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Review

Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review

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Abstract

Aim: To examine the clinical course of gamma-hydroxybutyrate (GHB) withdrawal and generate management guidelines. *Design:* Review and analysis of all published reports of GHB or GHB precursor withdrawal identified from electronic searches. *Findings:* In total, 38 cases of GHB ($n = 28$) or GHB precursor ($n = 10$) withdrawal were identified, 36 of which were from the US. A rapidly deteriorating course into delirium (53% of cases) was typical for heavily dependent users. Symptoms were broadly similar to alcohol withdrawal but often occurred earlier in usage with delirium being associated with severe dependence as determined by more frequent ingestion. High dose benzodiazepines were effective in pharmacological management of GHB withdrawal. In benzodiazepine refractory cases withdrawal responded to other sedative agents, mainly pentobarbital or chloral hydrate. No withdrawal seizures but one death was recorded. *Conclusions:* GHB withdrawal is potentially life threatening and requires vigorous clinical management, preferably as an inpatient for severe cases. A management algorithm is proposed.

Keywords: Gamma-hydroxybutyrate; GHB; Withdrawal; Emergency department; Dependence; Treatment

1. Introduction

Gamma-hydroxybutyric acid (GHB), a naturally occurring short-chain fatty acid related to gamma-aminobutyric acid (GABA), rapidly produces effects that have been likened to a combination of alcohol (euphoria, reduced anxiety, drowsiness, loss of motor control) and ecstasy (enhanced sensuality, emotional warmth) (Galloway et al., 2000). As such, the illicit use of GHB and precursor agents, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) has steadily grown in the US and more recently in mainland Europe and the UK (Nicholson and Balster, 2001). GHB is used recreationally at raves ("liquid ecstasy") and to heighten sexual pleasure but it has also been used as a "health product" for sleep and bodybuilding, though any anabolic effects remain unproven (Nicholson and Balster, 2001).

Although animal studies have been inconclusive (Nicholson and Balster, 2001), clinical evidence has shown that GHB abuse can produce severe dependence and withdrawal. Two large clinical studies where GHB was prescribed as part of a treatment program for alcoholism, found that 10–15% of patients abused or became dependent on GHB (Addolorato et al., 1996; Gallimberti et al., 2000). The California Poison Control System recorded 30 cases of withdrawal from 356 GHB exposures in 1999 and an Internet help site on GHB recorded 184 cases of withdrawal across 33 US states by 2001 (Dyer et al., 2001). Although there have been individual reports on symptoms of GHB withdrawal and treatments used, no clear consensus exists on typical withdrawal features or effective management of these symptoms. We have, therefore, attempted to address these limitations by conducting the first review of all published clinical studies to evaluate the clinical course of GHB withdrawal and its treatment with a view of proposing practical management guidelines.

2. Methods

Studies (including case reports) of GHB or GHB precursor withdrawal identified using electronic searches of *Medline* and *Psychinfo* databases (January 1990–August 2002; search terms: gamma-hydroxybutyrate, gamma-butyrolactone,

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Table 1
Reported studies of GHB and GBL withdrawal

Reference	Country	Number of cases, n ($N = 38$)	Setting of clinical presentation/method of case identification
Galloway et al. (1994)	US	1	Specialist addictions centre
Friedman et al. (1996)	US	1	Acute psychiatric unit
Dyer and Andrews (1997)	US	1	Emergency department
Galloway et al. (1997)	US	3	Specialist addictions centre
Hernandez et al. (1998)	US	1	Acute psychiatric unit
Addolorato et al. (1999)	Italy	1	Specialist addictions centre
Craig et al. (2000)	US	1	Emergency department
Hutto et al. (2000)	US	1	Emergency department
Miglani et al. (2000)	US	1	Emergency department/acute psychiatric unit
Price (2000)	UK	1	Specialist addictions centre
Bowles et al. (2001)	US	1	Acute medical
Dyer et al. (2001)	US	7	Retrospective review of poison centre records
Mahr et al. (2001)	US	1	Specialist addictions centre
McDaniel and Miotto (2001)	US	9 (3 GBL)	Emergency department and neuropsychiatric unit
Miotto et al. (2001)	US	2	Specialist addictions centre
Schneir et al. (2001)	US	1 (GBL)	Emergency department
Sivilotti et al. (2001)	US	5 (all GBL)	Chart review of admissions to toxicology treatment centre

1,4-butanediol, withdrawal, dependency) are listed in Table 1. No reports of 1,4-BD withdrawal were identified. Data concerning age, gender, clinical presentation, type and extent of GHB use, management and medical complications were entered onto a computer statistics package (SPSS Version 10.0, 1999) for analysis. Where possible, an estimate of the GHB daily dose was made using the formula 1 teaspoon = 1 "capful" = 2 g GHB, though much variation in the concentration of illicitly prepared GHB has been reported (0.5–5 g per capful) (Miotto et al., 2001; Nicholson and Balster, 2001). GBL doses were calculated from the concentration of the preparation used, where possible. For comparison of subjects presenting with and without withdrawal delirium, the Student's t-test was used for continuous variables and χ^2 or Fisher's exact test for categorical variables. Skewed data were log transformed. Two-tailed α of 0.05 was used for all significance tests.

3. Results

Thirty-eight cases of GHB/GBL withdrawal were identified (see Table 1). Most were published in the past 4 years with the earliest dating back to 1994. GBL withdrawal was first reported in 2001, the year following reclassification of GHB as a schedule I controlled substance in the US. Schneir et al. (2001) reported a case of GBL dependence with intermittent use of 1,4-BD (in the form of ink jet printer fluid) but no primary 1,4-BD dependence was identified. Only two reports originated outside the US, one from Italy and one from the UK.

3.1. Pattern of GHB use and clinical features of withdrawal

Table 2 describes the pattern of GHB use and clinical features associated with GHB withdrawal in published reports. The male preponderance and wide age ranges reported perhaps reflect the varied settings of GHB use to date. Frequent dosing with a mean of every 4.4 h among these cases was a key feature of dependent use, though notably a withdrawal state was reported in two cases of once daily dosing (Sivilotti et al., 2001). However, 8-hourly dosing was the minimum frequency associated with withdrawal delirium. The minimum daily GHB dose associated with withdrawal was 18 g (about 9 teaspoonfuls) and for GBL 10 g or 2 oz of a preparation such as "Verve". Given that about 35 g per day is used therapeutically in alcoholism (Addolorato et al., 1996), it appears that withdrawal can occur with relatively light reported usage though this may reflect under-reporting of use among patients. Most were taking GHB for less than 2 years and withdrawal was seen after as little as 2–3 months of use. The majority using GHB (74%) rather than a GHB precursor in this sample may not reflect current patterns of use as GBL and other precursors are becoming more prevalent with restrictions on GHB sales.

The majority presented within 24 h of their last dose though there was wide variation (from 1 to 200 h). Thirty-four percent of cases reported or tested positive for other psychotropic drugs but none gave a history of co-dependence on another CNS depressant at the time of presentation. Few tested positive for GHB (11%) as toxicological confirmation has not been readily available.

The clinical withdrawal features listed in order of frequency in Table 2 are similar to those for alcohol with tremor, tachycardia, restlessness and delirium being common. Just over half of the cases reported delirium or hallucinations and a third required physical restraint which may reflect reporting bias towards the more severe cases. GHB withdrawal was also commonly presented as a psychosis in clear consciousness. The mean duration of GHB withdrawal (9 days) was again similar to that for alcohol. Three patients initially presenting with milder GHB withdrawal and discharged on

Table 2
Descriptive analysis of GHB and GBL withdrawal episodes ($N = 38$)

Descriptive variables	*n* (%)	Mean (S.D.) and range
Age ($N = 36$)		31 (10) (18–57)
Gender ($N = 36$)	23 male (64%)	
Pattern of use		
Form of GHB taken		
GHB	28 (74%)	
GBL	10 (26%)	
Time between doses in hours ($N = 24$)		4.4 (6.3) (0.5–24)
Estimated daily dose (g)		
GHB ($N = 21$)		48 (24) (18–100)
GBL ($N = 5$)		27 (20) (10–60)
Years of use ($N = 33$)		1.3 (1.0) (0.2–4)
Duration of withdrawal in days ($N = 31$)		9 (4) (3–15)
Hours since last dose at presentation ($N = 21$)		46 (55) (1–200)
Clinical features reported ($N = 38$)		
Tremor	28 (74%)	
Tachycardia	25 (66%)	
Anxiety or restlessness	23 (61%)	
Hallucinations	21 (55%)	
Auditory and visual	14 (37%)	
Visual, auditory and tactile	3 (8%)	
Visual only	3 (8%)	
Other	1 (3%)	
Delusions or paranoia	14 (37%)	
Psychosis in clear consciousness	5 (13%)	
Delirium	20 (53%)	
Insomnia	20 (53%)	
Diaphoresis	12 (32%)	
Hypertension	11 (29%)	
Nausea or vomiting	7 (18%)	
Toxicology		
Toxicological confirmation of GHB ingestion	4 (11%)	
Co-ingestants at presentation ($N = 29$)		
None	19 (66%)	
Alcohol	4 (14%)	
Cannabis	3 (10%)	
Benzodiazapines	3 (10%)	
Other (methamphetamines, LSD, opiates, phenobarbital)	3 (10%)	

reducing courses of benzodiazepines later represented with acute delirium (Sivilotti et al., 2001).

3.2. Features associated with withdrawal delirium

Withdrawal delirium was associated with more frequent ingestion of GHB prior to cessation than those without delirium (see Table 3) and there was a trend towards receiving a higher daily dose and a more prolonged withdrawal period. No differences were seen in the delirium and non-delirium groups in years of total GHB use, duration since last use at presentation or presence of confirmed co-ingestants at presentation.

3.3. Clinical management

In 82% of cases, detoxification was unplanned and medical treatment only commenced after the patient presented in crisis usually to an emergency department. Severe cases such as those with delirium required intensive supportive care in an acute medical setting. A tapering benzodiazepine regimen (usually diazepam or parenteral lorazepam) was used in 91% of cases but usually in combination with other drugs (82% of cases) mainly antipsychotics, anticonvulsants and non-benzodiazepine sedatives (barbiturates, chloral hydrate)—see Table 4. There were insufficient cases for a meaningful comparison of combination drug treatment with benzodiazepine treatment alone. The mean dose of benzodiazepine (in diazepam equivalents) used to manage the withdrawal period was 335 mg ranging from 20 to 2655 mg. Three cases of benzodiazepine refractory withdrawal symptoms were reported which responded to another agent (pentobarbital in two cases and chloral hydrate in one). Medical complications during withdrawal were described in five cases and included sepsis, myoglobinuria and Wernicke's Encephalopathy (without concurrent alcohol dependence) which responded to thiamine replacement. No frank withdrawal seizures were recorded but the single

Table 3
Comparison of pattern of GHB use between cases presenting with and without withdrawal delirium

	Withdrawal delirium		P[a]
	Absent ($N = 18$)	Present ($N = 20$)	
Form of GHB taken, *n* (%)			1.00
GHB	13 (72%)	15 (75%)	
GBL	5 (28%)	5 (25%)	
Time between doses (h), mean (range)	7.0 (1–24)	2.3 (0.5–8)	0.03[b,*]
Estimated daily dose (g), mean (S.D.)			
GHB	39 (23)	58 (23)	0.09
GBL	10 (10)	31 (15–60)	0.21[b]
Years of use, mean (S.D.)	1.1 (0.8)	1.5 (1.0)	0.24
Duration of withdrawal (days), mean (S.D.)	8 (4)	10 (4)	0.08
Duration since last dose at presentation (h), mean (range)	45 (2–200)	46 (1–140)	0.54[b]
Presence of another psychoactive drug at presentation, *n* (%)	6 (46%)	4 (25%)	0.27

[a] Student's *t*-test for continuous variables; χ^2 or Fisher's exact test for categorical variables.
[b] Data skewed, so ln transformed.
[*] Significant at the 0.05 level.

Table 4
Drugs combined with benzodiazepines in the management of GHB withdrawal ($N = 38$)

Drug	*n* (%)
Antipsychotic	15 (43%)
Anticonvulsant (valproate, carbamazapine, gabapentin)	8 (21%)
Barbiturate (pentobarbital or phenobarbital)	7 (18%)
Chloral hydrate	3 (8%)
Trazadone	3 (8%)
Thiamine	3 (8%)
Baclofen	2 (5%)
Clonidine	2 (5%)
Propranolol or labetolol	2 (5%)
Propofol	1 (3%)
Bromocryptine	1 (3%)

reported death during withdrawal followed a period of generalised, spastic muscular contraction on day 13 (Dyer et al., 2001). Post-mortem examination showed pulmonary oedema, cardiac enlargement and coronary artery disease without infarction. The cause of death was reported as a complication of GHB withdrawal.

4. Discussion

This review confirmed that GHB withdrawal has been little studied to date with just 38 published cases describing symptoms of withdrawal and even fewer describing treatment approaches. Reported cases may be biased towards symptom severity and singular dependency on GHB but are valuable as they give guidance on symptomatology and management of withdrawal states.

4.1. Clinical features of GHB withdrawal

Although it is difficult to predict the course of any one withdrawal episode, it is clear from this review of published reports that severe dependence as reflected in frequent ingestion of GHB can be associated with a severe, potentially life threatening withdrawal state that requires vigorous clinical management, preferably in an inpatient setting. Withdrawal symptoms were similar to those for alcohol but such symptoms were seen even after relatively short periods of GHB abuse. Withdrawal delirium was present in more than half of reported cases which, however, may have been biased towards symptom severity. Delirium was associated with more frequent ingestion of GHB and was not reported following an ingestion frequency of greater than 8 h or following a daily intake of less than 30 g of GHB or 15 g of GBL. Severe withdrawal lasted from 8 to 10 days and in the majority of cases was successfully treated with good supportive treatment and reducing benzodiazepines.

Withdrawals in cases co-dependent on another CNS depressant, opiate or stimulant drug are likely to be more severe but have yet to be described. In this sample, the presence of co-ingestants at presentation was not associated with a more severe withdrawal, and in fact, was more common among non-delirium cases.

4.2. Neurochemical basis of GHB withdrawal

GHB is structurally related to gamma-aminobutyric acid (GABA) but binds its own receptors in the hippocampus, cortex and dopimanergic areas. Recent lines of evidence, not least the finding that GHB is converted into GABA following ingestion, suggest GABA receptors (particularly GABA-B) are important mediators of GHB's psychotropic effects (Hechler et al., 1997; Nicholson & Balster, 2001; Carai et al., 2001). This perhaps explains why GHB withdrawal is clinically similar to that for alcohol and benzodiazepines whereby their effects are primarily or entirely mediated through GABA receptor stimulation (though predominately GABA-A in both cases). We speculate that the GHB withdrawal state might involve loss of inhibitory

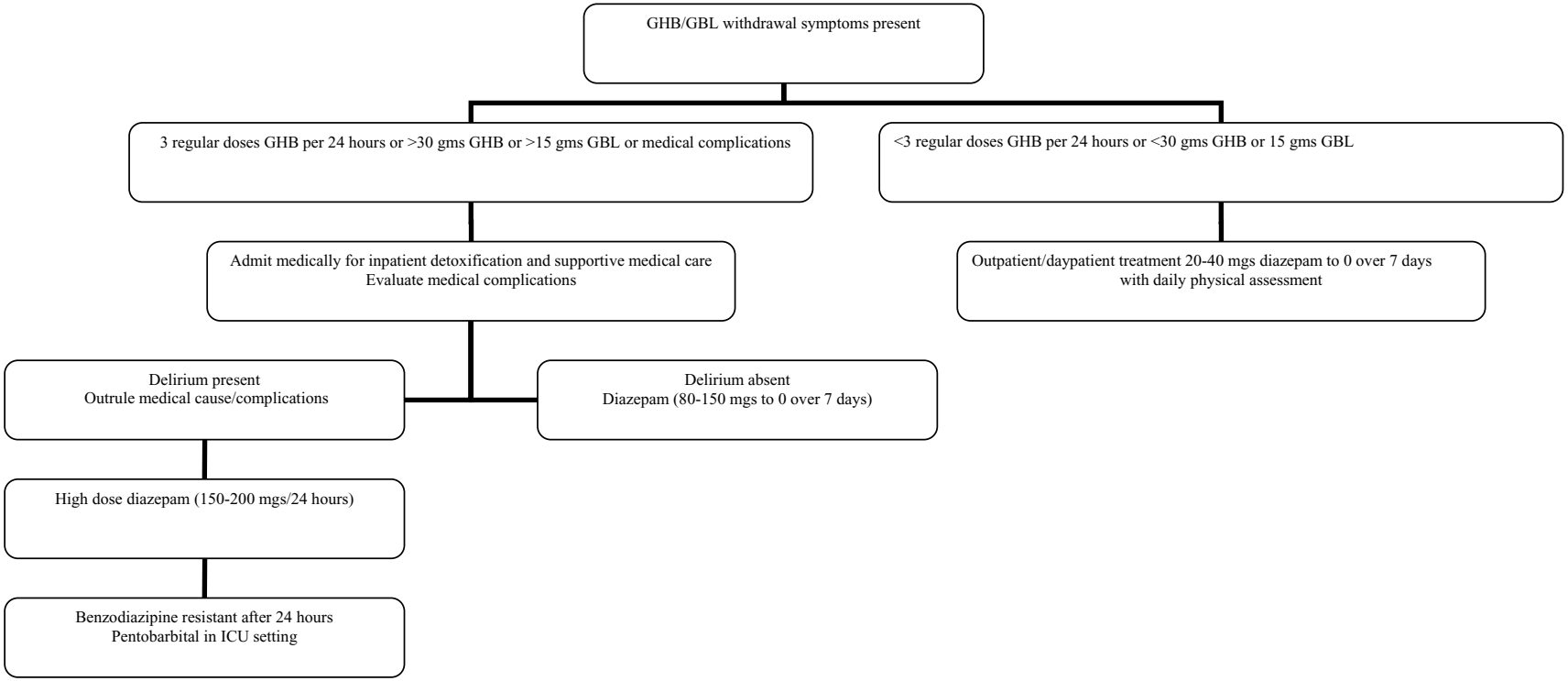

Fig. 1. Algorithm for the proposed management of GHB or GHB precursor withdrawal.

tone from GABA (B more effected than A) and GHB receptors (Dyer et al., 2001; Sivilotti et al., 2001). Benzodiazepines are indirect GABA-A agonists—acting to increase the receptors affinity for GABA rather than through direct stimulation—and are thus less effective when central GABA stores are depleted or when receptors are severely down regulated. Pentobarbital (unlike most other barbiturates) can also directly open GABA-A and voltage gated chloride channels (Sivilotti et al., 2001) and is therefore less dependent on GABA availability. This might explain the response of benzodiazepine resistant GHB withdrawal symptoms to pentobarbital. A similar phenomenon has been recognised with alcohol withdrawal (Dill & Shin, 2000).

It has been proposed that the risk of withdrawal psychosis relates to effects of GHB on GABA-B as severe psychological reactions have been reported in withdrawal from the GABA-B agonist, baclofen (Dyer et al., 2001). In animal studies GHB enhances dopamine concentration in the substantia nigra and the mesolimbic system both by reducing nerve firing and stimulating intracellular production (Nicholson & Balster, 2001) and one might speculate that augmented dopamine release within these areas during withdrawal contributes to the psychotic phenomena. However this is not supported by the lack of clinical efficacy of dopamine antagonists in GHB related psychosis.

4.3. Clinical management of GHB withdrawal

An algorithm for the management of GHB or GHB precursor is proposed in Fig. 1. Ideally, it is preferable to plan detoxification in advance so that withdrawal symptoms can be identified and treated early as most patients presenting symptomatically following enforced abstinence have presented with more severe symptoms and high risk of delirium (Schneir et al., 2001; Hernandez et al., 1998; Sivilotti et al., 2001). Dependent use with frequent ingestion every 8 h or less is associated with withdrawal delirium in more than 50% of the reported cases and inpatient detoxification should be strongly considered as with heavy use of GHB of more than 30 g per day. The initial presentation can be mild but symptoms often increase over hours or days to delirium with prominent psychosis even after a benzodiazepine course has been commenced. Severity of withdrawal may be underestimated by patients minimising dose and frequency of ingestion.

Withdrawal associated with less regular usage has been managed as an outpatient with a reducing benzodiazepine course in moderate doses (see Fig. 1). The benzodiazepine dose required to control severe GHB withdrawal varies considerably and very high doses may be required. The equivalent of over 300 mg/24 h of diazepam has been used in ICU settings (Craig et al., 2000). The barbiturate pentobarbital has been effective in cases of benzodiazepine resistance and should be considered when symptoms persist despite high dose benzodiazepine administration such as patients not responding to 150 mg or more of diazepam over 24 h. Although antipsychotic medications have been used in delirium/psychosis cases, they do not appear necessary (or sufficient) to manage GHB withdrawal. They have the theoretical drawback of lowering the seizure threshold, although no withdrawal seizures have been reported to date. Other agents such as anticonvulsants have an uncertain role in the management of GHB withdrawal and will need further evaluation. Symptomatic and supportive care in addition to sedation is required in a medical setting to prevent injury, hyperthermia and rhabdomyolysis.

5. Conclusions

The management of GHB withdrawal requires more study with prospective hypothesis driven trials of potentially effective agents. Apart from the agents mentioned, it has been suggested that propofol, sodium valproate and baclofen may have a role in resistant cases but with little evidence (Dyer et al., 2001). Currently, effective and safe management hinges on detecting and vigorously managing cases at risk of severe withdrawal, characterised by psychosis and delirium.

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