SYSTEMATIC REVIEW ARTICLE

Cognitive Impairment Following Clinical or Recreational Use of Gamma-hydroxybutyric Acid (GHB): A Systematic Review

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Abstract: *Background*: GHB (gamma-hydroxybutyric acid; sodium oxybate) is a general anaesthetic that is clinically used for the treatment of narcolepsy, cataplexy, alcohol withdrawal and alcohol relapse prevention. In addition, GHB is recreationally used. Most clinical and recreational users regard GHB as an innocent drug devoid of adverse effects, despite its high dependence potential and possible neurotoxic effects. At high doses, GHB may lead to a comatose state. This paper systematically reviews possible cognitive impairments due to clinical and recreational GHB use.

Methods: PubMed and PsychINFO were searched for literature data about the acute and residual cognitive deficits following GHB use. This review is conducted using the PRISMA protocol.

Results: A total of 43 reports covering human and animal data on GHB-induced cognitive impairments were eligible and reviewed. This systematic review found no indication for cognitive impairments after clinical GHB use. However, it supports the view that moderate GHB use may result in acute short-term cognitive impairments, whereas regular high-dose GHB use and/or multiple GHB-induced comas are probably neurotoxic resulting in long-term residual cognitive impairments.

Conclusion: These results emphasize the need for awareness among clinicians and recreational users to minimize negative health consequences of recreational GHB use, particularly when high doses are used and GHB-induced comas occur.

Keywords: GHB, Xyrem, illicit drugs, sodium oxybate, anaesthetic, neurotoxicity, cognition, memory.

1. INTRODUCTION

Gamma-hydroxybutyric acid (GHB) was developed in the early 1960s and was first used clinically as a general anaesthetic (Somsanit®). While still being used in some countries (*e.g.* France, Germany), its role as an anaesthetic has been vastly reduced [1] because it does not induce complete anaesthesia [2] and its duration of action is unpredictable [3]. Since the 1970's, GHB is used for the treatment of narcolepsy and cataplexy at daily doses of 4.5-9 g administered in two equally divided doses to normalize sleep patterns [4, 5]. GHB has also been used for the treatment of opioid and alcohol withdrawal and for relapse prevention in alcohol dependent patients [6-9], but awaits registration for these indications since a previous marketing application for the treatment of alcohol use disorder with Alcover®/Hopveus® was

not granted by the European Medicines Agency (EMA) [10]. Finally, GHB (Xyrem®) is used in the treatment of (serious) withdrawal syndromes in GHB dependent patients [11-13].

Since the 1990s, GHB is also used as a party drug. The primary aim is to go "swing" in dance/disco settings or to "chill out" in the home setting with friends (sometimes with sexual intentions) [7, 14]. Data about the prevalence of recreational GHB use is limited. In 2018, lifetime GHB use in the U.S. was around 0.6% [15]. In Europe, lifetime GHB use was 1% among ESPAD students with somewhat higher prevalence rates in Austria, Italy, Germany, Denmark and the Netherlands (around 2%) [16]. The most recent figure available from the UK was a last year use prevalence of 0.1% in adults aged 16-59 yrs. [17]. In Europe, current GHB-use seems generally low and limited to geographical areas and specific subpopulations [18-21]. One of those specific subpopulations is men who have sex with men (MSM) who use GHB as one of their preferred drugs during sex ('chemsex') [22-24]. In the United Kingdom, the increase in GHB-induced accidents and fatalities was mainly ascribed to

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its increased use by the gay community in London [25, 26]. For a comprehensive review about pharmacology, toxicology and context of use see Busardò and Jones [27].

Common doses for recreational GHB use range between 1 and 5 g per day (15-75 mg/kg) [28]. Generally, a dose of 0.5 g induces relaxation and disinhibition, 1 g elicits euphoric effects, and 2-3 g leads to a deep sleep [29]. However, tolerant users consume on average 4-5 g GHB daily [30].

Despite its relatively low user prevalence rate, it is important to highlight the potential adverse effects of GHB. GHB has a very high dependence potential and a narrow safety margin, causing disproportionally high intoxications and health incidents compared to other more frequently used recreational drugs. Surprisingly, recreational GHB users generally consider GHB as a cheap and harmless psychotropic drug and they are usually not aware of the potential adverse effect of 'passing out', a condition where the user is unconscious/comatose for several hours. Recreational GHB-users pass out, because GHB has a narrow safety margin: in non-habituated persons, an acute dose of 2-3 g GHB induces impaired consciousness or respiratory depression [29, 31], which resembles the usual daily therapeutic and recreational dose [14, 32]. In various surveys, more than half of the recreational GHB users reported some degree of unintentional loss of consciousness due to GHB [32-34]. GHB-induced coma is frequently observed at "rave parties" and dance festivals and in patients attending emergency departments [35].

Regular GHB use may cause severe dependence and serious withdrawal symptoms upon abrupt discontinuation of chronic, frequent use [36-38]. Prevalence of physical dependence in recreational GHB users ranges from 4-21%, with higher rates in heavy users [33, 39-41]. Upon drug discontinuation, moderate GHB users will usually experience a mild withdrawal syndrome, but withdrawal can be more severe in chronic and heavy users of GHB and can be much more serious than previously assumed [42, 43]. Data about GHB related treatment demand is scarce; in the Netherlands, 1.4% of all current GHB users were in treatment for a primary GHB use disorder in 2015 [44].

As illustrated in Fig. (**1**), GHB is released endogenously from presynaptic neurons and binds to GHB receptors, which are primarily located in the hippocampus, the caudate nucleus, and the frontal cortex [37, 45]. Low physiological concentrations of GHB cause a decrease in dopamine in the striatum and cortex [46] and the endogenous role of GHB has been suggested to maintain physiological states, like sleep [31]. However, at high (exogenously induced) concentrations of GHB, the mesocorticolimbic dopamine pathway is activated by binding of GHB to GABA-B receptors, especially in the GABAergic neurons in the Ventral Tegmental Area (VTA) [46, 47], causing a decrease in GABA release and an increase in dopamine release in this area. This mechanism of disinhibition of dopamine is largely responsible for the addiction potential of GHB. In chronic GHB abuse, the dopaminergic neurons that express GABA-B receptors become downregulated, thereby causing both a dysfunctional dopaminergic and GABAergic system [48]. This will presumably also lead to deficits in cognitive functioning, as the mesocorticolimbic system is closely intertwined with the hippocampus.

GHB-induced comas resemble the state of general anaesthesia. In this respect, it is of interest that the clinical use of general anaesthesia has been associated with a cognitive disorder, called POCD (Post-Operative Cognitive Dysfunction). POCD remains a poorly understood syndrome [49], characterized by impairments of memory and concentration and a reduced capacity to handle information [50-52]. Importantly,
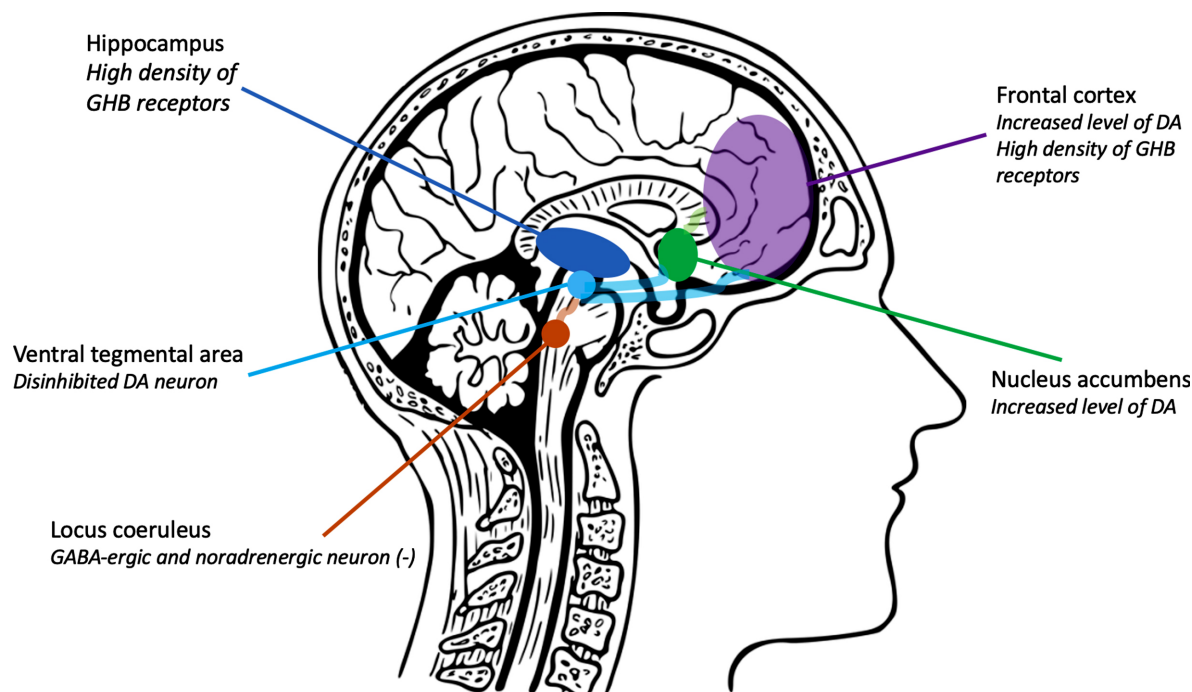
Fig. (1). Topographical overview of the GHB targets in the brain and its effects on the dopaminergic system. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

POCD may appear after surgery under general anaesthesia, but independently of the anaesthetic drug [53] and the type of anaesthesia (general or spinal) [54]. Remarkably, most frequent GHB-users were not concerned about potential neurocognitive impairments induced by GHB-intoxication and/or GHB-induced comas [33, 55]. The risk of neurotoxicity, including cognitive impairment, associated with GHB use and GHB-induced coma has been previously reviewed [56-58]. The aim of the current study is to present an updated systematic review about cognition impairments in recreational GHB users, including acute cognitive effects of lower doses of GHB and sustained cognitive effects of higher doses of GHB and GHB-induced comas.

2. METHODS

2.1. Approach

This review is conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA) [59] to assist in data retrieval, with subsequent data charting into three key themes: 1) cognitive impairment due to GHB use in animals and 2) in humans, and 3) cognitive impairment following GHB-induced comas.

PsycINFO, PubMed and Google Scholar were systematically searched for eligible reports up to August 2020. To identify relevant articles, we used a combination of search terms pertaining to i) GHB and synonyms ii) cognitive impairment, incl. learning behaviour and memory, and iii) GHB-induced unconsciousness *i.e.* coma. In addition, the reference lists of included studies were searched manually for relevant publications. The applied search string and the PRISMA checklist are presented in the Supplementary material.

2.2. Eligibility Criteria

Studies describing the effect of or the association between GHB use and cognitive impairment were considered for inclusion if they were reported full text in either Dutch, English, German or French. Human studies with a small
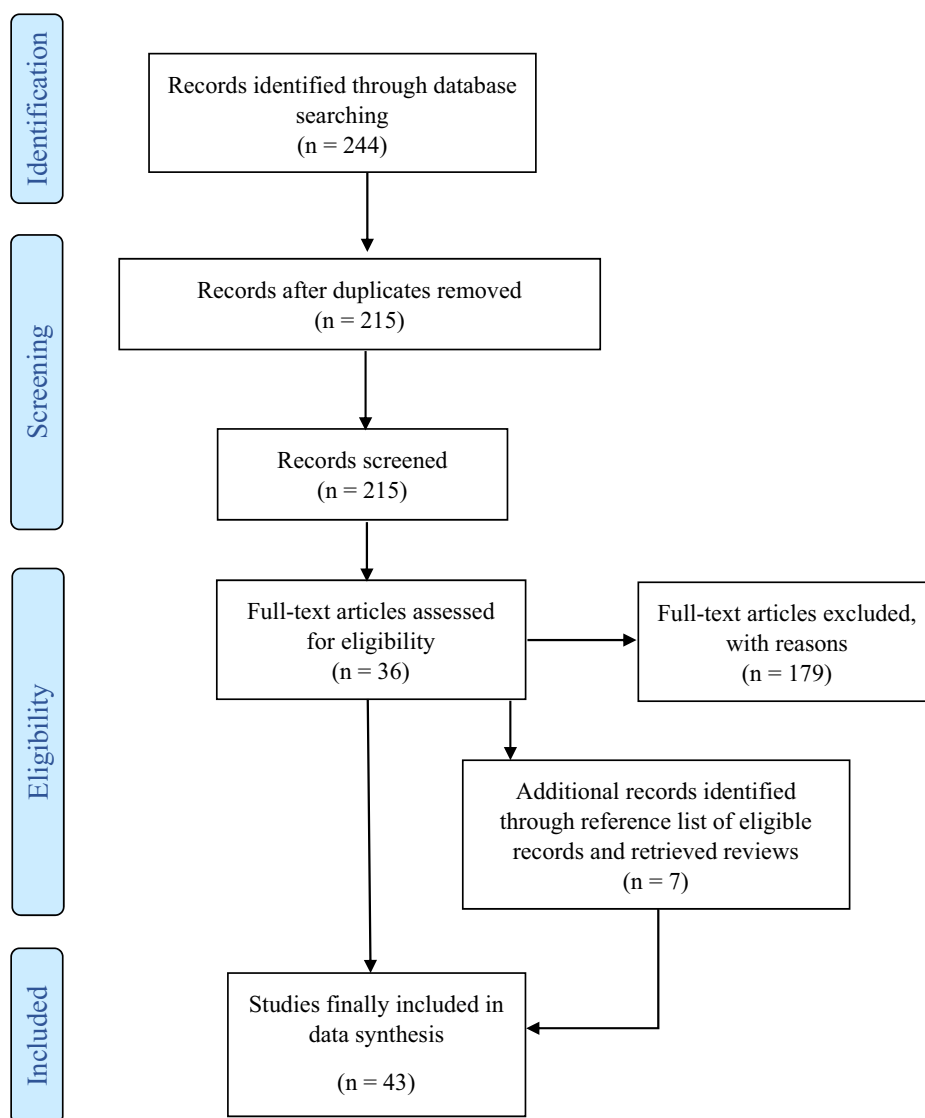
Fig. (2). PRISMA flow diagram. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

sample size (< 8) were excluded. Further exclusion criteria: reviews, non-controlled studies, comments, and case reports.

2.3. Study Selection

Two researchers (JvA and TB) were involved in the selection of appropriate reports, which were executed in two rounds. Initially, 244 studies were retrieved, of which 215 unique reports remained after the removal of duplicates. These 215 reports were further processed *i.e.* the title and abstract were screened to determine eligibility applying the inclusion and exclusion criteria mentioned above. In a second round, the reference list of the selected 36 studies and the reviews retrieved *via* the search were screened for additional relevant publications (JvA and TB). In total, 43 papers were finally included. Fig. (**2**) shows the PRISMA diagram of the identification, screening, and inclusion of the reports.

3. RESULTS

There were 24 animal studies, 14 human studies on the acute effects of GHB use, and 5 studies on the sustained effects of GHB use and GHB-induced comas.

3.1. Animal Studies

Several studies show acute effects of GHB on cognitive functioning in animals [60-65]. Studies demonstrate residual and long-lasting impairments in memory, spatial learning and social behaviour in rats after GHB administration [64, 66, 67]. Furthermore, repeated GHB administration induced working memory and spatial memory impairments and neuronal damage (cell loss) in the prefrontal cortex and hippocampus in rats [63]. One study has shown that the disrupting effects of low dose GHB (100 mg/kg, intraperitoneally) on

Table 1. **Neurocognitive effects and damage of GHB in animal studies.**

No.	N [*]	Dose (mg/kg) [1]	Species	Outcome	Refs.
1	12	10, 50, 100	Rat	Impairment of memory tasks	[60]
2	11 [2]	100	Rat	Impairment of memory and learning tasks	[61]
3	8 [2]	100-300	Rat	Impairment of memory tasks	[62]
4	7	10, 100	Rat	Impairment in spatial and working memory and neurological damage, reversal by GHB receptor antagonist	[63]
5	-	100	Rat	Impairment of memory	[64]
6	12-17	100	Rat	Impairment in fear memory, reversal by GHB receptor antagonist	[65]
7	12	500	Rat	Behavioural sedation, impairment of residual memory and social interaction	[66]
8	12	50, 300 p.o.	Rat	Impairment of memory and altered $GABA_B$ receptor expression	[67]
9	16	0.5 - 10 s.c.	Chicken	Impairment in memory, reversal by $GABA_B$ receptor antagonist	[68]
10	12	1000	Rat	Impairment in motor performance, reversal by $GABA_B$ receptor antagonist	[69]
11	6	1000	Rat	Behavioural sedation, reversal by $GABA_B$ antagonist	[70]
12	-	100	Rat	Impairment of memory and altered NMDA receptor expression	[71]
13	6	500 nM, 1 mM	Rat	Reduction of glutamate levels	[72]
14	5	-	Mouse	Neurological deficits, reversal by $GABA_B$ receptor antagonist	[73]
15	12	50, 300 p.o.	Rat	Downregulation of gene expression in prefrontal cortex and hippocampus of genes involved in cognition and memory	[74]
16	-	1000	Rat	Altered gene expression in hippocampus and prefrontal cortex	[75]
17	-	10	Rat	Decrease in antioxidant enzymes	[77]
18	5	500	Mouse	Altered gene expression	[78]
19	12	500	Rat	Altered protein expression, involved in neuroplasticity and neuroprotection	[79]
20	12	100, 300	Rat	Limits effects of ischaemic induced stroke	[80]
21	10	300	Rat	Reduction of ischaemic effects	[81]
22	7	100	Mouse	Recovery neurological effects after ischaemic stroke	[82]
23	6	100 to 500	Rat	Dose-dependent reduction of mobility, but not working memory	[83]
24	3	125, 250 mg/kg	Monkey	Somnolence and altered reaction, no effect on working memory	[84]

*per group; [1]i.p. if not mentioned otherwise; [2]in total; i.p. = intraperitoneal; p.o. = per os; s.c. = subcutaneous.

fear memory, an indicator for retrograde amnesia, in rats were mediated through the GHB receptor by reversing these effects with a GHB receptor antagonist [65]. Other studies indicate other receptors to be involved in the neurocognitive deficits induced by GHB. Foremost, the $GABA_B$ receptor was proposed as the receptor responsible for GHB's negative effects on memory and learning [67], as $GABA_B$ receptor antagonist reversed the effects rather than specific GHB receptor antagonists [68, 69]. Van Nieuwenhuijzen *et al*. [70] demonstrated that GHB-induced sedation in rats was independent of both GHB and $GABA_B$ receptors, possibly pointing towards other receptor mechanisms involved. In fact, one study has shown a decrease in glutamatergic NMDA receptors in the frontal areas of rats after repeated GHB administration, possibly explaining GHB-induced deficits in learning and memory [71]. In addition, GHB-induced cytotoxicity of neurons was suggested to be mediated by glutamate release, most likely *via* the $GABA_B$ receptor [72, 73].

GHB downregulates gene expression of genes involved in cognitive functioning that are expressed in brain areas, including the hippocampus, frontal cortex and caudate-putamen [74]. Furthermore, gene expression involved in oxidative stress and synaptic plasticity in the adult rat hippocampus and prefrontal cortex was altered by GHB administration [75, 76], confirming earlier findings that GHB induces oxidative stress [77]. Long lasting gene expression in the hippocampus and prefrontal cortex of adult mice was also modified after GHB administration, particularly genes that are involved in oxidative stress, learning and memory [78]. These findings suggest that GHB caused neuronal damage and cognitive deficits by changing gene expression. This is supported by the fact that proteins involved in neuroprotection against oxidative stress are downregulated and proteins involved in apoptosis are upregulated by GHB [79]. In contrast, other studies indicate a neuroprotective effect of GHB in ischaemia/hypoxia and excitotoxicity in the rodent brain [80-82]. In addition, acute doses of GHB do not seem to impair working memory or inhibition in rats and rhesus monkeys, respectively [83, 84]. Taken together, animal data until now suggests that GHB is detrimental for processes of cognition and memory and may cause oxidative stress and neuronal damage. An overview of GHB animal studies on brain and cognition is given in Table **1**.

3.2. Acute Effect of GHB on Cognition in Human Studies

The studies where patients with narcolepsy are treated with Xyrem® (4.5-9 g daily in two equally divided doses) indicate generally mild and reversible side effects, including nausea, headache, insomnia and dizziness [85]. Xyrem® post-marketing data mentioned impairment of attention and working memory at an unknown frequency, with a higher occurrence when combined with the use of valproic acid [86].

In a survey of 42 recreational GHB-users 13% and 45% of daily GHB users reported amnesia during and after GHB use, respectively [33]. In another study, anterograde amnesia, a form of memory loss or lack of awareness, was reported by all 51 regular GHB users [87]. In addition, 29% and 41% had ever experienced, within 1-4 hours after ingestion, impaired

memory or "passing out", respectively [87]. Anterograde amnesia was also reported by victims of sexual assault following malicious GHB-drugging [88-90]. Experimental studies that examined the acute effects of GHB on learning and memory are summarized in Table **2** [91-104]. In two small (n=8; n=12) cross-over studies, Abanades *et al*. showed that GHB (40-72 mg/kg) dose-dependently impaired the performance in the digit symbol substitution test; a test measuring general cognitive impairment related to (mild forms of) brain damage, dementia, and depression [91, 92]. In a doubled-blind, cross-over study with 14 volunteers with histories of drug abuse [94], GHB (2-18 g/70kg) caused dose-related memory impairment, but the effect was lower than after triazolam use (0.5-1 mg/70kg). In a subsequent study performed in human volunteers [95], administration of GHB (4.5 g/70kg; 65 mg/kg) produced less impairment of psychomotor, working memory, and episodic memory tasks than triazolam (0.1-0.5 mg/70kg), a drug known to produce robust anterograde amnesia [105]. Compared to alcohol dosed up to 120 g/70 kg (1.7 ‰), GHB dosed up to 10 g/70 kg (140 mg/kg) had less severe memory impairing effects and a shorter time course [96]. These studies collectively show that GHB induces memory impairment that was less severe than those induced by triazolam, pentobarbital or alcohol. In studies with low GHB doses, the acute cognitive effects of GHB were even milder. Modest cognitive impairment was observed by GHB at 10 mg/kg [98, 99] and at 15-30 mg/kg [101], whereas 20 mg/kg had no significant effects on basal cognitive functions [93] and 12.5-25 mg/kg GHB had no effect on attention, vigilance or psychomotor co-ordination [97]. It remains to be established whether the GHB-induced amnestic effects in humans are reversible or lead to persistent neurotoxic damage *i.e.* cognitive impairment.

3.3. Residual Cognitive Impairment Following GHB-Use and GHB-Induced Comas

Animal studies showed that moderate to high doses of GHB have been associated with residual and long-lasting cognitive alterations and changes in brain structures such as the hippocampus or the Pre-Frontal Cortex (PFC). Whether such alterations also occur in recreational GHB-users, particularly in those experiencing multiple GHB-induced comas have been recently investigated by Pereira *et al*. [55, 106-110]. For their investigations, they recruited 81 participants equally divided over three groups: (a) chronic users of high GHB doses (≥25 times in preceding two years) with multiple GHB-induced comas (≥4) with or without a GHB-use disorder (GHB-Coma group); (b) regular users of moderate GHB doses that never had a GHB-induced coma (GHB-NoComa group); and (c) a control group of mild polydrug users who never used GHB, since polysubstance use is a common habit among GHB users (No-GHB group). Cognitive performance was assessed by neuropsychological tests, structural magnetic resonance imaging (sMRI, DTI), task-based functional MRI (fMRI), and resting state fMRI (rsfMRI).

Pereira *et al*. found that heavy GHB-users who had multiple GHB-induced comas (*i.e.* GHB-Coma group) perform worst on verbal memory and self-reported higher levels of anxiety, stress, depression, and impulsivity [55, 106, 108]. Moreover, in fMRI studies using episodic memory, working memory, and emotion processing tasks, the GHB-Coma

Table 2.   Acute effects of GHB on cognition in human studies.

Nr.	N	Dose	Outcome	Refs.
1	8	40-72 mg/kg	Impaired performance (digit symbol substitution test)	[91]
2	12	40 and 60 mg/kg	Impaired performance (digit symbol substitution test)	[92]
3	16	20mg/kg	Positive effect on social and non-social cognition, but no effect on basal cognitive functions, like visual working memory, delayed verbal recall and reaction time	[93]
4	14	2-18 g/70kg	Impaired memory	[94]
5	15	4.5 g/70kg	Impairment of psychomotor, working memory, and episodic memory tasks	[95]
6	15	20 and 35 mg/kg	Reduced performance but increased conflict monitoring	[96]
7	12	12.5-25 mg/kg	No effect on attention, vigilance, or psychomotor co-ordination	[97]
8	10	10 mg/kg	Impaired visual temporal processing (critical nicker frequency)	[98]
9	10	10 mg/kg	Impaired short-term memory (digit retention test)	[99]
10	14	1.0-10 g/70kg	Except for word recall, GHB significantly decreased all measures of cognitive performance	[100]
11	12	1.0 to 2.0 g/70kg	No effect on coordinative skills, and critical flicker fusion frequency	[101]
12	49	2.5g/70kg	No effect on perceptual learning, motor learning, and verbal memory	[102]
13	24	2.25 g/70kg	Deleterious effect on Choice reaction time, Critical tracking test, Digit vigilance, Numeric working memory, but not spatial working memory	[103]
14	13	30 mg/kg	No effect on psychomotor performance and subjective alertness, or memory consolidation	[104]

group showed a compromised capacity to interpret and encode new memories, reduced focus, and problems in interpreting negative emotions compared to the other two groups [106-108]. Furthermore, lower functional connectivity between the left hippocampus and the amygdala was also associated with the effect of moderate doses of GHB without GHB-induced comas (*i.e.* GHB-NoComa group) [106]. However, in contrast with the demanding cognitive processes stated above, brain alterations associated with this effect appear to be more pronounced during resting state functional connectivity in the GHB-NoComa group when compared with No-GHB group [109, 110]. This suggests that even moderate doses of GHB are associated with alterations in the capacity to reach normal states of rest and an adequate categorization of emotional stimuli that last beyond the acute intoxication phase. In these "rest processes" higher doses of GHB or multiple GHB-induced comas do not seem to further affect brain function.

The results of the studies performed by Pereira *et al.* showed that in the GHB-Coma group, functional alterations were associated with structural differences in brain regions known to control these functions. More precisely, long-term memory problems were observed at the level of both the interpretation (primary visual areas) and memory encoding (hippocampus) regions of the brain. Working memory processing also seems to be affected in the GHB-Coma group, as shown by a reduced capacity to focus attention when differentiation between high levels of interference is required (lower activity of the DLPFC). No follow-up studies to residual cognitive impairment after cessation of GHB-use have been performed yet, so that it is not clear whether these observed effects are reversible or not.

4. DISCUSSION

Clinical studies have shown that general anaesthesia is associated with acute and long-term cognitive impairment [50-52, 111, 112]. Since heavy recreational GHB users may become comatose following a high dose of GHB (> 50 mg/kg) [29, 31], it was hypothesized that high dose GHB uses and/or repeated GHB-induced comas are a prominent risk factor of residual cognitive impairment [57].

Animal studies indicate that altered gene expression and related neurotoxic effects in the brain are probably responsible for the acute memory and emotion processing deficits [64, 66, 67] (cf. Table **1**). In rodents, GHB-induced changes in social behaviour and disruptions in long-term and working memory are mainly associated with changes in brain regions that are known to mediate episodic memory and learning [113], *i.e.*, the medio temporal lobe (primarily in the hippocampus) and in regions of the PFC such as the DLPFC and the anterior cingulate cortex [63, 66, 77-79, 114-116], regions which are rich in GHB-binding sites and most sensitive to GHB-induced neurotoxicity [63, 67, 77, 79, 114].

Data from human studies reviewed here indicate that moderate GHB use may result in acute short-term cognitive impairments and changes in resting state processes, whereas regular high-dose GHB use and/or multiple GHB-induced comas are probably neurotoxic, resulting in long-term residual cognitive impairments (cf. Table **2**). In humans, GHB affects the same brain areas as seen in rodents (hippocampus and DLPFC), considering that the recreational use of high doses of GHB and/or repeated GHB-induced comas were associated with anatomical abnormalities at a microstructural level in pre-

frontal and limbic white matter, brain regions typically involved in impulsivity, goal-directed behaviour, memory, and affect regulation. The functional abnormalities in the processing of these cognitive processes may be based on structural alterations in these brain regions. Moreover, as already mentioned, these regions are rich in GHB-binding sites and highly sensitive to GHB-induced neurotoxicity. Though the results of Pereira *et al.* [106-110] indicate that regular use of high doses of GHB and/or multiple GHB-induced comas are associated with impaired neurocognitive functions and abnormalities in brain functions and structures, no follow-up data is available. As such, it remains to be established whether these impairments and abnormalities are permanent or reversible after (long-term) abstinence. Moreover, it cannot be excluded that these brain abnormalities were already present before the onset of GHB-use, and that they represented a risk factor for the onset of (frequent) GHB-use. Presumably, low doses of GHB (up to 30 mg/kg in habituated users) do not lead to irreversible cognitive impairments (cf. Table **2**).

It has been speculated that transient and prolonged unconsciousness leads to cerebral hypoxia, which leads to neurotoxicity [117], and associated disruptions in cognitive control, including memory disorders [118]. GHB-induced comas are deep states of unconsciousness that have been compared to the ones induced by general anaesthetics [57]. Though, in contrast with medical anaesthetics, GHB-induced comas are not accompanied by oxygen support and might expose the brain to hypoxia [119-121]. As a result, the functional integrity of sensitive brain regions to oxidative stress might be altered, leading to the observed cognitive impairment. Interestingly, when GHB is used clinically in patients with narcolepsy or alcohol dependence, virtually no cognitive impairments have been reported [85, 122, 123], which is presumably due to tolerance that has developed in these patients who chronically receive 4.5-9 g GHB daily.

CONCLUSION

Recreational GHB-use is associated with emergency attendances in cases of overdosing, leading to GHB-induced comas. GHB-users and many health professionals still have the prevailing and erroneous idea that regular use of GHB is not addictive and that GHB-induced comas are relatively harmless. The results summarized here consistently show that high dosages of GHB and/or associated GHB-induced comas may result in both acute and long-lasting residual impairments of cognitive functioning, and therefore highlight the need for public awareness to minimize the negative health consequences of regular recreational GHB use, in particular when related with GHB-induced comas.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

The study is conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

SUPPLEMENTARY MATERIAL

Supplementary material and PRISMA checklist are available on the publisher's website along with the published article.

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