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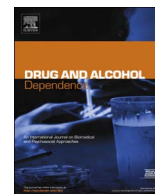
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Full length article

Treatment consumption and treatment re-enrollment in GHB-dependent patients in The Netherlands



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ABSTRACT

Background: The objective of this study was to assess treatment consumption and re-enrollment in treatment in patients with gamma-hydroxybutyrate (GHB)-dependence in Dutch Addiction Treatment Centers (ATCs) in comparison with other addictions.

Methods: A cohort-study using nationwide administrative data from regular Dutch ATCs associated with the Dutch National Alcohol and Drugs Information System (LADIS), covering an estimated 95% of ATCs. We selected in- and out-patients with alcohol, drug and/or behavioral addictions with a first treatment episode in 2008–2011 and consecutive treatments until 2013 ($n = 71,679$). Patients still in treatment at that date ($n = 3686$; 5.1%), forensic patients ($n = 1949$; 2.7%) and deceased patients ($n = 570$; 0.8%) were excluded, leaving 65,474 patients (91.3%). Of those, 596 (0.9%) patients had GHB dependence. We analyzed number of treatment contacts, treatment duration, admissions and admission duration of the first treatment episode, and re-enrollment (defined as having started a second treatment episode in the study period).

Results: GHB-dependent patients showed the highest number of treatment contacts, duration of treatment and chance of being admitted. Re-enrollment rates were 2–5 times higher in GHB-dependent patients than other patients with adjusted HR of other addictions ranging from 0.18 (95% confidence interval [CI]: 0.15–0.21) to 0.53 (95% CI: 0.47–0.61).

Conclusions: This study demonstrates high levels of treatment consumption and high rates of treatment re-enrollment in GHB-dependent patients. These findings highlight the urgency of developing effective relapse prevention interventions for GHB-dependent patients.

1. Introduction

Gamma-hydroxybutyrate (GHB) and its precursor gamma-butyrolactone (GBL) are popular drugs of abuse in several countries including the Netherlands. Although originally developed as an anesthetic, due to unpredictable side effects like vomiting, medical use is nowadays limited. As sodium oxybate, GHB is registered for treatment of narcolepsy and, in some countries, for treatment of alcohol withdrawal as well (Brunt et al., 2013a; Snead and Gibson, 2005). The well-reported euphoric and sexually stimulating effects of GHB have facilitated its development as a party-drug. Prevalence estimates of current GHB use in Australia, the United Kingdom and the Netherlands range from 0.1% to 0.4% in the adult population, whereas rates among regular nightclub attenders are considerably higher with a reported

current use prevalence of up to 10.5% (Corkery et al., 2015; van Amsterdam et al., 2012; Van Laar et al., 2012).

Over the last decade, medical complications as a result of GHB abuse have increased. In the Netherlands, Emergency Department (ED) presentations have increased from 300 in 2004–1200 in 2009 (Brunt et al., 2013a; Van Laar et al., 2012). Intoxications with GHB frequently occur, because of its narrow therapeutic window and short plasma half-life (van Amsterdam et al., 2012; Wood et al., 2011). Intoxications usually result in coma and may even be fatal, especially in the case of co-abuse of other sedative substances like alcohol (Corkery et al., 2015; Knudsen et al., 2008; Zvosec et al., 2011).

The high addictive potential of GHB has been recognized only since a decade (Snead and Gibson, 2005; van Amsterdam et al., 2012). In accordance, since 2007 a marked increase in GHB-related treatment

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seeking has been noticed in Dutch addiction treatment centers (ATCs; van Amsterdam et al., 2012). GHB users frequently report withdrawal symptoms upon cessation of daily use of GHB. Regular GHB use may result in tolerance and dependence in weeks, and many GHB-dependent users report an ‘around the clock’ dosing pattern in which they need to take doses every one or two hours as well as several nightly doses to prevent withdrawal symptoms (McDonough et al., 2004; Tarabar and Nelson, 2004; van Noorden et al., 2009). Abrupt decrease or discontinuation of heavy GHB use may result in a severe and life-threatening withdrawal syndrome characterized by autonomic instability, delirium and aggression (McDonough et al., 2004; Snead and Gibson, 2005; Tarabar and Nelson, 2004; van Noorden et al., 2009).

To date, studies that compare course and characteristics of GHB dependence with other addictions are lacking. Treatment of GHB dependence has neither been systematically investigated. Hence, no international guidelines exist (de Jong et al., 2013). Nevertheless, treatment of GHB dependence usually starts with inpatient detoxification due to the high level of physical dependence. Detoxification with benzodiazepines, the recommended treatment in most case reports and reviews, often appears problematic due to benzodiazepine-resistance (de Jong et al., 2012; McDonough et al., 2004; Sivilotti et al., 2001; van Noorden et al., 2014; Wojtowicz et al., 2008).

For several years, in Dutch ATCs detoxification with titration and tapering using pharmaceutical GHB is common. Results in terms of feasibility, effectiveness and safety are promising (de Jong et al., 2012; de Weert-van Oene et al., 2013; Dijkstra et al., 2016). However, reported relapse-rates appear to be high: after 3 months of follow-up, 65% of patients had relapsed in GHB abuse (Dijkstra et al., 2016).

Since GHB dependence is a relatively new phenomenon, very little is known about the course of GHB dependence, treatment effectiveness, and use of treatment facilities in addiction care. The high relapse rates reported by clinicians indicate a possible under-treatment compared to other addictions, that might be due to the complexity of GHB dependence, like the high physical dependence, the narrow therapeutic window and short plasma half-life, and the potentially life-threatening withdrawal syndromes.

We used nationwide administrative data to investigate treatment characteristics and separate treatment episodes in individual patients and compared GHB-dependent patients with other drugs of abuse and behavioral addictions. Under the assumption that re-enrollment in treatment after a terminated treatment episode would be indicative of a relapse in abuse, we studied re-enrollment in treatment: having started a second treatment episode in the study period. We hypothesized that, as compared with patients with other dependencies, treatment-intensity in GHB-dependent patients would be higher since the frequent need of inpatient detoxification of these patients will likely result in more treatment contacts and more ATC admissions. In addition, we hypothesized that because of the high relapse rates GHB-dependent patients more often had multiple treatment episodes than patients dependent on other common drugs of abuse or behavioral addictions.

2. Material and methods

2.1. Design and setting

We used administrative data of the Dutch National Alcohol and Drugs Information System (LADIS). The LADIS has been founded in 1986 and includes outpatient and inpatient clinical treatment data of 11 large ATCs in the Netherlands, covering an estimated 95% of all addiction treatments in the country (EMCDDA, 2015). Since 1994, all patients entering regular Dutch addiction care receive an identification number in LADIS, allowing to identify first and subsequent treatment episodes of every individual patient. Since 2007, the LADIS identification number is based on the Citizen Service Number, a unique personal number for everyone who is registered in Municipal Personal Records

Database in The Netherlands, minimizing the chance of duplicates in the database. A preliminary report on the GHB treatment data of 2007–2010 has been previously published in a Dutch addiction journal (Mol et al., 2014).

2.2. Participants

From 2008 to 2012 all 71,679 patients who initiated and completed a first treatment episode in regular Dutch ATCs associated with LADIS were selected, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) definition of ‘first treatment’ (EMCDDA, 2012). Patients were followed until December 31st, 2013. Patients who had not ended treatment by that time were excluded ($n = 3686$; 5.1%). Since GHB was not registered as separate drug-class in forensic addiction care ($n = 1949$; 2.7%), these patients were excluded from analyses. In addition, we excluded patients who had deceased during the first treatment episode ($n = 570$; 0.8%). In total 65,474 patients with a first treatment episode in the study period were included for analyses (91.3%). The following categories of primary addiction for which treatment was initiated were considered and used in analyses: GHB, cocaine, opioids, amphetamines, alcohol, cannabis, ecstasy, medication, gambling and a rest-category consisting of other substances as well as behavioral addictions like sexual addiction and game addiction (‘other’). In addition, information on co-abuse was available in LADIS, as well as the number of treatment contacts, number of ATC admissions, duration of admission (length of hospitalization in ATC) and duration of treatment. Available sociodemographic data included gender, age, and ethnic background.

2.3. Re-enrollment definition

Re-enrollment in treatment was defined as having started a second treatment episode in the study period. A second treatment episode was considered valid if the initiation date was after the recorded termination date of the first treatment episode. If a recorded termination date of the first treatment episode was lacking, initiation of a second treatment episode was defined if the new date was at least 6 months after the previous treatment contact. This is according to the international standard of EMCDDA (EMCDDA, 2012). If a second treatment episode had not started by December 31st, 2013, a single treatment episode was recorded for this patient.

2.4. Statistical analyses

Using descriptive statistics, we summarized the sociodemographic and clinical characteristics of primarily GHB-dependent patients and patients with other addictions. We used the median and interquartile range (IQR) in tables in case of skewed distributions. We used ANOVA to compare number of treatment contacts, duration of treatment, being admitted, and duration of admission between GHB and the other drugs of abuse and behavioral addictions. With regard to re-enrollment, we calculated several parameters. First, we calculated the proportion of patients that re-enrolled in the study period: the re-enrollment proportion. This proportion was the percentage of patients with more than one treatment episode, in which the time factor was not taken into account. The second parameter was the re-enrollment rate: after the first treatment episode, patients were followed until a next treatment episode, or until the end of the study period. The re-enrollment rate takes time at risk or person years (product of the number of patients and follow-up time) into account, but not the fact that patients could get lost to follow-up. The re-enrollment rate was calculated as follows: number of patients with a second treatment episode $\times 100$ / sum of person years, and can be interpreted as the number of patients per 100 that had started a second treatment episode within one year after completing the first treatment episode. Third, we calculated the Hazard Ratios (HR) of re-enrollment with Cox regression models, by using the time at risk. In a

Table 1

Sociodemographic and clinical characteristics per primary substance use disorder (or gambling) in a sample of 65,474 patients with first treatment episode in Dutch addiction care in 2008–2012.

	N	Median age (IQR)	Male gender (%)	Dutch background (n, %)	Number of Treatment contacts (mean, SE) (median, IQR)		Treatment Duration 1st episode, days (mean, SE) (median, IQR)		Multiple substances abuse (n, %)
GHB	596	25 (21–30)	66.6	89.4	50.4 (3.62)	20 (7–51)	323.2 (13.52)	229 (90–430)	68.0
Cocaine	6479	29 (24–36)	82.2	64.3	29.0 (0.76)	11 (4–26)	257.9 (3.52)	169 (73–337)	61.6
Opioids	1627	36 (29–45)	77.8	29.0	32.3 (2.05)	10 (2–33)	314.6 (9.66)	169 (73–337)	44.2
Amphetamines	1626	23 (20–29)	71.9	80.0	31.8 (1.51)	11 (4–31)	279.1 (7.33)	186 (78–372)	62.5
Alcohol	31,87	44 (34–53)	69.2	68.4	26.3 (0.31)	11 (4–26)	270.7 (1.58)	186 (83–355)	27.0
Cannabis	15,879	23 (19–30)	77.0	63.6	22.1 (0.37)	10 (3–22)	230.8 (1.99)	155 (64–305)	33.4
Ecstasy	159	21 (18–29)	66.7	76.1	21.0 (3.09)	8 (3–23)	204.3 (18.25)	128 (57–255)	71.7
Gambling	3788	33 (25–43)	86.5	55.9	16.2 (0.54)	9 (4–17)	220.7 (3.74)	155 (74–291)	24.9
Medication	881	45 (36–54)	41.8	62.5	26.7 (1.41)	12 (4–30)	248.8 (9.32)	157 (60–330)	35.2
Other	2569	33 (22–45)	58.0	58.8	18.6 (0.85)	10 (3–23)	223.2 (4.73)	154 (64–292)	21.4

IQR denotes Interquartile Range; SE denotes Standard Error.

second Cox regression model, we adjusted for age, gender, ethnic background and co-abuse. We present the unadjusted cumulative incidence of re-enrollment (as% without re-enrollment) in Kaplan-Meier survival curve, and the time in which 10% of the patients had been re-enrolled ('time to 10% re-enrollment') from the survival table. All analyses were performed with IBM SPSS Statistics Version 21.0.

3. Results

3.1. Treatment characteristics

GHB dependence was the primary reason for initiation of treatment in 596 of 65,474 patients (0.9%) that had started a first treatment episode in Dutch addiction care in 2008–2011 and terminated treatment at ultimately December 31st 2013. Median age of the GHB-dependent patients was 25 years, 67% was male, and 89% had a Dutch ethnic background (Table 1). Median age of the other patients was significantly higher with 35 years ($F_{1,2} = 271.6, p < 0.001$). Number of treatment contacts and treatment duration were significantly higher in GHB-dependent patients as compared with the other drugs of abuse and behavioral addictions ($F_{1,9} = 46.7, p < 0.001$ and $F_{1,9} = 50.1, p < 0.001$, respectively; Table 1 and Fig. 1). Of all addictions, GHB dependence most often resulted in admission in an ATC. ($F_{1,9} = 106.3, p < 0.001$; Fig. 1). These findings were in line with our initial hypothesis. Mean duration of admission in GHB-dependent patients did not differ from most other dependencies (Fig. 1).

3.2. Re-enrollment

Re-enrollment risks per primary substance use disorder or gambling are presented in Table 2. As described before, re-enrollment was defined as having started a second treatment episode in the study period. The re-enrollment proportion, i.e. the percentage of patients that had re-enrolled, was 42.8 in GHB-dependent patients. Re-enrollment proportions in other patient categories ranged from 10.2 to 28.8. Per 100 GHB-dependent patients, 23.3 had re-enrolled per year (re-enrollment rate), while for the other drugs of abuse or behavioral addictions 3.8–11.0 had one re-enrollment per year. In an unadjusted Cox regression model, the HR of re-enrollment per substance was calculated with GHB as a reference. All other substances and gambling demonstrated significantly lower HRs for re-enrollment. In a second Cox regression model, we adjusted for age, sex, co-abuse and ethnic background. Again, GHB demonstrated the highest HR for re-enrollment. Taking GHB as a reference, adjusted HRs for re-enrollment ranged from 0.23 (95% CI 0.19–0.27) to 0.57 (95% CI 0.50–0.65). Women had a lower HR for re-enrollment (0.91; 95%CI 0.87–0.94) as

compared with men, and patients with co-abuse had a higher HR for re-enrollment (1.22; 95% CI 1.18–1.27) as compared with patients that abused a single substance (data not presented in tables). The time to 10% re-enrollment was 99 days in GHB-dependent patients, and 189–923 days in the other patients.

Fig. 2 presents the Kaplan-Meier curves for the cumulative incidence of re-enrollment (as percentage without re-enrollment, starting with 100%) of GHB and the other drugs of abuse and behavioral addictions. This figure illustrates the exceptionally high re-enrollment rates in GHB dependence as compared with other addictions.

4. Discussion

GHB dependence has only recently gained clinical significance, reflected by the rapid increase in treatment-seeking in addiction care over the past decade, and, as such, it is a relatively understudied phenomenon. Very little is known about treatment effectiveness and use of treatment facilities in addiction care. This study used administrative data of 65,474 patients in regular Dutch addiction care to compare GHB dependence with other drugs of abuse and behavioral addictions in terms of treatment characteristics and re-enrollment rates. We found that of all patients in addiction care, GHB-dependent patients showed the highest treatment intensity, as indicated by high admission rates, long admissions and high number of treatment contacts. In addition, GHB-dependent patients had the highest risk of re-enrollment into a new treatment episode in addiction care.

For a long time, the dependence liability of GHB was considered low. Studies on medical use of GHB (e.g., sodium oxybate in narcolepsy) found abuse incidences of less than one percent (Wang et al., 2009). Few studies in recreational GHB users indicated dependence liability in frequent GHB users (Freese et al., 2002; Miotto et al., 2001). By now, the dependence liability of GHB has been widely recognized (Brunt et al., 2013a; Snead and Gibson, 2005; van Amsterdam et al., 2012). In a study named 'the Dutch GHB Monitor', 274 patients with GHB dependence have been followed during regular addiction treatment including inpatient detoxification from 2010 to 2012. Most patients from the GHB Monitor have probably been included in the LADIS database as well. After 3 months of follow-up, 65% of the patients of the GHB monitor reported a relapse in GHB abuse (de Weert-van Oene et al., 2013; Dijkstra et al., 2016). This percentage is considerably higher than the re-enrollment rates we found in our study and can be explained by the fact that relapses occurred during ongoing treatment episodes (i.e. within 6 months after detoxification). Furthermore, in this study we measured treatment re-enrollments (and not relapse rates) after a terminated treatment episode. It can be hypothesized that not every patient with a relapse will reinitiate treatment. For

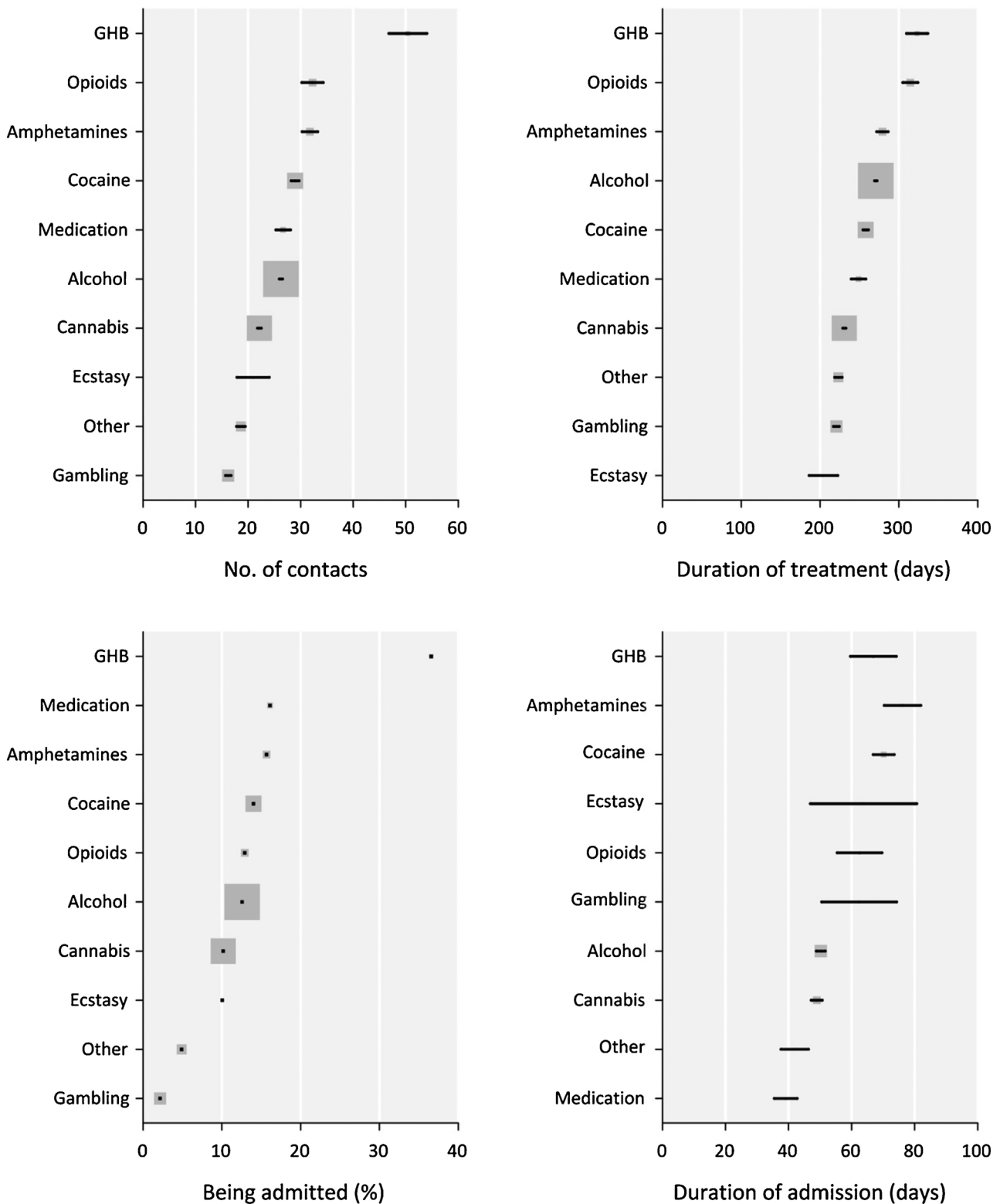


Fig. 1. Means including Standard Errors of treatment characteristics per primary drug of abuse (or gambling) in 65,474 patients with a first episode in Dutch addiction care from 2008 to 2011. The block size is indicative of the number of patients.

published relapse rates of other drugs of abuse, we found the same difference with relapse rates ranging from 40 to 60%, comparable with other chronic diseases, which are notably higher than the re-enrollment rates in our study (Hunt et al., 1971; McLellan et al., 2000; O'Brien 1997). Thus, using re-enrollment as a proxy for relapse is likely a conservative approach for studying relapse rates. Given the profoundly

high re-enrollment rates in GHB-dependent patients as compared with other drugs of abuse and behavioral addictions our findings are in line with the findings of the GHB monitor and clinical experience that GHB has high dependence liability with high relapse rates after detoxification. However, when interpreting this finding one has to keep in mind that these administrative data on treatment intensity and treatment

Table 2

Re-enrollment risks per primary substance use disorder (or gambling) in a sample of 65,474 patients with first treatment episode in Dutch addiction care in 2008–2012.

	N 65,474	Re-enrollment (n)	Re-enrollment proportion ^a (%)	Re-enrollment rate ^b	HR re-enrollment ^c (95% CI)	Adjusted HR re-enrollment ^d (95% CI)	Time to 10% re-enrollment ^e (days)
GHB	596	255	42.8	23.3	Ref	Ref	99
Cocaine	6479	1867	28.8	11.0	0.53 (0.47–0.61) [*]	0.57 (0.50–0.65) [*]	189
Opioids	1627	444	27.3	11.0	0.53 (0.46–0.62) [†]	0.67 (0.57–0.78) [*]	147
Amphetamines	1626	392	24.1	9.3	0.45 (0.38–0.52) [†]	0.45 (0.38–0.52) [*]	246
Alcohol	31,870	6792	21.3	8.0	0.38 (0.34–0.43) [†]	0.53 (0.47–0.60) [*]	303
Cannabis	15,879	3303	20.8	7.7	0.37 (0.33–0.42) [†]	0.40 (0.35–0.45) [*]	324
Ecstasy	159	29	18.2	6.2	0.31 (0.21–0.45) [†]	0.30 (0.21–0.44) [*]	466
Gambling	3788	632	16.7	5.8	0.28 (0.25–0.33) [†]	0.35 (0.30–0.40) [*]	448
Medication	881	139	15.8	5.6	0.27 (0.22–0.34) [†]	0.40 (0.32–0.49) [*]	489
Other	2569	263	10.2	3.8	0.18 (0.15–0.21) [†]	0.23 (0.19–0.27) [*]	923

Re-enrollment indicates having started a second treatment episode in the study period. Ref denotes Reference.

^a Re-enrollment proportion denotes the percentage of patients with re-enrollment.

^b Re-enrollment-rate denotes the number of patients with re-enrollment × 100/sum of person-years (number of patients per 100 with re-enrollment each year). HR indicates Hazard Ratio.

^c HR of re-enrollment in Cox regression model.

^d Adjusted for age, sex, co-abuse and ethnic background.

^e Time to 10% relapse denotes the time in days after which 10% of the patients had re-enrolled.

* p < 0.001.

characteristics lack details of the nature of treatment.

We were able to confirm our hypothesis that GHB-dependent patients showed the highest treatment intensity in terms of treatment contacts and ATC admissions of all dependencies and behavioral addictions in our study. In addition, if admitted, duration of admission was higher in GHB-dependent patients as compared with other patients. The high treatment intensity in GHB-dependent patients does not seem to prevent high re-enrollment rates. Although our administrative data did not include details of the treatment, we expect that, compared with treatments for other dependencies, daily clinical treatment for GHB-dependent patients is more focused on short-term outcomes (crisis management).

This focus on short-term outcomes is in line with the particular unpredictability of GHB, due to its narrow therapeutic window and short plasma half-life, as well as potentially life-threatening withdrawal syndromes, which play a more substantial role in GHB dependence than in other substance dependencies. This unpredictability of GHB and the frequent need for crisis management is confirmed by the Dutch GHB monitor in which one fourth of the admissions were emergency admissions and in which 84% reported one or several comas, 43%

reported one or more ED admissions, and 20% reported one or more Intensive Care Unit (ICU) admissions as a result of GHB use (de Weert-van Oene et al., 2013; Dijkstra et al., 2016). The focus on short-term outcome is also confirmed by the high relapse rates immediately after detoxification (26.7%) which makes it hard to achieve proper diagnostics and appropriate follow-up management. Several Dutch studies sought explanations for this high relapse and showed that anxiety, cognitive problems, unsupportive living environments and lack of daily activities are often mentioned as reasons for this fast relapse (Dijkstra et al., 2013; Beurmanjer et al., 2016a; Beurmanjer et al., 2016b). The lack of effective relapse prevention strategies now often leave clinicians empty-handed.

Our findings stress the importance of future studies on effective treatments of GHB dependence focusing on long-term outcomes besides short-term outcomes, especially relapse prevention. Currently, trials are being conducted in which baclofen will be studied in relapse prevention (Lingford-Hughes et al., 2016; Kamal et al., 2015). Besides abstinence, treatment goals focusing on stabilization should be considered to create a basis for abstinence in the future.

This is the first study that used administrative data to study

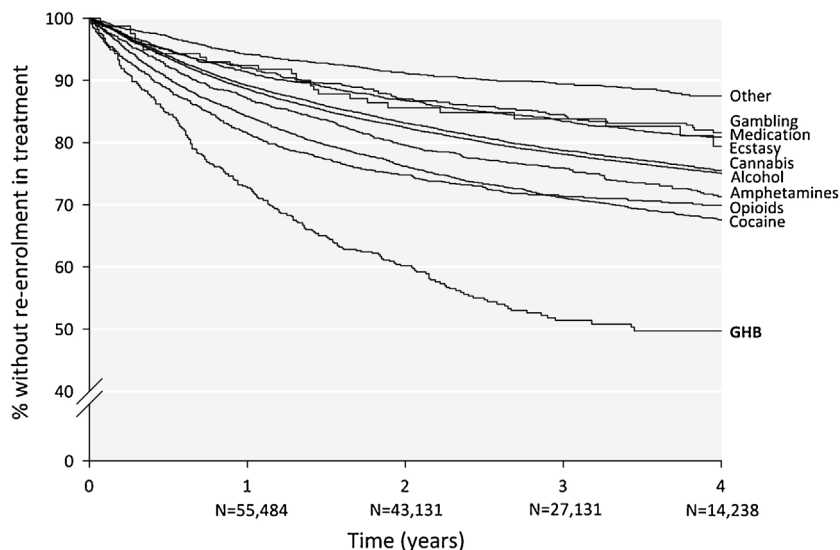


Fig. 2. Kaplan-Meier curves for the cumulative incidence of re-enrollment (displayed as % without re-enrollment in treatment) according to primary addiction in 65,474 patients with a first treatment episode in Dutch addiction care from 2008 to 2011. Re-enrollment was defined as having started a second treatment episode in the study period that ended 31st December 2013. Time indicates follow-up time in years.

treatment characteristics by means of treatment consumption parameters and re-enrollment rates. The large LADIS database with longitudinal data allowed us to compare GHB with the most common drugs of abuse and behavioral addictions, providing robust results. The estimated covering of 95% of Dutch addiction care treatments in LADIS makes these results largely generalizable to clinical practice in the Netherlands (EMCCDA, 2015).

Several potential limitations should be taken into account when interpreting our results. First, the administrative and pseudonymized data in LADIS prohibited us to directly investigate relapse-rates after successful treatment as clinical chart-data about relapse was not available. In addition, the administrative data was restricted to self-reported primary drug of abuse and possible co-abuse, which we used in our analyses. We were not able to clinically evaluate the primary reason for seeking treatment, nor the importance of possible co-dependencies or (mental) disorders (Brunt et al., 2013b). Second, patients who had died during follow-up, patients who had moved to another country, or patients who had started a second treatment episode in an ATC that is not covered by LADIS, have been censored since follow-up information about these patients was lacking. Third, we selected only patients with a first treatment episode in addiction care in the study period. This allowed us to compare patients in the same treatment phase. In the time-frame of the current study, the proportion of new GHB-dependent patients was relatively high. For example, the re-enrollment rate of patients with opioid dependence would have been 15.5 (instead of 10.5) if chronic patients would have been included as well. Nevertheless, in the latter case re-enrollment rates of GHB still would have been much higher than all other drugs of abuse (27.1). Finally, since the user-profiles of several dependencies show large differences (e.g., age and socioeconomic status), comparing these groups is complicated. Since characteristics like sociodemographic status were not available, adjusting for known variables did not resolve this issue of matching.

5. Conclusions

GHB-dependent patients show high treatment consumption and high treatment re-enrollment rates. These results stress the importance of future studies on treatment of GHB use disorders, including relapse prevention.

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Contributors

TM and BD designed the study and performed the first analyses and critically revised the manuscript. MvN wrote the manuscript and helped with the analyses, JW and WK helped with the analyses and critically revised the manuscript. All authors approved of the final manuscript before submission.

Conflict of interest

No conflict declared.

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