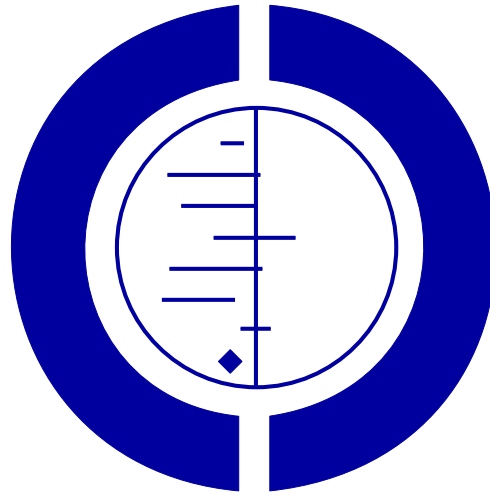# Gamma-hydroxybutyrate (GHB) for prevention and treatment of alcohol withdrawal (Protocol)

**Leone MA, Avanzi GC, Lo Iacono A, Vigna-Taglianti F, Faggiano F**

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# Gamma-hydroxybutyrate (GHB) for prevention and treatment of alcohol withdrawal (Protocol)

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## A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:
To evaluate the efficacy and safety of GHB in prevention and treatment of the AWS, more specifically
- to compare the efficacy of GHB with placebo or other drugs;
- to identify the most effective GHB dosage and schedules;
- to estimate the incidence of side effects;
- to carry out a risk-benefit analysis.

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## B A C K G R O U N D

Chronic excessive alcohol consumption may lead to dependence and hence to the alcohol withdrawal syndrome (AWS) in the event of abrupt reduction or cessation of drinking. AWS is a life-threatening condition. Its severity ranges from a moderate form characterized by tremor, nausea, anxiety, restlessness, insomnia to a more severe form with seizures, hallucinations, agitation and delirium. Progression to coma, cardiac arrest and death is also possible (Morton 1994; Pieninkeroinen 1992; Schuckit 1995).

All the signs and symptoms of the AWS result from alcohol-induced adaptations in the central nervous system (CNS). Alcohol usually acts in the brain like a depressant drug. During prolonged intoxication, the CNS adapts to these effects and alcohol tolerance ensues. The amount of GABA receptors decreases, whereas the amount of NMDA receptors increases (Tan 1997).

The main goals of the clinical management of AWS are to minimize the severity of symptoms, prevent its more severe manifestations such as seizure and delirium and facilitate entry into a treatment program to achieve and maintain abstinence from alcohol (O'Connor 1998).

Withdrawal from alcohol may or may not require pharmacological management, depending on the amount of drinking, the presence of symptoms, and the setting of detoxification (SIGN 2003). Probably three-quarters of patients can be detoxified successfully as out-patients without medication (SIGN 2003), whereas it is generally required for patient at risk or already presenting symptoms of withdrawal, for whom in-patient detoxification is recommended. Different classes of drugs have been used to prevent and treat AWS: benzodiazepines, neuroleptics, antiepileptics and others (Hillbom 2003).

Gamma-hydroxybutyric acid (GHB) is a short-chain fatty acid, a metabolite of gamma-amino-butyric acid (GABA). Its neuropharmacological and neurophysiological effects (Gessa 2000) include the modulation of some neurotransmitters such as dopamine, serotonin, acetylcholine and opioids. Similarity of the effects of GHB and alcohol on the CNS was first described in the early 1970's and subsequently confirmed (Agabio 1998; Colombo 1995; Colombo 1998; Frau 1995). Its alcohol-mimicking effect represents a rationale for using GHB in alcohol addiction treatment and in craving (Gallimberti 1989; Gallimberti 1992). Controlled clinical tri-

als (Addolorato 1998; Ceccanti 1995; Di Bello 1995; Moncini 2000; Nimmerrichter 2002) have demonstrated that GHB both prevents and suppresses withdrawal symptoms, and also improves the medium-term abstinence rate.

GHB was used in Europe for decades without reports of severe side-effects and incidents of abuse. When it became widely available in the US, as health food and body-building supplement during the 1980's, reports of adverse events increased to the point that the Food and Drug Administration (FDA 2006) ordered its removal from the market in 1990.

These adverse effects ranged from mild hypothermia, dizziness, nausea, vomiting, weakness, loss of peripheral vision, confusion, agitation, hallucination, decreased respiratory effort, unconsciousness and coma.

Deaths related to GHB ingestion are usually attributable to the mixing of GHB with other drugs. Only one case has been ascribed to GHB alone (CDC 1997).

In short, GHB has proved effective in several studies. It may be accompanied by some side-effects. A clear balance between effectiveness and harmfulness, however, has not yet been established. Currently, GHB is licensed for treatment of alcohol withdrawal in Italy and Austria.

# OBJECTIVES

To evaluate the efficacy and safety of GHB in prevention and treatment of the AWS, more specifically

- to compare the efficacy of GHB with placebo or other drugs;
- to identify the most effective GHB dosage and schedules;
- to estimate the incidence of side effects;
- to carry out a risk-benefit analysis.

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# CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

## Types of studies

Randomized Controlled Trials (RCT), quasi-Randomized Controlled Trials and Controlled Clinical Trials (CCT) evaluating the efficacy and the safety of GHB in preventing or treating the AWS in comparison with placebo or other pharmacological treatments.

## Types of participants

Alcohol dependent patients diagnosed in accordance with appropriate standardized criteria (e.g., criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R 1994) or equivalent) or as defined by the authors, in therapy with GHB to prevent or to treat AWS. All patients will be included regardless of age, gender,

outpatient or inpatient setting, and history of previous detoxification treatments.

## Types of intervention

Trials will be included if they compare patients undergoing alcohol detoxification (prevention) or in a state of alcohol withdrawal (treatment):

- GHB vs. placebo for prevention of AWS;
- GHB vs. placebo for treatment of AWS;
- GHB vs. other drugs for prevention of AWS;
- GHB vs. other drugs for treatment of AWS;
- GHB combined with other drug vs. placebo for prevention of AWS;
- GHB combined with other drug vs. placebo for treatment of AWS;
- GHB combined with other drug vs. other drugs for prevention of AWS;
- GHB combined with other drug vs. other drugs for treatment of AWS.

...

## Types of outcome measures

Information relating to a variety of outcomes regarding prevention of AWS and treatment of overt AWS will be collected on standardized forms for each treatment arm. These are categorized as measures of global severity, severity of single symptoms and signs, and other short-term and long-term efficacy outcomes:

**Primary outcomes:**

(1) Global severity of overall alcohol withdrawal syndrome as measured in prespecified scales, including Clinical Institute Withdrawal Assessment for Alcohol [CIWA-Ar] score, and others

(2) Severity of single symptoms and signs:
*Symptoms:*

- Hallucinations (tactile, auditory, visual)
- Clouding of sensorium
- Agitation and restlessness
- Anxiety and depression measured with either qualitative or quantitative scales (STAI, SDS Zung or others)
- Alcohol withdrawal delirium··

*Signs:*

- Tremor
- Nausea and vomiting
- Paroxysmal sweats

- Epileptic seizures

**Secondary outcomes**

(3) Length of stay in intensive therapy
(4) Additional medication needed
(5) Percentage of abstinent at the end of the study
(6) Retention in treatment as Number of dropouts per arm, Retention rate, Average stay in the detoxification program
(7) Mortality
(8) Adverse side-effects
...

**Long term outcomes**

(9) Relapse of alcohol consumption
(10) Craving, as measured in specified scales (including Craving scale, LCCR-1, and others)
(11) Duration of abstinence
(12) Rebound phenomena after treatment discontinuation
...

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Drugs and Alcohol Group methods used in reviews.

We used the following search strategy, according to the "Cochrane Drug and Alcohol Group", based on the search strategy developed for MEDLINE but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. No language, publication and time restrictions will be applied.

We will search the following electronic databases:
MEDLINE (1966 to present)
EMBASE (1988 to present)
PsycINFO (1967 to present)
CINAHL - Cumulative Index to Nursing and Allied Health Literature (1982 to present)
The Cochrane Library (2006, issue 2)
Cochrane Drugs and Alcohol Group Register of Trials (April 2006)

We will scan review articles, as well as the studies they include and exclude, to look for other relevant studies. We will review relevant editorials, commentaries, letters to identify useful bibliography. Personal contacts with other research and review teams working in the field, as well as with authors of the included studies will be made to identify other potentially relevant studies. Pharmaceutical companies will also be contacted to obtain unpublished trials.

The following search strategy will be applied to the mentioned databases:
1. exp ghb or ghb.mp
2. gamma-hydroxybutyrate.mp

3. 4-hydroxy butyrate.mp
4. gamma hydrate.mp
5. gamma-hydroxybutyrate sodium.mp
6. gamma hydroxybutyric acid.mp
7. gamma-OH.mp
8. sodium oxybate.mp
9. sodium oxybuty.mp
10. sodium 4-hydroxybutyrate.mp
11. sodium hydroxybutyrate.mp
12. 4 Hydroxybutyric Acid.mp
13. Oxybate Sodium.mp
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp Alcohol-related disorders/
16. exp Drinking behavior/
17. alcohol$.mp
18. withdraw$.mp
19. drinking behav$.mp
20. 15 or 16 or 17 or 18 or 19
21. 14 and 20
22. limit 21 to human

## METHODS OF THE REVIEW

Two authors (Leone and Vigna-Taglianti) ) will scan abstracts for relevance, will review whole reports, assess trials for inclusion, extract the outcome data specified above as well as the following data. The two authors will be blinded to authorship list in the process. Any disagreements will be solved by a third author (Faggiano) assessing the trials.

**Methodological/trial design:**
a. Method of randomisation
b. Method of control of confounding for quasi-randomized trials
c. Method and level of blinding
d. Whether any patients had been excluded from the reported analyses
e. Attrition
Trials will be classified in three quality categories, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006) high, moderate and low risk of bias. A sensitivity analysis will be performed based on this classification, comparing the results of meta-analysis with or without the lowest quality category. Where data are missing, attempts will be made to obtain them from the original authors.

**Patient/demographic information:**
a. Total number of patients allocated to each arm in any protocol
b. Demographic characteristics
c. Setting (out- or in-patients)
d. Whether medication is started immediately after the onset of withdrawal or not
e. Factors related to the alcohol withdrawal episode (severity of symptoms, time since the last drink)

f. Risk factors (previous detoxification or withdrawal episodes, years of alcohol use, mixed abuse of drugs)

## Data analysis plan:

The primary meta-analysis will be focused on intention-to-treat outcomes and will include all randomized patients, analysed in the treatment group to which they were allocated, irrespective of which treatment they actually received. A secondary "protocol correct" analysis for relevant outcomes will also be undertaken.

Clinical heterogeneity will be assessed by reviewing the differences across trials in characteristics of recruited patients and treatment protocols. Methodological heterogeneity will be assessed by reviewing differences in trial design. Statistical heterogeneity will be assessed using a Chi-squared test (p-value = 0.1). ). I-squared statistic will also be calculated (Higgins 2003). Any clinical or methodological heterogeneity discovered will be treated by subgroup analysis. If data will be insufficient for subgroup analyses, sensitivity analyses will be performed.

Dichotomous outcomes will be expressed as relative risks with 95% confidence intervals.

Continuous outcomes will be expressed as weighted mean difference or, where possible, as standardized mean difference.

Time-to-event outcomes will be expressed as hazard ratios.

Funnel plots will be assessed for asymmetry, and possible sources of such bias, including publication bias, will be considered.
..

## POTENTIAL CONFLICT OF INTEREST

## ACKNOWLEDGEMENTS

## SOURCES OF SUPPORT

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# C O V E R   S H E E T

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