapering (DeTiTap) with off-label use of pharmaceutical GHB as an alternative treatment option to benzodiazepines in which monitoring in a high-care medical setting would be no longer necessary. The results of a previously conducted open-label consecutive case series of 23 GHB-dependent patients were promising (de Jong et al., 2012): the DeTiTap procedure seemed to be feasible, effective and safe in this small patient sample. These results justified a larger naturalistic study (de Jong et al., 2013) in patients that requested professional treatment for their GHB addiction.

In this paper, we report on 274 GHB-dependent patients who underwent detoxification with DeTiTap in six different Dutch Addiction Treatment Centers (ATCs). The objectives of the study were as follows: First, to evaluate the feasibility of the DeTiTap procedure in terms of compliance with the detoxification procedure; Second, to evaluate the effectiveness by means of completion rates, the subjective and objective withdrawal severity, craving, psychological symptoms, and the need for co-medication; Third, to assess the safety of the detoxification procedure in terms of the occurrence of complications. The final aim was to assess relapse rates at follow-up after three months.

2. Method

2.1. Study design

We conducted an observational multicenter study in which GHB-dependent inpatients underwent detoxification according to the DeTiTap procedure using pharmaceutical GHB with a follow-up at three months after discharge. This Dutch GHB monitor 1.0 was conducted from March 2011 to December 2012 in six ATCs in the Netherlands. The Medical Ethical Research Committee (METC Twente) and Central Committee on Research Involving Human Subjects (CCMO) approved the study protocol and considered that the study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). Off-label use of pharmaceutical GHB for GHB detoxification was approved by the Health care Inspectorate (Dutch IGZ). A preliminary report of the main results of the study has been published in a Dutch journal (de Weert-van Oene et al., 2013).

2.2. Participants

Patients were treated in six participating ATCs providing all levels of care defined by the American Society of Addiction Medicine (ASAM) (Novadic-Kentron, Tactus, IrisZorg, Victas, Verslavingszorg Noord Nederland, and Brijder). Patients were between 18 and 60 years old when admitted to the detoxification unit (ASAM Levels of Care 4). They were diagnosed with GHB and/or GBL dependency according to the Diagnostic and Statistical Manual of Mental Disor-

ders IV-TR (American Psychiatric Association, 2000) general criteria for psychoactive substance dependence. Pregnant women were excluded. All participants provided written informed consent for off-label use of pharmaceutical GHB and use of anonymized data for research purposes.

2.3. Treatment procedure

Pharmaceutical GHB was used off-label and produced by different pharmacies (depending on the ATC) with concentrations varying from 100 to 400 mg/ml GHB. The DeTiTap procedure followed the standardized practice-based protocol by Kamal et al. (2013):

- After admission patients received the initial dose of pharmaceutical GHB within 2.5 h after the last self-administered dose to prevent withdrawal. To avoid the risk of intoxication this first dose was less than 70% of the equivalent of the reported self-administered illicit GHB dose at a time (based on an average 'street' concentration of 650 mg/ml). The calculated dose of 70% was reduced by 0.75 to 2.25 g, to be established by the clinician. This relatively large range was allowed because of major individual differences in medical history, clinical state, level of GHB use and estimated plausibility of the patient's self-reported doses.
- The second dose was administered after an interval of two to three hours (depending of the interval of GHB use) and contained 70% of the last reported dose (see Table 1 for example). In case of concomitant alcohol dependence, an additional 0.75–1.5 g per GHB dose was advised. Low doses of long-acting benzodiazepines (mostly diazepam, max. 20 mg/day) could be prescribed in case of dependence on benzodiazepines, cocaine, cannabis, or amphetamine, and were kept stable during DeTiTap.
- During the titration phase the doses of pharmaceutical GHB could be adjusted every two to three hours depending on the patient's self-reported symptoms and observations by the nurse and physician. Consecutive GHB doses were adjusted until the patient experienced an acceptable level of withdrawal symptoms and their blood pressure and heart rate were stable and within the normal range, the so called stabilization dose.
- The detoxification phase followed the day after titration by tapering the GHB on a fixed daily schedule consisting of two to three hour dose intervals. The dose was tapered off by 0.3 g per GHB gift each day (see Table 1). Additional medication was provided in case of hypertension (metoprolol 50–100 mg), extreme anxiety (diazepam 5–10 mg), or insomnia (temazepam 10 mg for maximal two consecutive nights).
- The recovery phase started when the patients had completely discontinued the pharmaceutical GHB and was intended for physical recovery. The duration of this recovery phase varied depending on the amount of GHB use before admission and the course of withdrawal symptoms, but lasted six days on average.

2.4. Procedure

Detailed information about GHB use, dependence and mental wellbeing was acquired at baseline (see Instruments) by trained study nurses. In case of emergency admission this information was acquired at admission by the addiction physician. Upon admission the information about GHB use was confirmed and physical examination was performed by the addiction physician. Subjective and objective withdrawal scales were completed 30 min before each GHB dose by both patient and nurse. Baseline blood pressure and heart rate were recorded. Patients also reported on subjective withdrawal 30 min after the GHB dose during titration days. Craving visual analogue scales (VAS) were recorded daily at 10:30 pm

Table 1Example^a of a tapering schedule of pharmaceutical GHB (in gram) with a 3 h interval.

Time schedule	T	Detoxification days														
	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
08:00 am	4.5	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
11:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
14:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
17:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
20:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
23:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
02:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
05:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
Total (g GHB):	38.1	36	33.6	31.2	29	26.4	24	21.6	19.2	16.8	14.4	12	9.6	7.2	4.8	2.4

^aExample is based on a male patient, 23 years old, history of social anxiety disorder, uses home-brewn GHB since 4 years daily, uses 12 ml GHB every 60–90 min, 2 GHB doses during the night. Calculation detoxification schedule patient: 12 ml street GHB * 0.65 g/ml * 70% = 5.46 g pharmaceutical GHB minus 1 g = 4.5 g starting dose pharmaceutical GHB. Dosing every 3 h including 2 nightly doses.

At discharge additional measurement instruments were administered. After discharge, patients received treatment as usual at an addiction treatment center. These treatments varied from short individual cognitive behavioral treatment interventions to extensive multidimensional therapy. At three month follow-up patients were questioned about their GHB use by means of self-report.

2.5. Instruments

Table 2 presents a detailed overview of the instruments administered during the study.

2.5.1. Measurement of addicts for triage and evaluation. The MATE (Schippers et al., 2010) was designed as a diagnostic aid of relevant patient characteristics. For the present study Sections 1 and 4 were used to define participants' current substance use (last thirty days), lifetime substance use, and GHB and/or GBL dependency according to the DSM-IV-TR.

2.5.2. GHB questionnaire. The GHB questionnaire is a for this study self-developed questionnaire about the pattern of GHB use consisting of the number of years of use, total daily dose in grams, grams per dose and interval between doses.

2.5.3. Depression anxiety stress scale (DASS). The DASS is a 21-item self-report instrument measuring depression, anxiety and stress over the past week on a four-point Likert-scale, from 'not at all or never' (0) to 'very much/most of the time' (3) (Brown et al., 1997; Lovibond and Lovibond, 1995). Scores for depression, anxiety and stress were calculated by summing the scores for the relevant items and multiplying by two (range between 0 and 42). Recommended cut-off scores for severity labels are shown in Table 4.

2.5.4. Brief symptom inventory (BSI). The BSI measures the levels of psychopathology and is a shortened form of the Symptoms Checklist-90-revised (SCL-90-r) (Derogatis, 1992). The BSI is a 53-item self-report symptom scale measuring nine dimensions (Table 4). The score per dimension ranges from 'not at all' (0) to 'extremely' (4) (Derogatis, 1993).

2.5.5. EuroQol-5D (EQ-5D). Patient's reported quality of life (Dolan, 1997; EuroQol Group, 1990) was measured with the EQ-5D, a 5-item self-report instrument with a three-point scale (1 = no problems, 2 = some problems, and 3 = extreme problems). The EQ-5D index was calculated according to the Dutch algorithm for the general population, ranges from 0.594 to 1 (1 being perfect health). Participants self-rated their health on a vertical, visual analogue scale (EQ-5D VAS) where the endpoints are labelled from 'Best

imaginable health state' (100) to 'Worst imaginable health state' (0) (EuroQol Group, 1990).

2.5.6. Subjective withdrawal scale (SWS). The SWS measures withdrawal symptoms experienced by the patient and is based on the format of the Subjective Opiate Withdrawal Scale (Handelsman et al., 1987) and proved to have good psychometric quality (Dijkstra et al., 2007). All subjective criteria from DSM-IV-TR withdrawal syndromes were added to the SWS. The SWS consists of 33 items, rated on a scale from 0 to 4 (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). The total SWS score ranges between 0 and 132.

2.5.7. Objective withdrawal scale (OWS). The nursing staff reported their observations using the OWS, based on the Objective Opiate Withdrawal Scale (OOWS) (Handelsman et al., 1987). The OOWS contains 13 objectively observable physical signs that reflect common symptoms of opiate withdrawal. We extended the OOWS in the Dutch translation with all observable withdrawal symptoms from other psychoactive substances including alcohol as included in the DSM-IV-TR (American Psychiatric Association, 2000). The resulting OWS finally consisted of 22 items, rated as present or absent during a 10-min observation by the nursing staff.

2.6. Data analysis

Frequencies and descriptives were calculated for patient characteristics. One-way ANOVA and Pearson's chi-square tests were performed to analyze differences between included and excluded patients, one or more admissions, and between abstinence and relapse at follow-up. Compliance to the DeTiTap procedure was evaluated by the duration of the titration and detoxification phases and titration doses of GHB.

Effectiveness was evaluated by detoxification completion rates, experienced subjective (SWS) and objective withdrawal symptoms (OWS), craving (VAS), psychological symptoms (BDI, DASS) and use of concomitant medication. Paired *t*-tests were performed to analyze the difference in withdrawal 30 min before and 30 min after each GHB dose. To illustrate the course of withdrawal during DeTiTap only the results before GHB doses are reported. For this, the mean scores per patient per day were calculated and because of the multiple responses and missing values, a restricted maximum likelihood Linear Mixed Model (LMM) was used to assess change in SWS scores over time and to relate the changes to covariates (fixed effects). The intercept and subjects were added as random effects. Prior to analysis the severity of withdrawal symptoms was normalized using log transformation. Change in frequency of general symptoms (BSI and DASS) were analyzed by paired *t*-tests.

Table 2
Overview of instruments administered during the study.

Instruments	T1. Baseline	T2. Admission	T3. Discharge	T4. Follow-up
MATE	X			X
DASS	X		X	
EuroQol-5D	X		X	
BSI	X		X	
GHB questionnaire	X			
Follow-up questionnaire				X
Medication list		X	X	
SWS	X	X	X	
OVS	X	X	X	
Craving (VAS)	X	X	X	

Measurement of Addicts for Triage and Evaluation (37), Depression Anxiety Stress Scale (DASS), Brief Symptom Inventory (BSI), Subjective Withdrawal Scale (SWS), Objective Withdrawal Scale (OVS).

The safety of the detoxification procedure was evaluated by describing the occurrence of hospital admissions.

GHB abstinence three months after detoxification was defined as a self-reported total abstinence of GHB use in the last 30 days. If patients reported GHB use they were defined as non-abstinent.

All statistical tests were two-sided; *p*-value was considered statistically significant at the 0.05 level (2-tailed). IBM® SPSS® Statistics version 19 for Windows was used for all the computations.

3. Results

3.1. Patient characteristics

From February, 2011 to August, 2012, 354 inpatient GHB detoxifications were performed, of which 278 were monitored according to the study protocol (78.5%). Absence of the trained study nurse was the main reason for un-monitored detoxifications and this differed significantly between ATCs. Unmonitored patients did not differ in age, amount of detoxifications or detoxification outcome, but in these patients the proportion of emergency admissions was lower. Four patients were excluded because they underwent a benzodiazepine tapering as their GHB use was very low. Of the 274 detoxifications, 16% included re-admissions (9 patients had been re-admitted three to four times during the study period), hence a total of 229 unique patients were involved in this study. Table 3 provides the sociodemographic and clinical characteristics of these patients.

One fourth of the admissions were emergency admissions, of which most were re-admissions. Compared with patients with a single admission for detoxification, patients with re-admissions did not differ in years of GHB use, age or gender. Patients with re-admissions did report significantly more prior GHB-related emergency room (ER) admissions (76.9% versus 47.2%, $F = 12.8$, $p \leq 0.001$) and intensive care unit (ICU) admissions (50.0% versus 20.3%, $F = 15.3$, $p \leq 0.001$). Also, patients with re-admissions used significantly more GHB ($M = 72.4$ g, $SD = 45.3$) compared to patients without re-admissions ($M = 56.0$ g, $SD = 40.3$) during the study period ($F = 5.6$, $p = 0.02$). Daily GHB doses for the whole group ranged from 10 to 312 gram, mean dose per day was 58.8 g ($SD = 41.6$) and mean dose at a time 4.0 g ($SD = 2.3$); 10% (also) used GBL. A small proportion of the admissions were involuntarily (6.2%).

3.2. Course of the detoxification procedure with pharmaceutical GHB

The titration phase took an average of 1.9 ($SD = 1.0$) days. Mean duration of completed detoxification was 10.6 ($SD = 6.3$) days, excluding the titration phase. Of 274 detoxifications, 39 (14.2%) were incomplete. Twenty-one patients discontinued detoxification

voluntarily due to different reasons. Nine drop-outs were involuntarily discharged due to aggression, nine to illicit drug abuse during admission confirmed by self-report. There was a suspicion of illicit substance abuse (mostly supplementary illicit GHB) during detoxification in 20.9% of the patients, and it was confirmed in 13.2%. Almost one third of the patients left the ATC immediately after detoxification (recovery days $M = 3.0$; $SD = 4.3$). The mean total number of admission days of all patients was 14.9 days ($SD = 8.0$).

In most detoxifications the dose for titration and detoxification was in line with the DeTiTap procedure. Mean first and second titration doses were respectively 2.7 g ($SD = 1.1$) and 2.9 g ($SD = 1.2$) with a range of 0.75–7.5 g, respectively 67.5% and 72.5% of the reported self-administered illicit dose.

During the titration day(s) the median stabilization dose was 3.2 g ($SD = 1.2$), 80% of the illicit GHB dose. The first and second titration doses appeared to be the exact stabilization dose for 40.9% and 57.1% of the detoxifications, respectively. Most of the patients however received higher stabilization doses, respectively 56.5% versus 41.9%.

Fig. 1 presents a graphical representation of the total pharmaceutical GHB dose per detoxification day. The pharmaceutical starting dose per day was about 50% lower than the total street GHB taken by patients per day before admission. The differences between street GHB and pharmaceutical GHB for dose at a time (70%) and dose per day (50%) is because of the differences in interval: patients were using street GHB more frequently (almost every one and a half hours) compare to the dosage schedule of pharmaceutical GHB (every two or three hour).

3.3. Symptoms

3.3.1. Subjective withdrawal symptoms. The mean SWS score before the first titration dose was 29.4 ($SD = 18.1$), decreasing to 24.7 ($SD = 16.3$) at the end of the first titration day. During titration days SWS scores differed significantly ($t = 18.2$, $p \leq 0.001$) 30 min before ($M = 22.5$, $SD = 16.9$) and 30 min after GHB doses ($M = 16.9$, $SD = 14.1$). Furthermore, the SWS scores before GHB doses (Fig. 2a) decreased significantly over time ($F = 11.3$; $p \leq 0.001$).

Patients with higher doses of pharmaceutical GHB ($F = 10.0$; $p \leq 0.01$), more detoxifications in the past ($F = 8.4$; $p \leq 0.01$), higher level of reported symptoms of depression ($F = 23.4$, $p \leq 0.001$), anxiety ($F = 10.3$, $p \leq 0.01$) and stress ($F = 27.3$, $p \leq 0.001$) at baseline experienced higher levels of subjective withdrawal, indicated by SWS scores. Women experienced higher score on the SWS than men ($F = 7.3$; $p \leq 0.01$), as did patients with emergency admissions ($F = 6.5$; $p = 0.01$). In contrast to what we expected, significantly ($F = 4.0$, $p = 0.02$) less severe SWS scores were found for patients that self-cooked their GHB compared to those who obtained GHB from a dealer or friend. We could not detect significant differences between GHB and GBL users due to the low number of GBL users.

Table 3
Baseline characteristics of unique patients (n = 229) at first admission.

Characteristics		n
Age in years, mean (SD)	28.8 (7.2)	229
Gender		229
Male	69.0%	
Female	31.0%	
Country of birth		216
The Netherlands	96.8%	
Other	3.2%	
Living situation		215
Living alone	34.9%	
Living with husband partner and/or children	24.7%	
Living with parents	26.5%	
Other	14.0%	
Street GHB use, mean (SD)		
Mean age at first GHB use	25.0 (7.4)	206
Mean years of GHB use	4.2 (3.3)	216
GHB use last 30 days	29.7 (1.4)	218
Estimated GHB dose at a time, gram	3.88 (2.1)	205
Estimated mean daily GHB dose before admission, gram	56.0 (40.3)	207
Concomitant substance use, mean (SD)		207
Alcohol use last 30 days	13.1 (11.6)	118 (57%)
Cannabis use last 30 days	17.0 (12.1)	88 (43%)
Opioid use last 30 days	13.7 (11.6)	4 (2%)
Cocaine use last 30 days	09.1 (10.7)	63 (30%)
Stimulant use last 30 days	14.8 (12.2)	86 (42%)
Sedative use last 30 days	21.5 (11.2)	74 (36%)
Other drug use last 30 days	26.2 (08.3)	123 (59%)

Table 4
DASS and BSI.

	Baseline		Discharge		t-test	df ^{a,b}	p-value
	mean	(sd)	mean	(sd)			
BSI	n = 211		n = 134				
Somatisation	1.56	1.01	0.62	0.58	9.55	114	≤0.001
Cognitive problems	2.01	1.106	0.99	0.88	11.84	114	≤0.001
Interpersonal sensitivity	1.47	1.18	0.60	0.82	8.98	122	≤0.001
Depression	1.78	1.13	0.87	0.88	11.28	113	≤0.001
Anxiety	1.75	1.04	0.91	0.83	8.56	114	≤0.001
Hostility	1.29	1.05	0.48	0.45	9.05	114	≤0.001
Phobic anxiety	1.23	1.15	0.54	0.72	7.58	114	≤0.001
Paranoid ideation	1.51	1.13	0.67	0.72	9.15	110	≤0.001
Psychoticism	1.36	1.05	0.65	0.71	9.06	113	≤0.001
General psychopathology (total score)	1.60	0.95	0.74	0.60	11.03	109	≤0.001
DASS ^a	n = 215		n = 134				
Depression	18.03 ³	(11,71)	12.21 ²	(10,26)	4.91	94	≤0.001
Anxiety	16.14 ⁴	(10,25)	11.73 ³	(9,08)	4.09	94	≤0.001
Stress	20.48 ³	(10,50)	14.32 ^{1/2}	(9,89)	5.21	94	≤0.001
Total	54.72	(29,47)	38.25	(25,62)	5.49	94	≤0.001

1 = normal, 2 = mild, 3 = moderate, 4 = severe, 5 = extremely severe.

^a Cut-off scores for DASS severity labels are as follows for depression (normal 0–9, mild 10–13, moderate 14–20, severe 21–27, extremely severe ≥28), anxiety (normal to mild ≤9, moderate 10–14, severe 15–19, extremely severe ≥20), and stress (normal 0–14, mild 15–18, moderate 19–25, severe 26–33, extremely severe ≥34).

^b Baseline information did not differ significantly between patients with both baseline and discharge measurement on the DASS and BSI and patients with no or one measurement on the DASS and BSI.

Readmission ($F \leq 0.01$, $p = 0.92$) and the amount of pre-admission GHB consumed, both per dose ($F = 0.2$, $p = 0.66$) and per day ($F = 3.3$, $p = 0.07$) showed no significant differences in terms of SWS scores. Finally, patients with higher SWS scores at the titration phase experienced higher SWS scores during the detoxification phase as well (Pearson $r = 0.7$, $p \leq 0.001$).

3.3.2. Objective withdrawal symptoms. Patients started the titration phase with a mean OWS score of 3.5 (SD = 2.9). The OWS score

differed significantly ($t = 12.5$, $p \leq 0.001$) 30 min before ($M = 3.6$, $SD = 2.8$) and 30 min after GHB dose ($M = 16.9$, $SD = 14.1$) during titration days. The course of OWS scores before GHB dose (Fig. 2b) changed over time ($F = 7.4$, $p \leq 0.001$).

3.3.3. VAS craving. At baseline patients reported a mean VAS craving score of 5.2 (SD = 3.0), whilst on the first titration day the mean VAS craving score was 6.0 (SD = 2.8). As shown in Fig. 3 the

Fig. 1. Total pharmaceutical GHB dose per detoxification day (mean and standard error of the mean).

mean VAS craving score significantly decreased over time ($F = 7.3$, $p \leq 0.01$).

3.3.4. Change in general symptoms. Patients reported high (DASS) or above average (BSI) symptoms of psychopathology compared to psychiatric outpatients. DASS and BSI symptoms decreased significantly during detoxification (Table 4). Although few patients still scored 'very high' on the BSI at discharge (15.7%, vs. 52.9% at admission), 47% scored 'high to very high'. The same was seen for severe/extremely severe anxiety on the DASS (30.5% of the patients vs. 50.2% at admission). Fewer patients experienced stress (from 36.4% to 15.6%) and depression (from 38.5% to 17.9%) on the DASS at discharge.

3.3.5. Complications and concomitant medication. Before admission the majority of the patients used psychotropic medication, such as benzodiazepines (22.3%), antipsychotics (14.0%), antidepressants (4.3%) and hypnotics (14.0%; Table 5a).

During DeTiTap 17 patients (7.4%) developed hypertension. Hypertension was treated mostly with metoprolol (50–150 mg) given once or twice (see Table 5b). Fifty patients (23.7%) developed anxiety and/or agitation, which was treated mostly with diazepam (5–30 mg). Five patients (2.1%) developed psychosis, extreme restlessness and/or delirium and received antipsychotics or benzodiazepines (see Table 5b for a detailed overview of co-medication). Four of those were sent to the general hospital. Two other patients were sent to the general hospital due to intoxication. Five patients returned to the ATCs the same day, one patient was admitted to the psychiatric ward for two days. All patients continued detoxification at the ATCs (Table 6).

3.4. Relapse rates

A follow-up visit was scheduled three months after discharge from the ATC. Of the 274 detoxifications, 96 (35.0%) were lost to follow-up. Those who were lost to follow-up did not differ significantly on baseline variables and detoxification outcome from patients with follow-up assessments. Of the remaining 178 patients, 64.6% had relapsed into GHB use during the three months

Table 5a

Co-medication related to co-abuse or pre-diagnosed psychiatric or somatic problems before admission per unique patient.

Indication	n applied medication
Hypertension	n = 6 n = 1 treated with nifedipine (60 mg) n = 3 treated with metoprolol (100 mg) n = 2 treated with propranolol (40–80 mg)
Psychosis	n = 32 n = 4 treated with olanzapine (15–20 mg) n = 3 treated with haloperidol (2.5–5 mg) n = 2 treated with abilify (10–15 mg) n = 23 treated with quetiapine (150–300 mg)
Depression	n = 10 n = 2 treated with citalopram (30 mg) n = 2 treated with venlafaxine (75–188 mg) n = 1 treated with escitalopram (15 mg) n = 3 treated with paroxetine (20 mg) n = 1 treated with amitriptyline (25 mg) n = 1 treated with agomelatine (25 mg)
Intestinal	n = 26 n = 11 treated with omeprazole (20–40 mg) n = 15 treated with loperamide (2–10 mg)
Co-abuse	n = 51 n = 44 used diazepam (5–60 mg) n = 2 treated with chlordiazepoxide (30–60 mg) n = 3 treated with oxazepam (50–300 mg) n = 2 switched between diazepam (5–40 mg) and domperidone (20 mg)
Sleep disorders	n = 32 n = 10 treated with quetiapine (25–100 mg) n = 6 treated with nozinan (12.5–25 mg) n = 4 treated with mirtazapine (15–30 mg) n = 6 treated with melatonin (5 mg) n = 6 treated with promethazine (25 mg at night)

after detoxification. Of these patients, 26.7% reported relapse immediately after detoxification. Mean duration of abstinence was 8.4 weeks ($SD = 4.2$). Daily GHB use was reported by 36.5% of the patients at follow-up. Half of the patients reported current GHB use at follow-up (21.5 days ($SD = 11.5$) out of 30). Patients also reported

Fig. 2. (a) Mean (and standard error of the mean) severity subjective withdrawal symptoms (SWS) before GHB doses per day during titration (T), detoxification (D), and recovery (R) phases. Scores for this figure are calculated and presented when $n > 20$. (b) Mean (and standard error of the mean) severity objective withdrawal symptoms (OWS) before GHB doses per day during titration (T), detoxification (D), and recovery (R) phases. Scores for this figure are calculated and presented when $n > 20$.

the use of alcohol (51.5%), benzodiazepines (37.4%), cocaine (26.9%), amphetamines (26.9%), and cannabis (23.4%) at follow-up.

4. Discussion

In this open-label multicenter study in 274 GHB-dependent inpatients, we found that successful detoxification from GHB was achieved in 85% of the cases using the DeTiTap procedure with pharmaceutical GHB. In most patients, detoxification was achieved in 12.5 days. During titration and detoxification the withdrawal symptoms and craving, as well as symptoms of depression, anxiety and stress significantly decreased over time. Several symptoms were found to influence the course of subjective withdrawal symptoms. Main complications were hypertension and anxiety. Six patients had to be admitted to a general hospital for observation, but all returned to the ATCs to continue detoxification. Relapse rates were high at 69% at follow-up three months after discharge.

Although the prevalence of GHB abuse and dependence has increased in recent decades, there have been no clinical trials investigating GHB detoxification treatments (Schep et al., 2012). Published case reports and case series mostly present acute unplanned detoxifications complicated by severe withdrawal syndromes that are difficult to manage in a general hospital. According to the sparse literature, high-dose benzodiazepine administration appears to be the first-line treatment, with, if necessary, barbiturates, baclofen, or propofol as second line management options, combined with monitoring in an ICU (Schep et al., 2012).

This open-label study with off-label use of pharmaceutical GHB was conducted due to the absence of studies and guidelines on safe and effective detoxification procedures in ATC settings, the presence of complicated GHB withdrawal case studies, and a rapid increase in the number of GHB users (Kamal et al., 2013). The advised titration and detoxification regimen proved to be feasible and we confirmed the effectiveness and safety of this DeTiTap pro-

Fig. 3. Mean (and standard error of the mean) experienced craving (measured with a VAS scale) per day during titration (T), detoxification (D), and recovery (R) phases. Scores for this figure are calculated and presented when $n > 20$.

Table 5b

Co-medication for symptomatic treatment during titration and detoxification phase.

Withdrawal Symptoms	Titration	Detoxification	Total unique patients
Hypertension	n = 10 n = 1 treated with metoprolol (50–150 mg) n = 5 treated with metoprolol (50 mg) n = 4 treated with metoprolol (100 mg)	n = 11 n = 3 treated with metoprolol (100 mg) n = 7 treated with metoprolol (50 mg) n = 1 treated with propranolol (10 mg)	n = 17
Anxiety	n = 17 n = 16 treated with diazepam (5–20 mg) n = 1 treated with oxazepam 25 mg	n = 26 All were treated with diazepam (5–30 mg)	n = 31
Agitation	n = 4 n = 3 treated with biperiden (2–4 mg) n = 1 treated with diazepam (10 mg)	n = 9 n = 7 treated with diazepam (5–30 mg) n = 1 treated with quetiapine (50 mg) n = 1 treated with dipiperon (20 mg)	n = 12
Anxiety + agitation	n = 6 n = 4 treated with diazepam (5–40 mg) n = 1 treated with biperiden (4 mg) n = 1 treated with beperiden (2 mg) + oxazepam (100 mg)	n = 3 n = 2 treated with diazepam (5–30 mg) (n = 1 switched from diazepam 5–10 mg to oxazepam (100 mg) + biperiden (2 mg) n = 1 treated with oxazepam (25 mg)	n = 7
Psychosis and/or Delirium and/or Extreme Agitation	n = 2 Patients were treated besides GHB increase with haloperidol (2–4 mg) + biperiden (1–2 mg)	n = 4 n = 3 treated with haloperidol (2.5–4 mg) + diazepam 10–20 mg + biperiden (1–2 mg) n = 1 treated with haloperidol (2.5 mg) + dipiperon (40 mg) + lorazepam (3–4 mg) + patient used also diazepam (30–40 mg)	n = 5

cedure using pharmaceutical GHB in a large group of patients that requested professional treatment for GHB addiction in different Dutch ATCs. Substantial co-medication was given during DeTiTap, partly because of comorbid substance use and psychiatric symptoms at baseline. Extra medication to treat anxiety and/or agitation was necessary in about 25% of the cases in relatively low doses. Due to the risk of severe and complicated withdrawal syndromes, the expertise of relevant healthcare practitioners (like nurses and addiction physicians) was and is necessary.

The naturalistic multicenter design of the present study forced us to use data provided by the resident nurses and physicians. Absence of the trained study nurse was the main reason for missing data and this could have influenced our results, although no mean-

ingful differences were found between patients with and without missing data. The same applies for missing data due to unmotivated patients for filling in questionnaires at discharge.

In our protocol, GHB detoxification was performed by using short-acting pharmaceutical GHB as substitution therapy, as no long-acting GHB was available. Although GHB has various multiple neurological properties, like (in)direct binding to GHB, GABA(A), and GABA(B) receptors (Brunt et al., 2014), alternatives should be investigated. One case study showed positive results for the GABA(B) agonist baclofen in GHB detoxification (LeTourneau et al., 2008), although the overlap in the neurobiological pathway and intoxication symptoms of GHB and baclofen can cause severe intoxications if used simultaneously (Kamal et al., 2015). Other options

Table 6
Overview of hospital admissions.

Case (age/gender)	Prominent withdrawal symptoms/complications	GHB dose	Day	Management	Medication
Case 6 (32/m)	Intoxication even before start of the detox	2.2 g	T1	Check up in GH	No medication
Case 2 (24/m)	Admitted in ATC with delirium and aggression	2.1 g	T1	After consult GH back to ATC the same day	Increase GHB
Case 4 (18/f)	Intoxication due to abuse outside the prescription: severe sedation and anxiety	0.9 g	D1	Only observation for few hours in GH, detox continued at ATC	Diazepam 10 mg
Case 3 (38/m)	Delirium	Start 2.2 g, at time of complication 1.9 g	D3	Treated in ATC after a quick check in GH	Increase GHB
Case 1 (37/m)	Delirium, anxiety and agitation	Start 3.1 g, at time of complication 2.2 g	D4	After examination GH back to the ATC the same day	Increase GHB, diazepam 15 mg, zyprexa 20 mg
Case 5 (39/m)	Delirium, poor response on medication	9 g	D7	Admitted to psychiatric ward of GH for three days, then continued treatment in ATC	Lorazepam 2.5 mg/d, haloperidol to 10 mg/day, then increase GHB + diazepam when needed up to 30 mg/d

GH = general hospital; ATC = addiction treatment centre.

for GHB detoxification worth investigating include dexmedetomidine or phenibut (Samokhvalov et al., 2013; Schep et al., 2012). More systematic research should be performed with pharmaceutical GHB in which the efficacy and safety will be assessed, as compared to other potential treatments, e.g., benzodiazepines and/or baclofen.

The daily amount of illicit GHB use in this study population was strikingly high, as well as the high percentage of prior ER and ICU admissions, emergency detoxification admissions, and the high prevalence of reported symptoms of depression, anxiety, and stress. General sociodemographic characteristics were nevertheless similar to GHB-dependent patients treated in Dutch ATCs (Wisselink et al., 2014), although unmonitored patients had fewer emergency indications and underwent fewer detoxifications in total. The high relapse rates immediately after detoxification and at three month follow-up require attention in future research and practice.

In conclusion, the DeTiTap procedure seems a feasible and safe alternative for GHB detoxification with benzodiazepines, although randomized controlled trials with different agents should be performed to establish efficacy and safety. Detoxification is part of a total treatment program aimed at the maintenance of abstinence and the high relapse rates warrant further investigation.

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Contributors

Boukje Dijkstra managed the GHB monitor, did most of the analysis and wrote first draft of the manuscript. Rama Kamal was as PhD involved in the acquisition of data and part of the data analysis. Martijn van Noorden was involved in the study conception,

study design and interpretation of the data analysis. Hein de Haan, Anton Loonen and Cor de Jong were involved in the study conception, study design and supervision of the project. All authors revised the manuscript critically and give final approval of the version to be submitted.

Conflict of interest

No conflict declared.

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