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The therapeutic potential of gamma-hydroxybutyric acid for alcohol dependence: balancing the risks and benefits. A focus on clinical data

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There is an increasing interest in studying the role of GABAergic medications in the treatment of alcohol dependence. The GABAergic drug gamma-hydroxybutyric acid (GHB) has been investigated in Europe as a possible treatment for alcohol dependence. In some European Countries, GHB has been approved as a treatment for alcohol dependence. However, this drug has also shown addictive properties, therefore raising questions about its safety in treating alcohol-dependent subjects. More recent research is focusing on the possibility of identifying alcohol-dependent subtypes without risk of developing GHB abuse. Finally, GHB and naltrexone combined together represent a possible approach deserving future investigations.

Keywords: alcohol craving, alcohol dependence, alcohol withdrawal syndrome, GHB, GHB abuse and dependence

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1. Introduction

1.1 Alcohol dependence

Alcohol dependence is a chronic disease with a multifactorial etiology and is characterized by excessive drinking, alcohol craving, loss of control, tolerance and physical dependence [1]. Chronic alcohol consumption is able to affect the brain, altering its neurochemical properties. These long-lasting changes in the brain are supposed to be based on the neurobiology of alcohol dependence [2]. Alcohol affects virtually all neurotransmitter or neuromodulator systems, either directly or indirectly [2]. Long-term exposure to alcohol causes adaptive changes in several neurotransmitter systems, including gamma-aminobutyric acid (GABA) receptors, glutamate receptors and central norepinephrine activity [3]. Alcohol enhances the inhibitory GABAergic transmission, mainly via a potentiation of the $GABA_A$ receptor function and possibly through an indirect increase in GABA release [4]. Alcohol also inhibits the excitatory glutamatergic transmission through its action on glutamate receptors [5]. In addition to glutamate and GABA receptors, alcohol has also shown to interact with several other neurotransmitter receptors such as serotonin, glycine and nicotinic acetylcholine receptors [6-8]. Additionally, alcohol induces presynaptic changes in neurotransmitter release, in particular stimulating dopamine release in the ventral striatum/nucleus accumbens area [9-11].

1.2 Pharmacological treatment of alcohol dependence

The advances in the field of neuroscience have contributed significantly to developing the rationale for investigating pharmacological compounds, as part of

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the clinical management of alcohol-dependent subjects. In fact, the concomitant use of pharmacological and psychological approaches could produce an additive effect in the control of the compulsive desire for alcohol and in maintaining alcohol abstinence [12]. As a consequence, several medications have been investigated as a treatment for alcohol dependence [13-16]. In particular, while disulfiram has been used for several decades, more recently three new treatments (oral and long-acting intramuscular naltrexone, and acamprosate) have received regulatory approval for alcohol dependence in the USA. Unlike disulfiram, these compounds target neurobiological processes that are thought to be involved in the pathophysiology of alcohol dependence. Naltrexone is widely used in the USA, in Australia and in several European countries but, for example, is not licensed in the UK. Acamprosate has been used for years in Europe, but it was approved in the USA only in 2004. Furthermore, the general perception is that the overall efficacy is modest, despite the fact that some patients have profound responses to these medications. Also, there is no agreement as to whether the combination of these medications (e.g., naltrexone and acamprosate) might be better than either drug alone [17]. Therefore, there is a substantial need for discovering innovative ways to provide effective pharmacotherapy for alcohol dependence. Among new possible neuropharmacological targets in treating alcohol dependence, there is an increasing interest in studying medications working on the GABA system, such as topiramate, baclofen, gabapentin and gamma-hydroxybutyric acid (GHB) [18].

The GABAergic compound GHB has been investigated in Europe as a possible treatment for alcohol dependence. The present review summarizes the clinical studies testing GHB in the treatment of alcohol dependence. Although GHB has been approved in Italy and Austria as a treatment for alcohol dependence (Alcover®, CT San Remo Pharmaceuticals) [19], this compound has also shown addictive properties, raising questions about its safety in the treatment of alcoholic patients.

1.3 Gamma-hydroxybutyric acid

1.3.1 Chemical profile and neurobiology

GHB is a short-chain 4-carbon fatty acid found endogenously in various mammalian cerebral areas, in particular in the hypothalamus and basal ganglia [20]. The primary precursor of GHB in the brain is GABA. GHB is formed in the brain from GABA-derived succinic semialdehyde (SSA) via a specific succinic semialdehyde reductase (SSR). GHB can be reconverted back to SSA via a GHB dehydrogenase, and the GHB-derived SSA can be converted back to GABA. SSA can also be metabolized by succinic semialdehyde dehydrogenase (SSADH) to succinic acid [21].

Gamma-hydroxybutyric properties indicate that this compound might play a role in the brain as a neurotransmitter or neuromodulator [22]. For example, there is evidence that GHB might have GABA-mimetic effects *in vivo* [23]. $GABA_B$ receptors might play a greater role than $GABA_A$ receptors in mediating the effects of GHB [24]. In particular, GHB might act at $GABA_B$ receptors both directly as a partial agonist and indirectly through GHB-derived GABA [21]. In 1982, Benavides *et al.* first described specific binding sites for GHB in the brain of rats [25]. These binding sites are distributed in the brain of several mammals. For example, a high density has been found in areas such as the hippocampus and cortex, while a lower density exists in the cerebellum [26]. More recently, a GHB receptor has been cloned and characterized in both rat [27] and human [28] brain.

GHB receptors have large functional (and probably structural) homologies with the $GABA_B$ receptors. However, GHB receptors are able to bind GHB and some structurally related analogs, but not GABA [29]. Although GHB binding sites have been described, the exact mechanism of action of GHB remains elusive owing, in part, to apparent GABA-mediated effects [30,31].

A part of the well-known GABA-mimetic effects, GHB may also work on several other neurotransmitters. For example, systemic administration of low doses of GHB in the rat inhibits burst activity and modulates firing of the dopaminergic terminals. With increased GHB concentrations, the initial decline of the dopamine release is followed rapidly by a tissue accumulation of dopamine in the rat brain [32]. Additionally, *in vivo* and *in vitro* experiments demonstrate that GHB could influence the serotonergic activity in the brain, directly or indirectly, via an interaction with other systems (e.g., dopamine, GABA) [32]. In particular, higher doses of GHB in rats induce an increase of the serotonin turnover in the striatum and mesolimbic areas. Furthermore, at high doses, GHB increases the release of endogenous opiates like donorphin and beta-endorphin in rats, although GHB does not seem to be a direct opiate receptor agonist [32]. GHB is also able to induce a reduction of the hippocampal acetylcholine release by the involvement of $GABA_B$ receptors [33].

1.3.2 Clinical indications

Gamma-hydroxybutyrate was identified and synthesized more than 40 years ago [34]. GHB was first developed as a central nervous system depressant [35] and used as an anesthetic adjuvant for minor surgical procedures in laboratory as well as in clinical settings [36-38]. The use of GHB as an anesthetic is now decreasing, although it is still approved in Germany for intravenous anesthesia [24].

In the 1970s, GHB was found to be effective in the treatment of narcolepsy [39,40]. In particular, nightly doses of GHB were shown to improve the structure of sleep in narcoleptic patients, reducing the number of nocturnal awakenings and daytime attacks of cataplexy [41]. In the USA, Canada, the European Union and Switzerland, GHB is now designed as orphan drug status for the treatment of narcolepsy (Xyrem®, Jazz Pharmaceuticals, Inc., Valeant Pharmaceuticals International, and UCB). In particular, in the USA, through a limited distribution program, the FDA approved GHB

(Xyrem®) as a schedule III controlled substance to treat a small subset of patients with narcolepsy who have episodes of weak or paralyzed muscles (i.e., cataplexy).

2. Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol dependence

2.1 GHB in the treatment of alcohol withdrawal syndrome

There is an increasing interest in investigating non-benzodiazepine GABAergic compounds in the treatment of alcohol withdrawal syndrome (AWS) (see [42]).

The rationale for testing GHB as a pharmacological compound in the treatment of AWS is the alcohol-mimicking profile of GHB in the central nervous system [43]. In animals, GHB can suppress ethanol withdrawal syndrome in alcohol-dependent animals [44,45]. In terms of mechanism of action, the close similarity of the pharmacological profiles of GHB and alcohol has led to the hypothesis that GHB works as a 'substitution' of alcohol in the central nervous system [44,46,47].

Consistent with animal data, clinical studies demonstrated the efficacy of GHB in reducing symptoms of AWS. In particular, Gallimberti *et al.* [48] did a small, randomized, double-blind study showing that GHB (50 mg/kg t.i.d.) was able to reduce withdrawal symptoms. More recently, the efficacy of GHB (50 mg/kg in 3 divided doses) has been successfully demonstrated in a larger sample of inpatients who developed AWS symptoms after being admitted to different clinical settings (e.g., psychiatry, internal medicine, surgery) [49].

Three studies have compared GHB versus other pharmacotherapies for AWS. The first study compared GHB (50 mg/kg in 3 divided doses) with diazepam over 10 days [50]. The Clinical Institute Withdrawal Assessment for Alcohol Scale – revised (CIWA-Ar [51]) was used to assess the severity of AWS symptoms. The diazepam dose was 0.5 – 0.75 mg/kg body weight for the first 6 days; from the 7th day on, diazepam was reduced at least 25% daily and stopped on day 10 [50]. This single-blind comparative study showed no significant difference between the two groups receiving either GHB or diazepam in CIWA-Ar total score at baseline and at subsequent observations. Therefore, this study indicated that GHB might be effective as the 'gold standard' diazepam in the treatment of AWS. Interestingly, among CIWA-Ar subscores a significant reduction in mean score of anxiety on day 4 and of agitation on day 5 was observed in the GHB group with respect to the diazepam group, suggesting a more prompt effect of GHB in reducing these symptoms [50]. More recently, this comparative study was replicated by Nava *et al.* [52] in 42 inpatients affected by severe AWS. The patients were treated with GHB (50 mg/kg/day q.i.d.) or diazepam (0.5 mg/kg/day q.i.d.) for 3 weeks using an open-label design. This study demonstrated that GHB was more effective than diazepam in reducing both CIWA-Ar total score and CIWA-Ar mean subscores (tremor, paroxysmal sweats, anxiety and agitation) as well as in reducing cortisol levels at different observation times [52]. Several factors could explain the different results between this study [52] and the previous study by Addolorato *et al.* [50]. These factors include the difference in the frequency of GHB administration, different diazepam dosage and daily administration, study design and age and duration of alcoholism of the patients enrolled.

A double-blind study was designed by Nimmerrichter *et al.* [53] to assess two doses of GHB (50 or 100 mg/kg in 3 divided doses) compared with clomethiazole in the treatment of AWS. The results indicate no difference between the three treatment arms and no increase in withdrawal symptoms after tapering off the medications [53].

In each of these trials [48-50,52,53], no serious side effects were reported. Mild side effects included vertigo, drowsiness, dizziness, rhinitis, diarrhea and nausea. Moreover, the results reported by Nimmerrichter *et al.* [53] indicate that the lower dose of 50 mg/kg proved sufficient in the treatment of severe AWS since no difference was demonstrated between the two GHB-treated groups. Additionally, more frequent side effects (especially vertigo and diarrhea) were reported in the group treated by GHB 100 mg/kg [53].

2.2 GHB as an anti-craving drug in the treatment of alcohol dependence

The central role of GHB in modulating the activity of dopamine, serotonin, acetylcholine, opioids and GABA [20,54] led to the suggestion that GHB plays a role in reducing alcohol craving and alcohol consumption. Consistent with this rationale, GHB has been shown capable of inhibiting voluntary ethanol consumption in rats with ethanol preference [44,47,55].

In humans, GHB has been shown to reduce alcohol craving, promoting short-term [56] and medium-term [57,58] alcohol abstinence in alcoholic patients. In particular, Gallimberti *et al.* [56] carried out a randomized, double-blind study treating patients with GHB at dose of 50 mg/kg (divided into 3 daily doses) or placebo for 3 months. Compared with placebo, GHB was significantly superior in increasing the number of abstinent days, in reducing the number of daily drinks and in reducing alcohol craving [56].

A multicenter study investigated the efficacy, safety and tolerability of GHB in the treatment of alcohol dependence after a longer administration of GHB (6 months) [57] and using a longer follow-up of 1 year [58]. The study demonstrated GHB efficacy in reducing alcohol craving and in improving the abstinence rate. Moreover, GHB proved to be manageable, with few side effects, such as dizziness, sleepiness and tiredness, usually present only during the first 2 – 3 weeks of treatment with GHB.

In spite of the possible utility of GHB in inducing short-term [56] and medium-term [57,58] alcohol abstinence, about 30 – 40% of alcoholic participants were not totally alcohol abstinent during the treatment. Interestingly, those

patients not totally abstinent from alcohol sometimes described a temporary reduction of alcohol craving during the day but not enough to control completely their desire to drink alcohol during the entire day. This clinical observation led Addolorato and colleagues to hypothesize that those subjects might benefit from a greater fractioning of the same dose of GHB, therefore without increasing the dose of 50 mg/kg tested in the first study. This hypothesis was also supported by human laboratory studies showing the short half-life of GHB [59].

In order to test this hypothesis, a study was conducted, investigating the administration of GHB six times a day in subjects not totally alcohol abstinent after a previous treatment with GHB administered three times a day [60,61]. This study demonstrated the ability of GHB administered six times a day in promoting abstinence in a great percentage of those subjects not totally abstinent from alcohol after treatment with GHB administered three times a day. These results were consistent with the hypothesis that a greater fractioning of the same dose of GHB (50 mg/kg) could induce a significant reduction of alcohol craving and intake.

More recently, a 1-year, open-label study tested the efficacy of GHB (doses ranging between 25 and 100 mg/kg/day) in 'treatment-resistant' chronic alcoholics defined as patients who had previously received at least two treatments with psychoactive drugs (i.e., selective serotonin reuptake inhibitors [SSRIs], mood stabilizers, tryciclics) and/or self-help group intervention, without achieving alcohol abstinence and/or with episodes of relapse (heavy drinking) [62]. The results of the study showed that 60% of patients achieved a complete abstinence from alcohol ('full-responders') or at least showed a marked decrease of their alcohol consumption ('partial-responders') [62]. This study showed that the retention rate during treatment with GHB was significantly higher than the retention rate of the same sample treated with previous pharmacotherapies. Furthermore, this study confirmed that the only significant predictor of the retention rate was the six-times-daily fractionated administration of GHB [62], an observation in close agreement with the previous study by Addolorato *et al.* [60].

Laboratory studies with healthy subjects investigated the effects of administering alcohol and a single dose of GHB 50 mg/kg together. These experiments showed an increased rate of side effects, probably due to the combination of GHB and alcohol [63]. This effect was not observed in the clinical studies with alcoholics reported above. In fact, no side effects due to the combination of GHB 50 mg/kg (divided in 3 – 6 daily doses) and alcohol were observed in those alcoholics treated with GHB and still drinking during the treatment [56,58,60,61]. It is conceivable that the use of the same dose of 50 mg/kg divided in three to six daily administrations was able to prevent the occurrence of unsafe effects when associated with ethanol [64].

2.3 GHB compared and combined with other medications in the treatment of alcohol dependence

Some studies have compared GHB with other medications in reducing alcohol consumption and achieving alcohol abstinence. A 3-month randomized open-label study compared GHB (50 mg/kg of body weight t.i.d p.o.) versus naltrexone (50 mg/day p.o.) in maintaining alcohol abstinence in alcohol-dependent subjects. This study suggested a significant higher effect of GHB versus naltrexone in promoting alcohol abstinence [65]. However, this study also demonstrated that non-abstinent subjects relapsed in heavy drinking in the GHB group while in the naltrexone group, confirming the ability of naltrexone in reducing alcohol relapses. More recently, a 12-month study compared GHB (50 mg/kg/day), naltrexone (50 mg/day) and disulfiram (200 mg/day) in treating alcohol-dependent patients. Despite a trend in favor of GHB being observed, this study did not show any significant difference across the three treatments [66]. In these comparative studies, none of the patients treated with GHB developed craving for this drug [65,66].

On the basis of the first comparative study, Caputo *et al.* hypothesized that the combination of GHB and naltrexone might work better than either drug alone in the treatment of alcohol-dependent patients. Therefore, a 3-month, open-label study was performed. Alcohol-dependent subjects were randomly assigned to receive GHB, naltrexone or the combination of GHB and naltrexone [67]. The same doses of the previous comparative study were used [65]. The results of this study showed a significant higher effect of GHB and naltrexone combined in maintaining total alcohol abstinence than either GHB or naltrexone alone [67]. Moreover, relapses in heavy drinking tended to occur less frequently in the GHB + naltrexone group than in either GHB-only or naltrexone-only groups. These results are consistent with the hypothesis that the alcohol-mimic effect of GHB and the anti-reward properties of naltrexone work synergistically and that naltrexone may modulate GHB actions in alcoholics (**Figure 1**). Furthermore, no patients developed craving for GHB in the group treated with GHB + naltrexone. On the contrary, 10% of those subjects treated with GHB alone developed craving for GHB [67]. This observation is consistent with a previous observation by Caputo *et al.* [68] and may indicate that the anti-reward properties of naltrexone may be able to avoid the development of craving for GHB (**Figure 1**).

More recently, a 6-month, open-label study compared groups of alcohol-dependent patients randomly assigned to receive escitalopram, escitalopram + GHB, escitalopram + naltrexone, or escitalopram + GHB + naltrexone [69]. In this study, the combination of escitalopram + GHB + naltrexone resulted to be more useful in preventing alcohol relapses than GHB + escitalopram, naltrexone + escitalopram or escitalopram given alone [69]. These results are consistent with the notion that there are different craving profiles (i.e., reward, relief, obsessive) and with the hypothesis that different craving profiles can co-exist in the same subject [3].

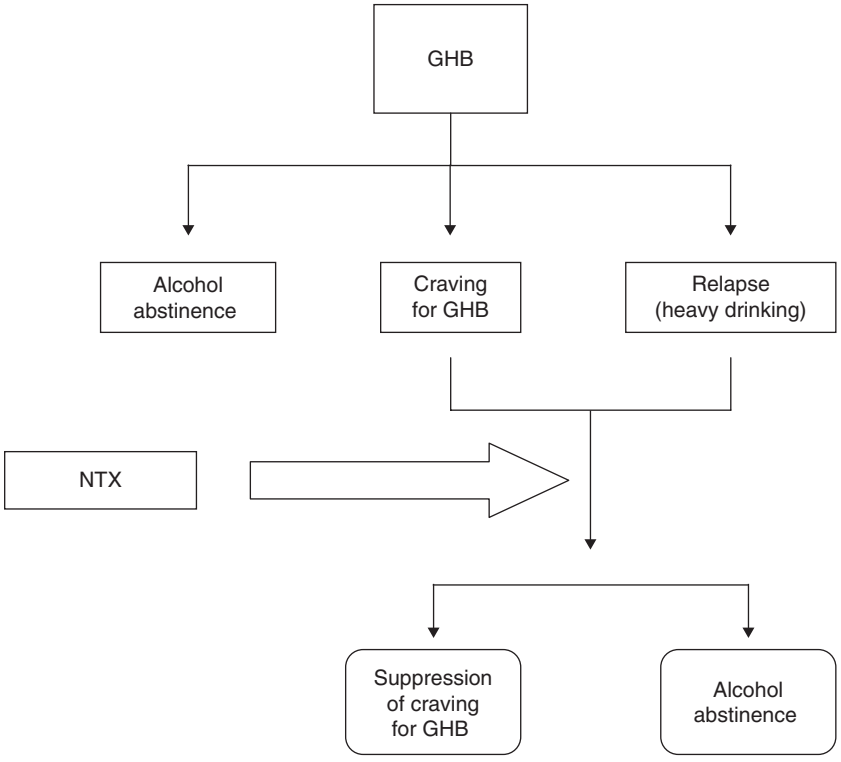

Figure 1. Hypothesis of a beneficial effect of gamma-hydroxybutyric acid (GHB) and naltrexone (NTX) combined in treating alcoholic patients. The alcohol-mimic effect of GHB and the anti-reward properties of NTX may work synergistically in reducing alcohol consumption, therefore promoting alcohol abstinence. Furthermore, the anti-reward action of NTX may be able to avoid the development of craving for GHB.
Modified from Caputo *et al.*, Eur Neuropsychopharmacol 2007 [67]; with kind permission from Elsevier.

As a consequence, the combination of different classes of medications, such as GHB, naltrexone and escitalopram may be more effective than a medication alone in reducing alcohol relapses.

2.4 GHB and possible differences related to alcohol-dependent subgroups

The identification of alcohol-dependent subtypes may assist in the ascertainment criteria for clinical trials performed in behavioral and pharmacological interventions [70,71]. As reported in detail in the section 3, craving for GHB and abuse of GHB represent crucial aspects during the use of this drug in treating alcohol-dependent patients. Therefore, it is of paramount importance to investigate ways to develop better manageability and safety of GHB in alcohol-dependent individuals. For example, the identification of subgroups of alcoholics more predisposed to develop this unfavorable effect is important. A recent study investigated the risk of developing craving for and abuse of GHB among different groups of alcoholics [72]. In this study, 47 alcohol-dependent patients were enrolled and treated with GHB orally administered (50 mg/kg of body weight t.i.d.) for 3 months. At the end of the study, the utility of GHB in promoting alcohol abstinence in the whole sample analyzed was confirmed. Craving for GHB was significantly higher in those alcoholics with previous cocaine dependence than in 'pure' alcoholics ('pure' alcoholics were defined as those patients with a diagnosis of alcohol dependence without other addictive disorders) [72]. Moreover, craving for GHB did not differ between 'pure' alcoholics and alcoholics with opioid dependence in remission. However, all alcoholics with opioid dependence in remission abused GHB. On the contrary, none of the 'pure' alcoholics abused GHB. In summary, this study suggests that the administration of GHB is not recommended in those alcoholics with a diagnosis of opioid or cocaine dependence, even if in sustained full remission.

3. Risk of GHB abuse and dependence

As mentioned above, GHB was approved for alcohol dependence in Italy and Austria. However, there are also some concerns about the use of this medication in an addicted population, since the addictive properties of GHB, potential of GHB abuse and/or dependence are related to its neurobiology. The intrinsic neurobiological activity of GHB might be mediated through the $GABA_B$ receptor and the GHB receptor. Studies *in vitro* have demonstrated that chronic GHB exposure may desensitize GHB and $GABA_B$ receptors,

thus reducing their ability to inhibit neurotransmitter release. Under conditions of chronic GHB intake, it is possible that compensatory mechanisms may occur that offset the inhibition of dopamine release, resulting in an increase of dopamine, GABA and/or glutamate release [21]. This scenario could contribute to the addictive properties of GHB. Addictive properties of GHB have been observed in both non-alcoholics and alcoholics. However, important differences exist between the use of GHB as a therapeutic option to treat alcohol-dependent subjects and the illegal use and abuse of GHB in non-alcoholics (see **Table 1**).

3.1 GHB abuse and dependence in non alcoholics

GHB's action as a depressant of the central nervous system is in some ways similar to those of classical sedative hypnotics such as barbiturates and benzodiazepines. On the basis of these properties, GHB has been used to treat insomnia [73]. On the other hand, GHB plays a role as a euphoriant. GHB's euphoria-inducing effect has made it popular as a recreational drug [74] in the USA and UK, where it is sold clandestinely mostly on the street [75], at 'rave' parties [76], in nightclubs [77] and on internet sites [78] under the names of 'liquid ecstasy', 'liquid X', 'Georgia Home Boy', 'Grievous Bodily Harm', 'Soap', 'Cherry Menth', 'G-Riffick', 'Salty Water', among others [79]. GHB has become a widespread drug of abuse in the USA since the 1980s. More recently, the recreational use of GHB has become popular in Europe as well [80].

In the spring of 1990, GHB appeared in the USA on the commercial market as a health food product to promote 'natural sleep' and weight loss. Moreover, GHB has been widely used in the body-building community because of its ability to promote muscle growth and decrease body fat [73,81]. GHB has been shown to stimulate the release of human growth hormone (GH) from the anterior pituitary [78]. However, in alcoholics there is no evidence that the short-term elevations in GH produced by GHB result in any increase in muscle mass [82].

The steep dose–response curve of GHB means that overdosing easily occurs, in particular when inaccurate and unknown doses of GHB are consumed, as in the case of GHB illegally sold on the streets [80]. As a consequence, in the last decades, cases of GHB toxicity have increased at hospital emergency departments. For example, a Swiss study reported that GHB accounted for 12.5% of intoxications at emergency departments in 2001, rising to 27.2% by 2003 [83]. Deaths from GHB use have been reported in the UK and elsewhere [84].

Signs and symptoms of GHB poisoning have been reported at doses of < 2.5 – 30 g. Adverse effects included dizziness, nausea, vomiting, myoclonic muscle movements (jerks), agitation, confusion, hallucinations, loss of peripheral vision and delirium. As a result of the high incidence of vomiting (> 50%), there is also a risk of pulmonary aspiration [85]. Doses higher than 10 – 20 g can decrease cardiac output and produce severe respiratory depression, seizure-like activity and coma [75,77,86]. No specific antidotes are available for the treatment of GHB intoxication. As a consequence, the acute medical treatment is only supportive. Some uncontrolled clinical studies have suggested that opioid antagonists such as naloxone may be effective on GHB intoxication, although the study design does not allow definitive conclusions to be drawn [80].

In some individuals, repeated and persistent use of GHB may lead to the development of physical dependence [80], including the presence of withdrawal. For example, 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 [87]. GHB withdrawal may include symptoms such as anxiety, insomnia and tremor. The clinical picture can rapidly deteriorate into delirium, hallucinations and/or psychosis. GHB withdrawal may require either an outpatient or inpatient treatment with benzodiazepines, depending on the severity of the symptoms. In particular, benzodiazepines represent the recommended treatment, though cases of GHB withdrawal unsuccessfully treated with benzodiazepines have been reported [88]. By November 1990, in the USA, 57 cases of GHB poisoning and related illnesses such as seizures and comas were reported in nine states [73,89]. The FDA issued a ban, removing GHB from the market. Because of its abuse potential, in the USA, GHB was classified as a schedule I controlled substance in 2000. As mentioned above, GHB is at present approved by the FDA as a schedule III drug only for the treatment of patients with narcolepsy who have episodes of weak or paralyzed muscles (i.e., cataplexy) [90].

3.2 GHB abuse and dependence in alcoholics

A survey analysis indicated that GHB has been administered orally as a maintenance treatment to 732 alcohol-dependent outpatients (50 – 100 mg/kg/day divided in 3 or more doses) for 132.2 ± 57.9 days [19]. These patients also attended supportive psychosocial programs, and the administration of GHB was entrusted to a family member. A percentage of these patients (varying according to the different reports from 2.6 to 10.1%) showed craving for the drug and increased the dosage (up to 6 – 7 times the recommended dose) [19,58,91].

Interestingly, Addolorato *et al.* [58] first reported the risk of GHB abuse in alcohol-dependent patients treated with GHB. However, a greater fractioning of the same dose of GHB was able not only to decrease alcohol craving and alcohol intake but also to reduce the incidence of GHB abuse [60,61]. Furthermore, in 1999 the first case of GHB dependence with withdrawal symptoms was reported in a woman treated with GHB for alcohol dependence [92]. In this report, GHB withdrawal syndrome was characterized by high anxiety levels, tremor, sweating, nausea without vomiting and tachycardia. Total regression of withdrawal symptoms was obtained within 2 h after oral administration of diazepam (20 mg).

Table 1. Main differences between the clinical use of GHB to treat alcohol-dependent subjects and the abuse of GHB in non-alcoholics.

	Clinical use of GHB in alcoholics	Abuse of GHB in non alcoholics
Side-effects	Mild side effects, such as vertigo, drowsiness, dizziness, rhinitis, diarrhea, nausea, sleepiness	Mild and severe side effects, such as dizziness, nausea, vomiting (with risk of pulmonary aspiration), myoclonic muscle movements (jerks), agitation, confusion, hallucinations, loss of peripheral vision, delirium. Doses higher than 10 – 20 g can also decrease cardiac output and produce severe respiratory depression, seizures and coma
Anabolic effect with increased growth hormone (GH) release	Absent	Present
GHB physical dependence	Rare	Possible
Formulation	Standardized controlled concentrations	Inaccurate and greatly variable concentrations
Manufacturer	Synthesized by pharmaceutical industries	Synthesized by illegal laboratories
Availability	Only prescribed by specialized physicians in those countries where GHB is approved as a treatment for alcohol dependence	Sold clandestinely in several Countries, especially in the USA and UK

GHB: Gamma-hydroxybutyric acid.

We also note that the medium therapeutic dose of GHB in alcoholics is about five times lower than the minimum daily dose of GHB associated with withdrawal [93,94]. In addition, GHB withdrawal is usually present in those cases of nonclinical and self-administered prolonged abuse of GHB [95]. In alcoholics, withdrawal and physical dependence do not appear when GHB, used at therapeutic dosage, is discontinued.

In conclusion, GHB abuse and dependence during treatment for alcohol dependence is a limited phenomenon [78]. However, this risk remains an important concern, especially considering the use of GHB in an addicted population. Given the potential for abuse, GHB is not recommended to treat alcohol dependence, at least in those countries like the USA, where GHB is a schedule III controlled substance [90]. Furthermore, the use of GHB as a treatment for alcohol dependence requires caution, also in those countries where GHB is approved for alcohol dependence. A greater fractioning of the dose of GHB is strongly recommended [60]. Nevertheless, the use of GHB in alcohol dependence deserves further investigation, in particular considering the possibility of combining GHB with other medications (see section 2.3) as well as the possibility of identifying possible alcoholic subtypes better responding to GHB treatment (see section 2.4).

4. GHB, GABA system and alcohol dependence: how to move forward?

The clinical studies reported in the present review show the therapeutic potential of GHB for alcohol dependence. In particular, these studies suggest that GHB may be useful in treating AWS as well as in the long-term aim to achieve and maintain abstinence from alcohol.

However, studies on a greater number of patients are needed. For example, further comparative studies between GHB and benzodiazepines are needed to test the role of GHB as a treatment for AWS. The studies available until now present some limits, such as the different settings (e.g., inpatients vs outpatients) and the enrolment of patients with different severities of AWS. Furthermore, there are no data on the possible efficacy of GHB in more complicated forms of AWS, including seizures and delirium tremens. At present, benzodiazepines represent the gold standard in the treatment of AWS, in particular considering their ability both to prevent and treat the more serious complications, such as seizures and delirium tremens [42].

The ability of GHB to reduce alcohol craving and intake suggests that this drug may be useful in the long-term treatment of alcohol-dependent subjects. Also in this case, however, studies with a greater number of patients and with longer follow-up periods are needed. Recent research also points to the possible benefits of combining medications acting on different neurobiological targets. The combination of GHB and naltrexone is of interest because these two drugs work on several neurotransmitter circuits. For example, a possible future approach could be to investigate the role of naltrexone in those GHB-treated alcoholics who relapsed and/or developed a craving for GHB. Despite the small sample, the study combining GHB and naltrexone (see [67]) demonstrated the safety of this combination and provides the basis for studies testing GHB + naltrexone in a larger population.

As noted in the Introduction, there is an increasing interest in studying the role of GABAergic medications in alcohol dependence [18] (i.e., topiramate [96], baclofen [97] and gabapentin [98]). Therefore, it will be of interest to carry out studies comparing and/or combining GHB with other GABAergic medications.

The risk of GHB abuse underlines the need to develop valuable ways to reduce this risk when GHB is used as a therapeutic option for alcohol dependence. From this prospective, the recent study by Caputo *et al*. [72] indicates that GHB should not be administered to those alcohol-dependent individuals with history of either cocaine or opioid dependence. Future studies will have to continue this approach, trying to identify alcoholic subtypes with a higher response to GHB treatment but with a lesser risk of GHB abuse. This approach may include: i) the application of typology classifications (i.e., *early*- vs *late-onset alcoholics*, Cloninger typologies, Babor typologies, and many others; see [71]); ii) the application of intermediate phenotypes – or endophenotypes – to generate more homogeneous diagnostic groupings (see [99]); and iii) the identification of biological markers (i.e., genetic polymorphisms of the GABA receptor; see [100]) that may predict response to GHB treatment.

5. Expert opinion

Gamma-hydroxybutyric acid (GHB) has been proposed as a possible medication in the treatment of alcohol dependence. Although further studies are needed to confirm GHB efficacy in larger samples, the studies available demonstrate that GHB appears to be effective both in the management of AWS and in the maintenance of long-term abstinence [48-50,52,53,56-62]. GHB has also obtained regular approval for alcohol dependence in some European countries.

In the USA as well as in Europe, however, there has been increasing attention to the risk of GHB abuse and dependence. The recreational use of GHB is a serious problem, also considering the possible use of high doses with the consequent risk of toxicity. Moreover, the chronic abuse of GHB may lead to the development of GHB dependence.

GHB abuse seems a limited phenomenon when GHB is used at therapeutic doses to treat alcohol-dependent patients. However, cases of craving for GHB with consequent abuse of the drug and possible dependence may occur during its use to treat alcohol dependence. This feature strongly suggests that GHB must be used under strict medical surveillance and with a multidisciplinary approach that includes a supportive psychosocial program and the cooperation of a family member. Only physicians with experience in administering GHB to alcoholics should use this medication to treat alcohol dependence.

Finally, recent studies suggest the usefulness of combining GHB with naltrexone in treating alcohol-dependent subjects as well as the possible identification of alcohol-dependent subtypes at lower risk of developing GHB abuse. These studies provide the basis for future research whose goal will be to investigate an efficacious and safe use of GHB in the management of alcohol-dependent patients.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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