Gamma-Hydroxybutyric acid (GHB)

Expert peer review on critical review report (2)

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
   - There is evidence in animals and humans that GHB can produce a withdrawal syndrome if the substance is abruptly discontinued after regular chronic use. A systematic review of the withdrawal syndrome associated with GHB, 1,4-butanediol and gamma-butyrolactone was conducted by Wojtowicz et al in 2008 and recently reviewed by Wood et al in 2011.
   - Results of animal studies assessing the abuse liability of GHB have been mixed. Recently Goodwin and her colleagues (2011) conducted a study in which baboons self-administered GHB by injection. She found that high dose GHB can act as a reinforcer in non-human primates.
   - Carter et al (2006) compared the abuse liability of GHB, triazolam and pentobarbital in a population of recreational sedative abusers. They concluded that “Although the likelihood for GHB to be abused is intermediate to triazolam and pentobarbital, the possibility of accidental overdose (i.e. greater sedation than intended) with GHB appears to be greater”.

b. Consequences to individual and society because of misuse
   - GHB has a narrow margin of safety and numerous reports of intoxication and lethality have appeared in the literature. Often GHB is used in conjunction with other CNS depressants and when this occurs the adverse effects are exacerbated. A recent study compared emergency room admissions in individuals who had used GHB only, to those that had used GHB and other substances of abuse. They found that those who had used GHB and other substances had more severe symptoms (Galicia et al, 2012). In another recent study Zvosec and colleagues (2011) examined 236 GHB-related fatalities and concluded that GHB is lethal even without the presence of cointoxicants.
   - GHB poses significant danger to society when users drive under the influence of GHB. Users report a sudden loss of consciousness known as ‘G-napping’ while driving. (Gonzalez et al, 2005; Barker et al, 2007; Barker and Karsoho, 2008; Jones et al, 2008). Norway is the first country to propose legislative limits for non-alcohol drugs including GHB (Vindenes et al, 2011).

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)
   - Available data indicates that abuse of and dependence on GHB continues to be a public health issue. Of the 51 countries who responded to the WHO Questionnaire, 14 countries reported on the harmful use of GHB and 8 countries reported on the extent of harmful use.

d. Need of the substance for medical (including veterinary) practice
14 countries have authorized GHB as a medical or veterinary product. It is used as an anesthetic and other registered indications include depression, glaucoma, insomnia, narcolepsy with cataplexy and alcohol and opiate withdrawal. It is also used in neurotraumatology.

e. **Need of the substance for other purposes (e.g. industrial)**
   GHB is used in the production of a variety of polymers. GBL and 1,4BD are used as solvents in a number of industrial processes. GBL is also used as a starting material for other products.

f. **Measures taken by countries to curb misuse**
   In the USA an extensive risk management program (Xyrem Success Program) was put into place to prevent diversion and abuse by limiting distribution and by providing an educational program for physicians and patients on the proper use of the medicine. In the 2008 WHO questionnaire, 30 countries reported that GHB was controlled under legislation that intended to regulate availability.

g. **Impact if this substance is scheduled**
   In the 2008 WHO questionnaire, two countries (Armenia and Tuvalu) stated that medical availability would be affected if GHB were to be placed under stricter international control.

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

   Added in the sections above

   GHB overdoses can lead to profound coma which may be neurotoxic for the brain, especially those of young adults. (van Amsterdam et al, 2012)

**References**


Wood, DM, Brailsford, AAD and Dargan, PI. Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). Drug Test. Analysis 2011; 3: 417-425.


Barker JC and Karsoho H. Hazardous use of gamma hydroxybutyrate; Driving under the influence. Substance Use & Misuse (2008); 43: 1507-1520


Van Amsterdam JGC, Brunt TM, McMaster MTB and Niesink RJM. Possible long-term effects of \(\gamma\)-hydroxybutyric acid (GHB) due to neurotoxicity and overdose. Neuroscience and Biobehavioral Reviews (2012); 36: 1217-1227.

3. Other comments or opinions

It should be noted that the Netherlands recently re-assessed the risk potential of GHB and found it to be moderate to high. On this basis GHB was upgraded to Schedule 1 (hard drugs) of the Dutch Opium Act.

Reference


4. Expert reviewer’s recommendation on scheduling with rationale

GHB has psychoactive properties and produces toxic effects when used in supratherapeutic doses (ie doses that are used for recreational purposes). It has abuse potential and chronic regular use can lead to dependence. If the drug is abruptly discontinued a withdrawal syndrome ensues. This withdrawal syndrome can be serious and life threatening. GHB also has a very narrow margin of safety and numerous reports of intoxication and deaths (whether GHB is used alone or in combination with other CNS depressants such as alcohol) have been published. This poses a significant risk to individuals who abuse this drug. There have been reports of individuals driving under the influence of GHB and this poses a risk to society. Abuse of GHB has been reported in several countries including Australia and the Netherlands. GHB is used
therapeutically in several countries for a variety of indications such as treatment of opiate and alcohol dependence, narcolepsy and as an anesthetic. Data from the USA has shown that when GHB is used in therapeutic doses the extent of abuse is low. This is mostly due to the strict risk management program that has been established. However GHB continues to be abused in the USA and the source of the drug is from clandestine manufacture. On the basis of these issues, it is recommended that GHB be rescheduled to Schedule II of the 1971 Convention on Psychotropic Substances.