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# Clinical applications of sodium oxybate (GHB): from narcolepsy to alcohol withdrawal syndrome

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**Abstract. – Gamma-hydroxybutyrate (GHB) is a short chain fatty acid endogenously produced within the central nervous system (CNS) and acts as a precursor and metabolite of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Although, it is an illegal recreational drug of abuse, its sodium salt (sodium oxybate) has been utilized as a medication for a number of medical conditions.**

**The first aim of this review was to focus on current applications of sodium oxybate for the treatment of narcolepsy, with a particular emphasis on the key symptoms of this disorder: cataplexy and excessive daytime sleepiness (EDS).**

**Secondly, the effectiveness of sodium oxybate therapy for the treatment of alcohol withdrawal syndrome (AWS) and the maintenance of alcohol abstinence has been assessed.**

**Nowadays, sodium oxybate is the first-line treatment for narcolepsy and it is highly effective in meliorating sleep architecture, decreasing EDS and the frequency of cataplexy attacks in narcoleptic patients.**

**Sodium oxybate currently finds also application in the treatment of AWS and the maintenance of alcohol abstinence in alcoholics.**

**Most of the studies evaluating the efficacy of GHB in the treatment of AWS use a dosage of 50 mg/kg divided in three or four administrations per day.**

**Human studies showed that GHB (dose of 50 mg/kg, divided in three administrations per day) is capable to increase the number of abstinent days, reduce alcohol craving and decrease the number of drinks per day.**

**However, there is limited randomized evidence and, thus, GHB cannot be reliably compared to clomethiazole or benzodiazepines. Some randomized data suggest that GHB is better than naltrexone and disulfiram regarding abstinence maintenance and prevention of craving in the medium term i.e. 3-12 months.**

**It is recommended that GHB should be used only under strict medical supervision, since concerns about the abuse/misuse of the drug and the addiction potential have been arisen.**

*Key Words:*
Sodium oxybate, GHB, Narcolepsy, Alcohol withdrawal syndrome.

## Introduction

Gamma-hydroxybutyrate (GHB) is a short chain fatty acid and a potent central nervous system (CNS) depressant. It is endogenously produced within the CNS and acts as a precursor and metabolite of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Figure 1)[1,2]. It was first synthesized in the early 1960s'[3] and soon after was also discovered to be an endogenous compound[4]. Although, it is an illegal recreational drug of abuse, its sodium salt (sodium oxybate) has been utilized as a medication for a number of medical conditions.

In the 90s it became very famous among bodybuilders, who used it as a "steroid-accessory drug", in order to augment the growth hormone (GH) release; however, this correlation is debated[5-7].

Fatal cases involving GHB and the recently emerged new psychoactive substances (NPS), such as mephedrone etc., have also been reported[8].

GHB has been classified as a controlled compound in many countries, but its abuse still remains an issue due to the easier accessibility of precursor drugs such as γ-butyrolactone (GBL) and 1,4-butanediol (BD).

The majority of administered GHB dose (95-98%) undergoes hepatic metabolism via enzymatic pathways. A key route of metabolism is the oxidation by GHB dehydrogenase to produce succinic semialdehyde. Further oxidation of the latter leads to succinic acid, which enters the intermediary metabolism and is converted into water and carbon dioxide *via* the Krebs cycle[1].


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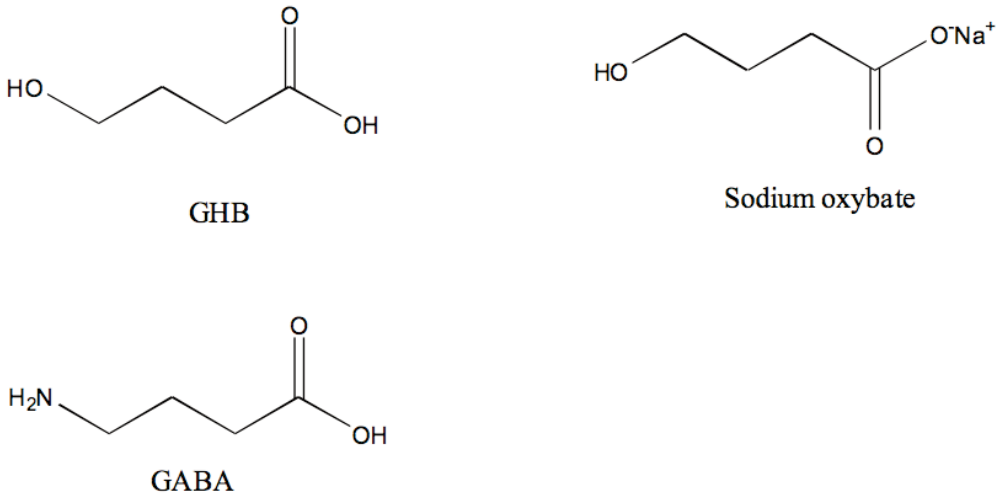


**Figure 1.** Chemical structures of GHB, sodium oxybate and GABA.

As mentioned above, GHB can be considered both a precursor and a metabolite of GABA. The amino acid glutamate moves through the blood-brain barrier and is decarboxylated to give GABA. Metabolism of GABA is achieved by an aminotransferase enzyme to produce succinic semialdehyde, which can either be reduced to form GHB or oxidized to produce succinic acid. The biosynthesis and metabolism of GHB are given in Figure 2[1].

GHB interferes with GABAergic neurotransmission and can be considered a $GABA_B$ agonist. The "GABA-releasing" neurons are mostly located in the cortex, hippocampus and amygdala. GHB receptors are localized in these sites, in pre- and postsynaptic cells and demonstrate high affinity for these G-protein coupled receptors[1].

Early studies showed a correlation between increased GHB (exogenously administered) blood levels and reduced levels of consciousness[9]. The first therapeutic use of GHB was to produce anesthesia[10,11].

Some potential therapeutic effects of sodium oxybate have been investigated including: impact

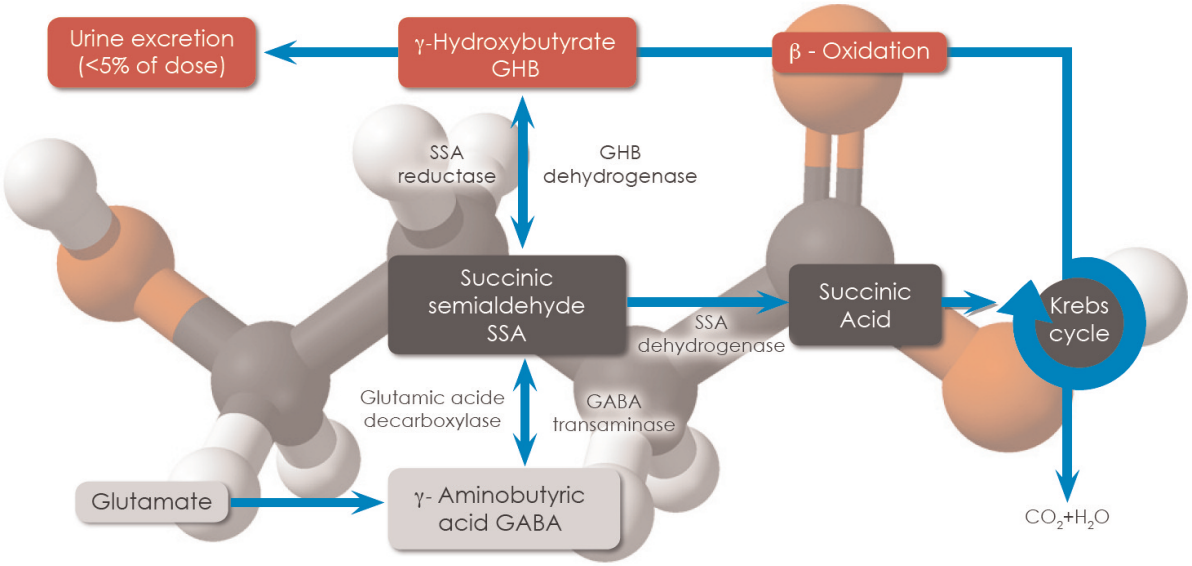


**Figure 2.** Biosynthesis and metabolism of GHB.

on anxiety conditions[12], treatment of diamorphine (heroin) dependence[13,14], relief of pain, tension and anxiety during childbirth[15], decrease of intracranial pressure[16,17], improvement of sleep fragmentation, pain and fatigue of fibromyalgia syndrome[18,19], treatment of infection[20] and hyperkinetic movement disorders[11,21,22]. However, it finds its wider application as a therapeutic agent in narcolepsy-associated cataplexy and alcohol withdrawal.

Sodium oxybate is considered to be a first-line agent for the treatment of the symptoms induced by narcolepsy such as: nighttime sleep fragmentation, EDS and cataplexy. GHB has a long history of over 30 years and it has the most well-documented clinical data among all the drugs evaluated in treating narcolepsy[23]. In July 2002 sodium oxybate (Xyrem®) was approved by the US Food and Drug Administration (FDA) as a substance for the treatment of cataplexy in narcoleptic patients[24] whereas in November 2005, its use was also approved by the FDA for the treatment of EDS in patients suffering from narcolepsy[11].

In some European countries including Italy and Austria sodium oxybate is registered as Alcover® for the management of alcohol withdrawal and detoxification in alcoholics[25-27]. While Xyrem® is used just before going to sleep in patients suffering from narcolepsy, Alcover® is administered approximately 4 times daily in order to reduce the desire for alcohol and alleviate withdrawal symptoms[28,29].

The first aim of this review is to focus on current applications of sodium oxybate for the treatment of narcolepsy, with a particular emphasis on the key symptoms of this disorder: cataplexy and EDS.

Secondly, the effectiveness of sodium oxybate therapy for the treatment of alcohol withdrawal syndrome and the maintenance of alcohol abstinence will be assessed.

### *Sodium Oxybate for the Treatment of the Symptoms of Narcolepsy*

Narcolepsy is a neurological disorder due to the loss of hypocretin (orexinergic) neurons in the lateral hypothalamus, probably caused by an autoimmune procedure. It is characterized by hypnagonic hallucinations, sleep attacks, EDS, cataplexy episodes, disturbed nighttime sleep patterns and sleep paralysis[30-33]. Cataplexy i.e. sudden loss of muscle tone, mostly triggered by strong emotions especially surprise or laughter[34], is a particularly troublesome symptom of narcolepsy; however, narcolepsy can also arise without cataplexy[35,36].

A variety of medications have been used for the treatment of the symptoms of narcolepsy. Psychomotor stimulants are used for excessive sleepiness relief whereas tricyclic antidepressants (TCAs) or selective serotonin re-uptake inhibitors (SSRIs) have been in use for a long time for the management of cataplexy. Although these drugs are effective and bring relief to some patients suffering from narcolepsy, they produce intolerable adverse effects in others, whereas other patients become tolerant to these drugs[37].

In general, the medications used for the treatment of narcolepsy, target the relief of the symptoms of this disease especially the key symptoms: cataplexy and EDS. The cause of narcolepsy is still not completely established; however, the damage of hypocretin/orexin neurons has been incriminated. The latter damage is associated with the inaction of neurotransmitters such as histamine, acetylcholine, norepinephrine and serotonin, leading to perturbation in the sleep/wake cycles of patients suffering from narcolepsy. Both stimulants and Monoamine Oxidase Inhibitors (MAOIs) have traditionally been utilized to counteract sleep attacks and EDS through catecholamines' breakdown inhibition. Modern drugs, referred to as wake-promoting agents, have recently become first resort drugs because of their high efficacy, a safer side effect profile and lower abuse potential. These agents not only act as dopamine reuptake inhibitors, but they have also been found to increase neuronal activity both in the orexin neurons and in the tuberomamillary nucleus. Antidepressants, such as SSRIs and TCAs act in a similar way to stimulants, as specific catecholamines' reuptake inhibitors[38].

Sodium oxybate is the sodium salt of GHB, which is a CNS depressant, and is therefore prescribed with caution. It is registered as a therapeutic agent (Xyrem®) and it has been approved in the EU for the treatment of narcolepsy with cataplexy, and in the USA for the treatment of EDS and cataplexy in narcoleptic patients (the only US FDA-licensed therapeutic agent for cataplexy)[38,39]. Although twice-nightly administration is required due to the short half-life of the drug, it is highly effective in meliorating sleep architecture, decreasing EDS and the frequency of cataplexy attacks in patients suffering from narcolepsy. It is therefore an important alternative or addition to the use of TCAs and selective

SSRIs for the management of the symptoms of narcolepsy[39]. Sodium oxybate, has a different mechanism of action compared to both stimulants and wake-promoting agents, since it binds to its own monadic receptor[38].

Nowadays, sodium oxybate is the first-line treatment for cataplexy and modafinil/armodafinil and sodium oxybate for EDS. GHB is effective for all symptoms of narcolepsy, whereas modafinil can only treat EDS. Amphetamines such as methamphetamine, lisdexamfetamine, dextroamphetamine or combination amphetamine salts or methylphenidate are alternative agents in the management of EDS. Moreover, atomoxetine or venlafaxine (norepinephrine reuptake inhibitors) are non-FDA approved drugs for cataplexy[40].

Due to the metabolic pathway of GHB, its pharmacokinetic interaction with other substances is limited. Taken in combination with modafinil/armodafinil its beneficial effects on sleepiness are enhanced. Adverse effects of sodium oxybate are moderate and it is well tolerated (adverse event withdrawal of appr. 3-10% after acute and chronic intake)[41], when taken as recommended[42]. Patients suffering from narcolepsy should be given the daily dose (4.5 g) of sodium oxybate (Xyrem®) immediately before going to bed. The short elimination half-life and the rapid absorption of GHB ensure that only a negligible quantity of the parent drug will remain un-metabolized in the blood the morning after[1].

GHB has a history of over 30 years and has the most well-documented clinical data among all drugs evaluated for the treatment of narcolepsy[23]. It was originally hypothesized[43,44], because of its already well known effects on slow-wave sleep (SWS) augmentation, rapid-eye movement (REM) facilitation and enhanced sleep consolidation, that GHB could decrease the sleep fragmentation which is one of the major symptoms in narcolepsy. The influential studies of Mamelak et al[44] and Broughton and Mamelak in narcoleptic patients represented the starting point in the understanding of GHB as a treatment agent for sleep improvement, cataplexy control and daytime alertness enhancement[11].

A systematic review and meta-analysis of randomized controlled trials on the effectiveness of GHB in narcolepsy has been conducted by Boscolo-Berto et al[45] The data were collected from 9 randomized controlled trials representing a total of 1,154 patients, of which 771 were GHB-treated and 383 placebo-treated. It was demonstrated that GHB is effective in curing major, clinically narcolepsy-associated symptoms and sleep architecture abnormalities. In detail, GHB decreased cataplexy strokes both on a daily and weekly basis, subjective nighttime awakenings, daytime sleep strokes on a weekly basis, subjective daytime sleepiness and sleep stage alterations. It was also found that GHB is able to increase sleep stages 3 + 4 and improve the CGI-c score. No significant alterations were noticed in total sleep time, night sleep latency, sleep stages 1 and 2 and REM sleep.

Narcolepsy with cataplexy frequently occurs during childhood often resulting in severe social and learning impairment. Although children currently undergo pharmacotherapy, only limited information on the safety and efficacy of medications for narcolepsy is available regarding the pediatric population. Due to the lack of international guidelines and registered drugs for childhood narcolepsy with cataplexy, physicians prescribe in an off-label manner the same treatments as adults. A good tolerability and efficacy of sodium oxybate has been documented in most of the patients tested (27 children age range: 6 to 16 years old) in a retrospective study[46]. The authors suggested further randomized controlled trials in the pediatric population suffering from narcolepsy with cataplexy.

Bogan et al[47] evaluated the response onset of sodium oxybate in the treatment of two of the main symptoms caused by narcolepsy: EDS and cataplexy in narcoleptic patients. Clinically meaningful improvements in EDS and cataplexy, were noticed in the majority of patients involved during the first 2 months, whereas a longer period is required to succeed maximum response. Thus the authors concluded that clinicians should be aware of the fact that the amount of time between the initial and maximum response may vary from weeks to months.

A possible mechanism of action of GHB in the treatment of cataplexy has been recently proposed by Szabadi[32]. The noradrenergic nucleus locus coeruleus (LC) is thought to be involved since it is crucial for the preservation of the muscle tone and stops activating during cataleptic episodes. Moreover, alpha-2 adrenoceptors augment in the LC in cataplexy, possibly because of "heterologous denervation supersensitivity" as a result of the weakening/loss of the orexinergic intake to the LC. The latter would lead to the sensitization of the auto-inhibition mechanism of LC neurons, which is mediated by inhibitory al-

pha-2 adrenoceptors. Emotional stimulus triggers the excitatory intake from the amygdala to the LC, leading to the "inactivation" of LC action through the supersensitive auto-inhibition mechanism. Since GHB is an agonist at both $GABA_B$ and GHB receptors, it may prevent a cataleptic stroke by lessening the tone of LC neurones through stimulating the inhibitory extrasynaptic GABA receptors in the LC, thereby augmenting the threshold for autoinhibition.

Moreover, it is hypothesized that the mechanism of action of GHB in promoting its therapeutic effects on narcolepsy is $GABA_B$ receptor associated. Black et al[48] investigated the effects of chronic administration of the $GABA_B$ agonist *R*-baclofen (*R*-BAC) and GHB on cataplexy and arousal state in two different mice models for narcolepsy: *orexin/ataxin-3 (*Atax), which represent the juvenile narcolepsy onset model and *orexin/tTA TetO diphtheria toxin* mice (DTA) which is more characteristic of a post pubertal onset. Mice were administered GHB at the dose of 150 mg/kg, *R*-BAC at 2.8 mg/kg or vehicle (VEH) for 15 days at the rest phase so as to mimic the dosage followed by narcoleptic humans (i.e. twice nightly GHB intake) and were EEG/EMG monitored. It was found that GHB did not enhance non-rapid eye movement (NREM) sleep duration or consolidation. However, NREM delta power augmented in the first hour after administration. Cataplexy was reduced from baseline in 57% of mice after GHB dosing and in 86% after *R*-BAC intake. Cataplexy increased in 79% of VEH treated mice. The authors concluded that *R*-BAC should be utilized as a therapeutic agent for narcolepsy since it was found to be more effective compared to GHB in the treatment of cataplexy and increased NREM sleep time[48]. Moreover, Lee and Douglass[34] after reporting two cases of narcoleptic patients suffering from multiple daily cataplexy attacks (one out of the 2 patients had been successfully treated with GHB, but had to cease the therapy for unrelated medical reasons) also suggest that baclofen could be an effective treatment for cataplexy since both individuals experienced almost complete resolution of this medical condition after treatment.

### *Sodium Oxybate for the Treatment of Alcohol Withdrawal Syndrome and the Maintenance of Alcohol Abstinence*

AWS includes numerous symptoms occurring in alcohol-dependent subjects following the reduction or interruption of ethanol use in heavy and chronic alcohol abusers.

Symptoms due to AWS usually begin about two hours after the last alcohol ingestion and their intensity may vary from mild to severe manifestations.

The most frequent are: anxiety, agitation, shakiness, nightmares, seizures and auditory, visual and tactile hallucinations, etc., whereas only in few cases the onset of very severe symptoms, such as delirium tremens may occur.

The above reported symptoms are strictly related to the modifications in numerous neurotransmitter circuits, which are involved in the alcohol pathway and represent a homeostatic alteration of the CNS[49,50]. The time of symptoms' onset after the cessation of alcohol use is reported in Figure 3.

There is clear clinical evidence that all symptoms related to AWS are due to the interruption of a continuous exposure of the CNS to alcohol.

Brain receptors are affected by a long-term consumption of alcohol and they have undergone some changes in order to carry on normal functioning.

There is a decrease in both GABA and GABA-receptor sensitivity levels[51,52] and the glutamate systems are activated[53], leading to a hyperactivity of CNS when alcohol is no longer present. Alcohol increases the inhibitory effects of GABA on efferent neurons, therefore suppressing neuronal function. As a consequence of chronic alcohol exposure, GABA receptors are less responsive therefore higher alcohol levels are necessary in order to obtain the same degree of suppression. This phenomenon is known as "tolerance"[54].

Alcohol also exerts its effects as an antagonist on N-methyl-D-aspartate (NMDA) receptor, leading to a decrease of the CNS excitatory tone. After long-term use of alcohol there will be an up-regulation of glutamate in order to sustain CNS homeostasis. In absence of alcohol in the readapted system, the GABA receptors will still show a lower response to the point of an unequal balance, favouring the excitatory neurotransmission because the glutamate remains unhampered[55].

Excitation of the CNS neurones in the form of autonomic hyperactivity like tremors, sweating, psychiatric symptoms, tachycardia and more serious complications, delirium and seizures, is often observed clinically in alcohol withdrawal manifestations[54].

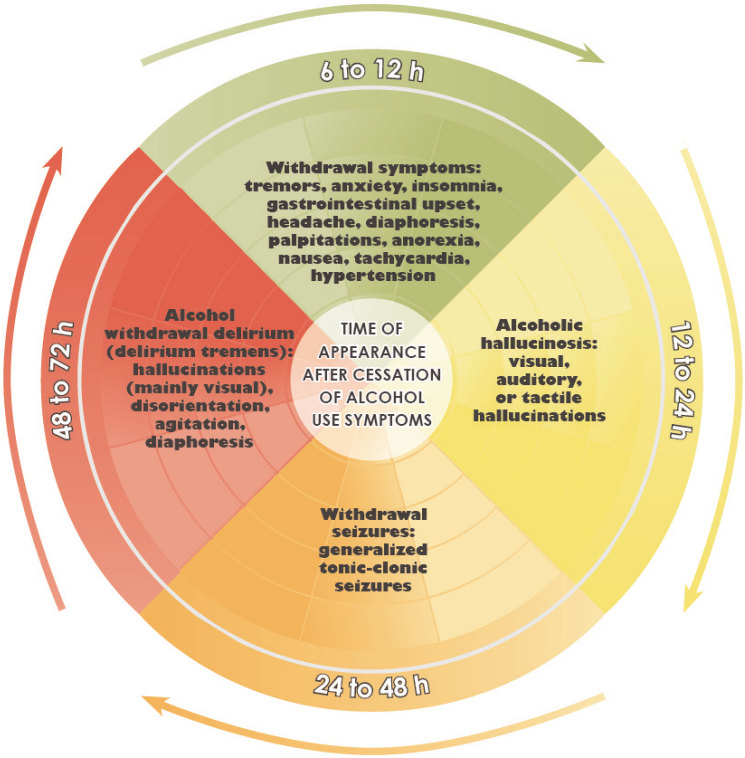


**Figure 3.** Most common symptoms in relation to time of appearance after alcohol cessation.

Another important neurotransmitter, which plays an important role in alcohol withdrawal conditions, is dopamine. The onset of autonomic overarousal and hallucinations is attributed to alcohol abuse and increase in dopamine concentrations. It has also been hypothesized that seizures due to withdrawal are the consequence of seizure threshold reduction due to kindling[56].

GHB exerts an alcohol mimetic activity which is related to the effects of the increase of dopamine by $GABA_B$ receptors in the mesocorticolimbic circuit[57].

Sodium oxybate as well as the GHB endogenously produced act both on GHB receptors and $GABA_B$ receptors. The high affinity binding between GHB and pre-synaptic GHB receptors determines a reduction of GABA release, whereas the low affinity binding of GHB with $GABA_B$ receptors determines a higher activation of the membrane receptors.

The administration of sodium oxybate principally leads to a decrease of GABA release from GABAergic neurons by the activation of GHB receptors[57]. The consequence of this activation determines the release of dopamine within the circuit and therefore this mechanism explains why GHB exerts alcohol mimic activity[57,58].

The efficacy of GHB in suppressing alcohol withdrawal symptoms through the conversion of GHB into GABA and the activation of $GABA_A$ receptors, has been demonstrated because when it is activated, the $GABA_A$ receptor selectively conducts Cl– through its pore, resulting in hyperpolarization of the neuron and the subsequent suppression of AWS manifestations.

Addolorato et al[59] have investigated in a randomized, controlled, single-blind study, by including 60 alcoholics, the efficacy and safety of sodium oxybate in comparison to diazepam for the treatment of alcohol withdrawal symptoms and the results obtained allowed the authors to conclude that both GHB and diazepam are effective in the management of alcohol withdrawal symptoms, however in the sodium oxybate group anxiety, agitation and depression were faster resolved.

In another study by Nava et al[60], where 42 alcoholics were enrolled, the effectiveness of sodium oxybate and diazepam for the suppression of severe AWS was evaluated and the results of the study highlight that GHB is slightly more efficient compared to diazepam in the suppression of AWS.

In both studies[59,60] sodium oxybate was administered at a dose of 50 mg/kg and divided into three or four daily administrations.

As above mentioned GHB has an ethanol-mimicking effect on CNS[61-63] and thus it has been shown that GHB is able to inhibit voluntary ethanol intake in rats having preference for the latter substance[61,62,64]. Human studies also showed that GHB (dose of 50 mg/kg, divided in three administrations per day) is capable to increase the number of abstinent days, reduce alcohol craving[65,66] and decrease the number of drinks per day[65]. The drug was also demonstrated to be manageable, producing few side effects including dizziness, tiredness and sleepiness that are usually overcome within 2-3 weeks. However, about 30-40% of alcoholics on GHB treatment fail complete abstinence from alcohol despite the fact that they sometimes achieve temporary decrease of alcohol compulsive desire. A study for the investigation of the efficacy of GHB, when given six times daily at the same dose of 50 mg/kg in subjects who failed alcohol abstinence under GHB treatment three times daily, was then conducted. A significant decrease of alcohol desire in a higher percentage of alcoholics who achieved complete abstinence was demonstrated[58,67]. The efficacy of GHB (25-100 mg/kg/day) has also been evaluated in "treatment resistant" chronic alcoholics, i.e. patients who had already attempted at least twice to be treated. It was shown that 60% of the subjects were "responders", either "full" i.e. successfully reached complete abstinence and social adjustment or "partial" i.e. decreased alcohol intake but did not achieve full alcohol abstinence[68].

A study for the comparison of the efficacy of oral GHB (50 mg/kg three times a day) and oral naltrexone (50 mg/day) in the maintenance of alcohol abstinence in patients mostly suffering from moderate dependence proved that GHB has better efficacy than naltrexone (66.7% and 35.3%, respectively)[69]. Another study investigating whether GHB or naltrexone or a combination of the latter agents could help in the maintenance of alcohol abstinence after treatment with escitalopram (which belongs to SSRI category) has also been conducted. It was shown that the combination therapy together with escitalopram is more efficient than GHB (+escitalopram), naltrexone (+escitalopram) or escitalopram alone, 83.3%, 50%, 33.3% and 18.1% respectively[58,70].

Leone et al[71] reviewed both controlled prospective studies and randomized controlled trials on the safety and efficacy of GHB compared to either placebo or other therapeutic agents for the prevention of relapse and the treatment of AWS. The authors concluded that the available randomized evidence is insufficient to determine with confidence whether there is difference between placebo and GHB or not, or to establish reliably if GHB is more effective compared to other agents for the treatment of AWS and the prevention of relapse. However, the limited randomized data suggest that GHB (50 mg) may be more efficient than placebo in the treatment of AWS, prevention of relapses and the desiring in formerly detoxified alcoholics (during the first 3 months of follow-up). No evidence in against or in favour of GHB were provided in comparison to clomethiazole or benzodiazepines, although some randomised data suggest that GHB is better than naltrexone and disulfiram regarding abstinence maintenance, prevention of craving in the medium term i.e. 3-12 months. The authors recommend taking into account their findings that GHB should be used only under strict medical supervision, highlighting the concerns about the abuse/misuse of the drug and the addiction potential[71].

## Conclusions

A variety of medications have been used for the treatment of the symptoms of narcolepsy, including psychomotor stimulants, TCAs, SSRIs and MAOIs. However, GHB has been used for over 30 years and has the most well-documented clinical data among all drugs evaluated for the treatment of narcolepsy[23].

Nowadays, sodium oxybate is the first-line treatment for narcolepsy and it is highly effective in meliorating sleep architecture, decreasing EDS and the frequency of cataplexy attacks in narcoleptic patients. Furthermore, adverse effects of sodium oxybate are moderate and it is well tolerated, when taken as recommended[42].

Its mechanism of action is different from stimulants and wake-promoting agents, since it binds to its own monadic receptor[38].

Moreover, a good tolerability and efficacy of sodium oxybate was documented in the majority of a pediatric population composed of 27 children (age range: 6 to 16 years old), who were suffering from narcolepsy with cataplexy and were tested in a retrospective study[46]. However, further randomized controlled trials in narcoleptic pediatric population are required.

Sodium oxybate currently finds also application in the treatment of AWS and the mainte-

nance of alcohol abstinence in alcoholics. AWS includes numerous symptoms which arise in alcohol-dependent individuals after reducing or interrupting ethanol consumption (in heavy and chronic alcohol abusers).

Most of the studies evaluating the efficacy of GHB in the treatment of AWS, use a dosage of 50 mg/kg divided in three or four administrations per day[59,60,69]. Furthermore, due to the rapid metabolism of the drug, administration of the same dose divided in 6 administrations has also been investigated[67].

Human studies showed that GHB (dose of 50 mg/kg, divided in three administrations per day) is capable to increase the number of abstinent days, reduce alcohol craving[65,66] and decrease the number of drinks per day[65]. Moreover, small amount of randomized data suggest that GHB may be more efficient than placebo in the treatment of AWS, prevention of relapses and desiring in formerly detoxified alcoholics (during the first 3 months of follow-up)[71].

However, there is limited randomized evidence and, thus, GHB cannot be reliably compared to clomethiazole or benzodiazepines. Some randomized data suggest that GHB is better than naltrexone and disulfiram regarding abstinence maintenance, prevention of craving in the medium term i.e. 3-12 months[71].

It is recommended that GHB should be used only under strict medical supervision, since concerns about the abuse/misuse of the drug and the addiction potential have been arisen[71].

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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