Gamma-Hydroxybutyric acid (GHB)

Expert peer review on critical review report (1)

35th Expert Committee on Drug Dependence, Hammamet, Tunisia
June 4-8, 2012
1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential:
The Critical Review Report quotes 10 human studies indicating withdrawal symptoms after abrupt discontinuation of regular chronic use. Those are similar to other CNS depressants (alcohol, sedative hypnotics) and include insomnia, anxiety and tremor, eventually complicated by delirium in frequent heavy users (1 study) and seizures (1 case) or death (1 case), but the clinical features have not been fully characterized. Two studies describe withdrawal symptoms in recreational users. Three reviews are mentioned. In a comparative study, GHB ranked 2nd to pentobarbital with respect to toxicity, taking into account withdrawal severity, cognitive impairment and lethality in overdose.

Animal studies: a withdrawal syndrome after chronic administration of GHB and GBL in baboons is also recorded.

The report summarizes: “tolerance and withdrawal has been observed at prolonged high dosage”.

Abuse potential:
Animal studies: the results in regard to reinforcing effects are not indicative of a profile of a highly abused substance.

Human studies: determining the abuse liability by testing the reinforcing potential of 19 hypnotic substances resulted in ranking GHB as 6 (after pentobarbital, methaqualone, diazepam, flunitrazepam and lorazepam), taking into account abuse liability studies and observed rates of abuse. Another study found the abuse likelihood of GHB to be intermediate to triazolam and pentobarbital.

b. Consequences to individual and society because of misuse

Consequences to individual

Review of data on intoxication show frequent involvement of alcohol and other substances, together with GHB in unknown dosages. No definite conclusions are made on the toxicity of GHB alone. “There is arguably still a need for comprehensive clinical data to be obtained from patients who have only taken GHB before definite conclusions can be made as to the toxicity of this compound in humans” (p.19).

A double-blind placebo-controlled study in human volunteers found decreased O2 saturation in modest dosages, but more adverse effects if combined with ethanol (p.33).

There are no reports mentioned on long-term effects of GHB intoxication, nor on cases using GHB alone for suicidal attempts. In one suicide with car exhausts GHB was found in blood and urine, together with fluoxetine and nortryptiline. One fatal case (fall from height) could be accident or suicide.

Fatalities: the review mentions around 78 cases or more globally, where GHB was involved (approximately 60 from USA, 8 from Europe, 10 from Australasia; more cases only mentioned in printed media and internet). Without detailed analysis of each case this is an
estimate only. Two factors are noteworthy: Frequent presence of other substances, especially alcohol, heroin and other opiates, and sometimes low blood concentrations of GHB (within the range of concentrations apparently produced postmortem as a product of decomposition; GHB is a natural metabolite of human metabolism). The review states that “deaths involving solely GHB are very rare” (p.24).

The review concludes that “more research and thorough analysis of GHB in fatalities and poisonings are still required before the true involvement of GHB can be established and accurate mortality and morbidity figures produced” (p.25)

Most of documented intoxications and fatalities involve illicit GHB.

Consequences to society because of misuse

In chapter 14, the review deals with the nature of public health problems related to misuse, abuse and dependence. It mentions that GHB can be easily manufactured from inexpensive ingredients and recipes obtained from the internet. The powder is mixed with water, and the unknown and variable concentration of the solution is responsible for many of the dangers associated with illicit GHB use.

Specific types of use and misuse are mentioned. One is about the possible growth hormone promoting properties of GHB, used in an attempt to increase muscle mass in bodybuilding. Another is the use as an apparent appetite suppressant. Again another is using the sleep-inducing properties in cases of insomnia or narcolepsy. And some use it as an adjunct in alcohol or opiate withdrawal. But mostly it is used for relaxation or for euphoria and eventually for sexual stimulation. These applications are usually propagated via Internet.

The review also mentions reports on GHB-facilitated sexual assault (‘date rape’) as a contentious area of GHB abuse. It concludes by saying “that the abuse and dependence on GHB continues to be a public health problem; however, the magnitude of the problem has decreased over the past several years” (p.35).

The various effects and respective target populations for abuse might indicate a wide abuse potential: however the EMCDDA report of 2008 suggests that the use “remains limited to some small subpopulations” (p.30).

Post marketing data for Xyrem® have not revealed evidence of abuse of this product. Abuse is mostly due to illicit GHB.

It is noteworthy that the review has no systematic data on accidents under the influence of GHB (only 1 of 34 cases listed in table 3 mentions “road accident”), nor data on dosages impairing driving behavior.

Other consequences are dealt with in the following sections.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

Misuse: GHB appears to be mainly used in USA and in Europe. The Drug Abuse Warning Network DAWN, based on emergency room data in USA, reported low incidence figures for GHB involvement and a continued downward trend (0.13% in 2005). The European Early Warning System (EWS) has only insufficient data to establish prevalence and identify
trends at the EU level. However, the European Monitoring Centre on Drugs and Drug Addiction EMCDDA in its 2011 annual report states that “the illicit use of ketamine and GHB has become a cause for concern for treatment services in a limited number of European countries” (p.31).

In a WHO survey of 2008, 14 out of 51 countries responding reported the use of GHB in a harmful way. Increasing misuse is reported from Australia, stabilisation from USA.

Illicit activities: A WHO report of 2008 mentions clandestine manufacturing in 8 countries, smuggling in 7 and diversion in 5 countries, other illicit activities in 4 countries. Seizures are reported from 8 countries (reports to UNODC on seizures in 2003 came from 4 countries, in 2004 from 6 countries). The prices per effective dose are comparatively low. For more recent information from INCB, see section 2 (additional information).

d. Need of the substance for medical (including veterinary) practice

Narcolepsy and associated cataplexy is an approved indication for prescribing Xyrem®(GHB) in USA since 2002, in the EU since 2005.

GHB is approved for anesthetic use especially for children in Italy and France, with declining use (also due to epileptic seizures and vomiting, and to unpredictable duration of action).

There is no information given on countries approving GHB for other indications. Instead, reports are quoted on other types of medical use. These include obstetric surgery and childbirth, treatment of anxiety, treatment of depression, sexual enhancement. Such use appears to be infrequent. More recently, GHB was found useful in the management of alcohol withdrawal, but limited by short half-life and abuse potential.

Marketing authorizations for GHB (Oxybate) as a medicine have been issued in 14 European countries, in USA and Canada. GHB is not included in the WHO list of essential medicines.

No use in veterinary medicine is mentioned. Nor are data on the epidemiology of medical use provided.

More information is presented under section 2.

e. Need of the substance for other purposes (e.g. industrial)

The production of many polymers uses GHB, and also GBL and 1,4-BD as solvents.

f. Measures taken by countries to curb misuse

The UN has scheduled GHB in the 1971 convention of psychotropic substances under schedule IV, with the obligations for all parties to report annually on manufacturing, export and import.

The US Drug Enforcement Administration DEA requires additional recordkeeping and reporting for products that contain GHB, in order to protect against diversion for illicit purposes.
The WHO survey of 2008 mentions that 30 countries have controls of GHB under legislation.

g. **Impact if this substance is scheduled**

Scheduling to schedule III would oblige recording and annual reports by retail distributors, hospitals, care institutions and scientific institutions on the amount of GHB they handled. Scheduling to schedule II would imply records on each acquisition. Use and abuse of illicit GHB, of gamma-butyrolactone GBL and 1,4-butanediol 1,4-BD would only be affected if precursors are controlled.

### 2. Additional information to the critical review report


The report provides updated information on trends in manufacturing, export and import of GHB. Comparing the data from 2008, 2009 and 2010 (in kg), a general upward trend is manifest:

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<tr>
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<th>Manufacture</th>
<th>Export</th>
<th>Import</th>
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<tr>
<td>2008</td>
<td>29’631</td>
<td>12’576</td>
<td>9’820</td>
</tr>
<tr>
<td>2009</td>
<td>36’888</td>
<td>12’731</td>
<td>14’401</td>
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<tr>
<td>2010</td>
<td>59264</td>
<td>12’791</td>
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b. **GHB report to the California Legislature** ([www.ceri.com/report.htm](http://www.ceri.com/report.htm))

The report by S.W. Fowkes reflects the trend to extend indications for medical use.

GHB is currently available by prescription in the US through compounding pharmacies. It has no formal drug status with the FDA (although 15 INDs are pending).

There are 15 INDs filed with the FDA for 1) improving sleep patterns and maintaining daytime alertness in narcolepsy, 2) reducing schizophrenic symptoms, 3) stabilizing Parkinson’s disease, 4) reducing nocturnal myoclonus (painful leg cramps at night), 5) improving memory problems, 6) stimulating natural growth hormone release, 7) decreasing pain and improving sleep in fibromyalgia, 8) relieving symptoms in Huntington’s chorea, 9) regulating muscle tone in dystonia musculorum deformans, 10) controlling tardive dyskinesia symptoms, 11) decreasing drug withdrawal symptoms (alcohol and opiates), 12) decreasing hyperactivity and learning disabilities in children, 13) inducing sedation and tranquilization, 14) relieving anxiety, and 15) lowering cholesterol.

### 3. Other comments or opinions

No other comments.
4. Expert reviewer’s recommendation on scheduling with rationale

Keep GHB in schedule IV

Moving it to schedule III would create an administrative burden on medical and research institutions handling GHB, which is not justified by diversion.

Public health problems are mainly due to the use of precursors, directly or for the illicit manufacturing of GHB. Their control need to be discussed.