Trends in GHB-related harms based on ambulance attendances from 2012-2018 in Victoria, Australia

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Declarations of competing interest

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Abstract (218 words)

Background and aims: Although the prevalence of gamma- hydroxybutyrate (GHB) use is relatively low globally, harms related to the drug appear to be increasing. Few existing studies present reliable, representative, population-level data on GHB-related harms. The aim of this study was to investigate trends in acute GHB-related harms within an ambulance database in Australia.

Design, setting and participants: Cross-sectional, retrospective analysis of data on all GHB-related ambulance attendances in the state of Victoria, Australia over a seven-year period (January 2012 – December 2018)

Measurements: Presentations were characterised based on patient demographics, transport to hospital, co-occurring substance use (i.e. GHB only, alcohol, methamphetamine, heroin, benzodiazepine, and cannabis), and clinical presentation (e.g. symptoms of anxiety, psychosis, depression).

Findings: There were 5,866 GHB-related ambulance attendances between 2012-2018, with prevalence rate increasing from 8.8 per 100,000 population in 2012 to a maximum of 21.7 per 100,000 population in 2017. Methamphetamine (OR 6.23, $p<0.001$) and benzodiazepine-related (OR 1.43, $p<0.001$) co-occurrences; ages between 18-29 (OR 6.58, $p<0.001$) and 30-39 (OR 2.02, $p<0.001$); and male gender (OR 1.23, $p<0.001$) were significant predictors of GHB-related attendances.

Conclusions: There has been a 147% increase in the prevalence of gamma- hydroxybutyrate (GHB)-related ambulance attendances in Victoria, Australia between 2012 and 2019, largely attributable to a growth in the proportions of people using GHB alone or concurrently with methamphetamine.

1. Introduction

Gamma-hydroxybutyrate (GHB) has typically been considered a 'party drug', used predominantly in recreational, festival and chemsex settings. However, research worldwide suggests a rise in GHB use and related harms, including increases in overdose fatalities (1). Accidental overdose can easily occur, because there is a narrow window between the dose required for recreational or euphoric effects (e.g. 100mg/L) versus lethal respiratory depression (500mg/L), with significant intra-individual variation in dose effects (2, 3). Fatalities can also arise with repeated dosing or combining the use of GHB with other CNS depressants, most commonly alcohol (3).

Global reports of increases in GHB-related harms may be attributable to a change in patterns of use, and co-ingestion with other drugs. Some authors suggest GHB is "seeping out", with more widespread use beyond previous discrete population groups or subcultures, recreational and chemsex settings, with changing patterns of polydrug use (4). Hockenhull and colleagues recently reported a 119% increase in GHB-associated deaths between 2014 to 2015 in London, a disproportionate increase in comparison to other drugs such as cocaine (25% increase) and MDMA (10% decrease) (2). They suggested that rising use of GHB within chemsex settings could be responsible and found that 72% of GHB-related fatalities also tested positive for stimulants (67% crystal methamphetamine or mephedrone). Case reports from other countries have also suggested growing use of stimulants (amphetamine, methamphetamine, mephedrone) concurrently with GHB (5, 6).

However, finding valid and reliable data on patterns of GHB use and harms is challenging, in part due to the relatively low overall prevalence of use in most countries (e.g. only 0.1% of Australians report GHB use in the previous 12 months (7)), which may make it difficult to identify and track patterns in large population-level surveys. Additionally, there are no

specific ICD-10 codes for GHB as it is included with other narcotics and hallucinogens, and therefore, drug-specific trends in morbidity or mortality data are not available (8). In Australia, previous data collection has relied on self-reported information from sentinel populations, including 'recreational' or 'party drug' cohorts (e.g. (9-11)), but these data may not be representative of use and related harms across the community.

An alternative and more representative method of characterizing acute drug-related harms is by examining data from acute health services, such as ambulance attendances. Paramedic recorded patient care records are a rich source of information of health conditions but use of these data is limited because they are unstructured, textual data. However, our specifically coded ambulance dataset (Ambo Project (12)), offers a unique opportunity to investigate GHB harms in greater detail, as the individual patient care records are coded, to provide valid and reliable identification of drug-related presentations and harms. These data can also identify use of other substances that co-occur with GHB, which is not possible with other datasets.

Accordingly, the aims of this paper were to analyse GHB-related ambulance attendances in order to identify and characterize patterns of acute harms relating to GHB, and co-occurrence with other substances; and to identify differences between attendances relating to GHB and those with other AOD substances.

2. Methods

2.1 Ambo Project

Data on GHB-related ambulance attendances were derived from the Ambo Project, an internationally unique surveillance system (12). The Ambo Project quantifies alcohol and other drug-related harms in the Australian state of Victoria, which covers approximately 26% of Australia's population. The data collection and coding methods from the Ambo Project

have been previously described (12, 13) but are briefly outlined here. Clinical patient care records are provided to Turning Point from Ambulance Victoria (AV), from the AV Data Warehouse, which includes data from VACIS® (the electronic patient care record system), computer aided dispatch, and other sources. A dataset, filtered to identify those with involvement of alcohol, other drugs, or mental health symptomology, is provided to Turning Point. A purpose built, systematic and validated coding system is used to capture information held in the clinical records. Specialist, trained research assistants scrutinise each record and assign relevant codes. The core criterion used in determining the involvement of a drug or substance is: "Is it reasonable to attribute the immediate or recent (not merely chronic) over- or inappropriate ingestion of the substance or medication as significantly contributing to the reason for the Ambulance Victoria attendance?", as determined through examination of the clinical record.

2.2 Defining GHB-related ambulance attendances

This study included ambulance attendances in Victoria (1 January 2012 – 31 December 2018) in which GHB use was identified as a significant contributor to that attendance. These are then termed GHB-related ambulance attendances. The inclusion criteria specify that GHB use must significantly contribute to the attendance, however other drugs or substances may have also been over- or inappropriately consumed. The dataset does not record who called for the ambulance, i.e. whether it was the individual themselves, or a bystander or concerned other.

2.3 Demographics

For all GHB-related attendances, patient demographics of age groups (<18, 18-29, 30-39, 40-49, 50-59 and ⩾60 years of age), gender (male/female), socio-economic status using Socio-Economic Indexes for Areas (Index of Relative Socio-economic Disadvantage) SEIFA-IRSD on the basis of residential postcode, were analysed, as well as the location of the attendance,

and transport to hospital. The rationale for the separation between <18 and 18-29 was to identify those aged under 18, who would not have access to licensed venues and for whom alcohol consumption is illegal. Population rates were calculated using estimated resident population data from the Australian Bureau of Statistics.

2.4 Co-occurring substance use

The co-occurrence of other substances within GHB-related attendances was first analysed on the basis of single substances, acknowledging that multiple substances can be ingested within a single attendance. Attendances where the person consumed alcohol, but the paramedic notes did not clearly indicate alcohol intoxication were coded as 'alcohol involved'. The coding rules are conservative, and the default code is for 'alcohol involved' unless there is clear evidence of alcohol intoxication.

Coding for amphetamines differs on the basis of substance information provided to the paramedics. "Speed", "meth", or "ice" are all coded under the broader category of 'amphetamines', and a further sub-category is provided for crystal methamphetamine, but this is only used when it is clearly specified that the drug was in solid form (i.e. "ice"). There is no sub-category for methamphetamine within amphetamines, however, because in Australia, the predominant amphetamine available is methamphetamine (14), this study describes the co-use of methamphetamine (of which crystal methamphetamine will be a component).

As preliminary examination of the data showed that alcohol and methamphetamine were the most common co-occurring substances, trends were further analysed on the basis of groups of GHB only; GHB with alcohol involved; GHB with methamphetamine involved, and GHB with both alcohol and methamphetamine involved. For analysis of alcohol, all presentations

with alcohol involvement were included, as any level of alcohol consumption could be considered to have an impact on GHB-related harms and presentations.

2.5 Clinical presentation

Clinical characteristics, and symptoms of anxiety, psychosis or depression are documented in the clinical patient care records of paramedics and based on observation of symptoms (i.e. not a clinical diagnosis).

2.6 Statistical analysis

Descriptive analysis was used to identify trends of GHB-related ambulance attendances and concurrence with other AOD-related cases. Relationships among GHB, concurrences and the explanatory variables were further examined in multivariate logistic regression analyses. In order to adjust the trends for population change over time, the rates of attendances have been calculated using estimated resident population provided by the Australian Bureau of Statistics for each year of data presented. Due to paramedic industrial action from Oct-Dec 2014, data were not collected for this period. Because our statistical tests did not take into account any time component and the estimated percentage of missingness was less than 2.8% without any expected distorting effect on the pattern of variables of interest, there was no statistical compensation for missing data. Statistical analysis was conducted in Stata/MP 15.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). This project was approved by the Eastern Health Human Research Ethics Committee.

3. Results

There were 5,866 GHB-related ambulance attendances in Victoria, Australia between 1 Jan 2012 and 31 December 2018. Table 1 shows the descriptive statistics and trends of variables

of interest over time in absolute and relative numbers. Prevalence of GHB-related attendances increased from 8.8% at 2012 to a maximum of 27.7% in 2017, an increase of 147%. A decrease in the prevalence rate to 14.2% was recorded in 2018. The mean age of individuals with GHB attendances was 26.0 years increasing slightly in recent years to 27.5 in 2018. The proportion of male gender and transport to hospital attendances remained consistent across time (60.2% and 84.2% respectively).

Table1 describes co-occurring substances within GHB-related attendances, and reports the number and proportion of attendances in each group. GHB only-related attendances followed an increasing trend over the study period; in spite of the decrease of total cases in 2018, the proportion of GHB only related-attendances was the highest in this year (30.3%). When other substances were co-occurring, methamphetamine and alcohol were the two most common substances. The relative rate of GHB with co-occurring alcohol involvement, heroin and cannabis remained constant over the study period with an average rate of 23.0%, 1.9% and 4.2% respectively. In contrast, GHB with co-occurring methamphetamine use increased over the study period from 24.7% in 2012 to 33.9% in 2018. Co-occurrence with benzodiazepines varied with a maximum of 8.3% in 2012 and a minimum of 4.4% in 2015.

The results of multivariate logistic regression are presented in Table 2. The co-occurrence with methamphetamine had a higher odds ratio (OR=6.23, $p < 0.001$) than other co-occurrences, followed by benzodiazepines (OR=1.43, $p < 0.001$). Age group significantly predicted GHB-related attendances. The 18-29 and 30-39 age groups had 6.58 and 2.02 times higher risk ($p<0.001$) respectively than those aged less than 18 years old. Males had higher likelihood of a GHB-related ambulance attendance than females, with an OR of 1.23 ($p<0.001$). The Co-occurrence with alcohol, heroin, cannabis, having history of a mental health disorder and those older than 40 years of age were associated with decreased

likelihood of a GHB-related attendance. Socioeconomic status did not show a strong relationship with GHB-related attendances.

The clinical presentations of GHB-related attendances in the context of co-occurring substance use are shown in Table 3. Those who used GHB with methamphetamine were more likely to present with symptoms of psychosis or anxiety than those who used GHB alone or with alcohol.

4. Discussion

In summary, our analysis of ambulance attendances in Victoria over the period 2012-2018 suggests that GHB-related acute harms are rising, with a 147% increase in prevalence rates , totalling 5,866 attendances over the seven-year study period. This increase in acute presentations is largely attributable to a growth in the proportions of people using GHB alone or GHB with methamphetamine, whereas the rates of GHB use with alcohol has declined over the study period. This finding in a representative Australian sample is consistent with emerging evidence from case reports and coroner's data internationally (2), raising important implications for frontline clinicians, drug treatment and harm reduction services.

The trend of GHB and methamphetamine co-consumption may be driven by a number of factors. Pharmacologically, GHB is a central nervous system (CNS) depressant (15) and use can result in respiratory depression and lowered conscious state (15). Individuals using GHB may seek to prolong periods of euphoria by countering sedation with stimulants such as methamphetamine (6). Conversely, individuals who use methamphetamine in a regular or dependent manner may aim to use the sedative effects of GHB to manage stimulant withdrawal symptoms (16, 17). The latter is potentially the most likely driver, given the growing proportion of dependent methamphetamine-using adults in the Australian population over the time period in this study (18) and mirrored in other markers of acute health burden such as ambulance (19), emergency and psychiatric inpatient presentations (20). For instance, data from the Ambo Project suggest that methamphetamine-related ambulance attendances in Victoria increased significantly over the 2012-2018 time period, from 872 in 2012 to 3024 in 2018. Additionally, this is consistent with a recent Australian audit of GHB withdrawal management, which found that 100% of those experiencing GHB withdrawal within a residential withdrawal unit also used stimulants such as methamphetamine (21).

Importantly, individuals who use GHB in combination with stimulants may take greater risks and utilize fewer harm reduction strategies, contributing to greater harms in comparison to other polydrug-using cohorts. Recent evidence from a study of 1400 polysubstance-using festival attendees suggests that people who identified past-year GHB use were less likely to avoid mixing stimulant drugs, or to reduce relative amounts when mixing multiple drugs, when compared with those who did not use GHB (22).

Our findings contrast with Australian data from both national and sentinel population surveys that suggest the prevalence of GHB use is static or declining. For instance, 0.1% of respondents from the Australian 2016 National Drug Strategy Household survey reported past 12-month GHB use, unchanged from the 2013 and 2010 survey data (7). Data from sentinel populations of 'recreational' drug users in the Ecstasy and related Drugs Reporting System (EDRS), found a static proportion of Victorian participants (between 9-14%) who reported recent use of GHB (past six months) over the period investigated in our study (14). Other jurisdictions report similar findings, with stable prevalence of recent use in respondents over the past six years in NSW (11-12%), SA (5-9%), NT (2-4%), WA (1-4%) or Tasmania (0-1%) (23-27). In terms of harms, our data is consistent with international literature pointing to rising GHB-related harms in the UK (2) and Europe (28).

Our findings suggest important differences in the characteristics of individuals presenting with GHB-related harms when compared with previous studies. A similar study using this dataset in 2008 identified the majority of attendances in people aged under 25 years, used GHB alone (58.5%) rather than in combination with other substances (29). Our data suggest a shift to older individuals using the drug in combination with other substances (57.2%), with overall declines in alcohol co-consumption and increase in methamphetamine co-consumption. This is consistent with a potential change in the pattern and context of GHB use

and could explain the differences between our data and that identified by other Australian sources.

The majority of Australian data on GHB to date has been derived from surveys conducted in such sub-populations, with convenience samples of recreational MDMA-using adults. It has previously been argued that such datasets present an opportunity to monitor trends in emerging harms related to GHB and shifts in characteristics of users and patterns of use (30). However, our data highlights the limitations of focussing on trends in drug prevalence and related harms within a single sentinel population, with a risk of missing changes in harms when patterns of use change to include other previously unidentified sub-cultures. The data presented here are derived from a database of all state-wide ambulance attendances related to alcohol and other drugs and/or mental health and therefore present a representative picture of pre-hospital harms.

Importantly, acute presentations of methamphetamine with GHB are characterised by a picture of psychiatric (anxiety, psychosis) symptoms, markedly different from the pattern observed in people using GHB alone or in conjunction with alcohol, where sedation and lowered conscious state are the presenting risk (15). This has clinical implications for paramedics who are responding to calls to attend to a GHB overdose, and for acute management of these patients within emergency department settings.

Finally, the trends observed in this dataset highlight the need for further research into acute harms associated with concurrent use of GHB and methamphetamine to identify other dependent, treatment-seeking populations that may warrant adapted models of care.

This study has a number of limitations. The results reflect the Victorian population, which represents approximately 26% of Australia's population, but may not be reliably extrapolated to populations that vary significantly from that of Victoria. Ambulance data may not include

all harms arising from GHB use, only acute events requiring medical intervention. Further, the coding of data is reliant on what is recorded in the paramedic clinical records, with the identification of substances based on paramedics' clinical acumen and observations, and information provided by the patient and others at the scene, not toxicological testing. The data does not include presentations where GHB use was unknown or unintentional and therefore may under-report GHB-related attendances. Despite these limitations, ambulance attendance data provide a robust and well-validated means to identify emerging trends in drug-related harms.

In conclusion, we found that GHB-related ambulance attendances in Victoria, Australia have been rising over the last seven years, particularly due to increasing trends towards GHB and methamphetamine co-use. Our results highlight the need for new approaches to harm reduction and treatment strategies for this group.

Table 1: Characteristics of GHB-related ambulances attendances in Victoria

	2012	2013	2014*	2015	2016	2017	2018	Total
Attendances (n)	493	754	431	895	1,148	1,339	928	5,866
Prevalence per 100,000 population	8.8	13.2	7.4	14.8	18.6	21.7	14.2	-
Mean age (SE)	26.4 (8.3)	24.6 (6.5)	25.4 (7.0)	24.6 (6.6)	26.6 (7.6)	26.3 (7.5)	27.5 (7.6)	26.0 (7.4)
Male (percentage)	126 (59.4%)	301 (61.1%)	443 (58.8%)	532 (59.5%)	696 (60.6%)	828 (61.7%)	567 (61.8%)	3,303 (60.2%)
Transport to hospital	410 (83.2%)	643 (85.3%)	361 (83.8%)	768 (85.8%)	960 (83.6%)	1,123 (83.7%)	774 (83.4)	5,040 (84.2%)
GHB only† (% total GHB attendances)	99 (20.1%)	179 (23.7%)	106 (25.0%)	240 (26.8%)	322 (28.1%)	363 (27.1%)	281 (30.3%)	1,590 (27.1%)
Concurrence with Alcohol (% total GHB attendances)	135 (27.4%)	166 (22.0%)	101 (23.4%)	194 (21.7%)	253 (22.0%)	304 (22.7%)	195 (21.0%)	1,346 (23.0%)
Concurrence with Meth/amphetamine (% total GHB attendances)	122 (24.7%)	219 (29.0%)	114 (26.5%)	272 (30.4%)	363 (31.6%)	370 (27.6%)	315 (33.9%)	1,770 (30.2%)
Concurrence with Heroin (% total GHB attendances)	11 (2.2%)	7 (1.0%)	9 (2.1%)	13 (1.5%)	25 (2.2%)	24 (1.8%)	21 (2.3%)	110 (1.9%)
Concurrence with Benzodiazepine (% total GHB attendances)	41 (8.3%)	43 (5.7%)	15 (3.5%)	39 (4.4%)	55 (4.8%)	66 (4.8%)	60 (6.5%)	319 (5.4%)
Concurrence with Cannabis (% total GHB attendances)	18 (3.7%)	19 (2.5%)	21 (4.9%)	37 (4.1%)	55 (4.8%)	53 (4.0%)	41 (4.4%)	244 (4.2%)

GHB: Gamma-hydroxybutyrate,
*2014 data do not include October, November and December attendances due to unavailability of records
Based on residential address of people involved
†GHB only attendances excluding alcohol, illicit drug or other substance-involved presentations

Table 2: Predictors of GHB-related ambulance attendances

Predictive variable	Odds ratio	95%CI	P-value
Age			
<18	-	-	-
18-29	6.58	5.25 – 8.25	<0.001
30-39	2.02	1.59 – 2.58	<0.001
40-49	0.67	0.50 – 0.90	0.007
>50	0.09	0.06 – 0.13	<0.001
Gender, male	1.23	1.13 – 1.34	<0.001
Socioeconomic status	1.004	1.0031-1.0043	<0.001
Alcohol involved	0.34	0.31 – 0.38	<0.001
Meth/amphetamine involved	6.23	5.67 – 6.85	<0.001
Heroin involved	0.27	0.20 – 0.38	<0.001
Benzodiazepine involved	1.43	1.20 – 1.70	<0.001
Cannabis involved	0.53	0.43 – 0.65	<0.001
History of mental health disorder	0.19	0.17 - 0.21	<0.0001

Table 3: Clinical presentations of GHB-related ambulance attendances by concurrent substance use

Clinical Symptoms		GHB only		GHB + alcohol		GHB + MA		GHB + alcohol + MA		χ2	p value
		n	%	n	%	n	%	n	%		
Total		2,543		1,045		1,469		301			
Symptoms of anxiety	Not stated	2,516	98.9	1,029	98.5	1,383	94.2	292	97.0	90.90	<0.001
	Present	27	1.1	16	1.5	86	5.8	9	3.0		
Symptoms of psychosis	Not stated	2,523	99.2	1,033	98.9	1,389	94.5	292	97.0	97.03	<0.001
	Present	21	0.8	12	1.1	80	5.5	9	3.0		
Symptoms of depression	Not stated	2,529	99. 5	1,034	98.9	1,457	99.2	296	98.3	5.75	0.124
	Present	14	0.5	11	1.1	12	0.8	5	1.7		

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