INVITED EDITORIAL

Does Gamma-Hydroxybutyrate (GHB) Have a Role in the Treatment of Alcoholism?

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Alcoholism (alcohol abuse and dependence) is a chronic disorder affecting both brain and behavior that has worldwide public health consequences. Primary goals for alcoholism pharmacotherapy include mitigating withdrawal, maintaining abstinence and reducing the severity of relapse, usually in combination with behavioral treatment or self-help groups. Currently, only three medications for the treatment of alcoholism are approved for use in the USA—disulfiram, acamprosate and naltrexone—and the efficacy of each is modest at best. In this context, the recent Cochrane Review of the use of gamma-hydroxybutyrate (GHB) for the treatment of alcoholism is a welcome addition to the literature (Leone et al., 2010). The Cochrane Collaboration is a group of >27,000 volunteers in >90 countries who prepare, maintain and make accessible systematic reviews of the effects of healthcare interventions tested in randomized controlled trials (RCTs), with the goal of helping clinicians to make well-informed decisions about health care. Cochrane Reviews have a reputation for stringent assessment methods and generally cautious conclusions. In this case, the authors conclude that, despite some limitations, there is enough evidence to recommend GHB’s use both for treating alcohol withdrawal and for preventing relapse. In fact, they argue that GHB is more effective than either naltrexone or disulfiram, the current mainstays in alcoholism pharmacotherapy.

GHB, or as a pharmaceutical product, sodium oxybate, is a pharmacologically intriguing short-chain fatty acid structurally similar to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and is approved for treatment of alcoholism in Italy. GHB is a weak agonist at the inhibitory GABAB receptor and a potent agonist at the newly characterized excitatory GHB receptor (Cash et al., 1999), which is densely expressed in many areas of the brain, including the cortex and hippocampus. Dopamine is released following GHB receptor stimulation by low concentrations of GHB, but dopamine release is inhibited by higher doses of GHB that stimulate GABAB receptors, leading to a biphasic response. Conversion of exogenously administered GHB to GABA also induces an indirect activation of GABAA and GABAB receptors that is responsible for GHB’s sedative and anxiolytic effects. Dopamine release is initially inhibited, then increased via the GHB receptor.

It is likely that this GABAergic activity mediates GHB’s effects on withdrawal and relapse. Exogenous GHB may ameliorate alcohol withdrawal (which results from reduced GABAergic activity in the central nervous system) because of its conversion to GABA and indirect activation of GABAA receptors. Its efficacy in relapse prevention might be due either to ‘normalization’ of GABA receptors or through ‘substitution therapy’, as GHB affects the GABAA receptor in a similar fashion to alcohol.

The Cochrane Review suggests that, in detoxification, GHB may be superior to benzodiazepines in its ability to treat some but not all symptoms of alcohol withdrawal, and suggest that GHB has potential for the treatment of unexpected withdrawal (as in alcoholics hospitalized for trauma or elective surgery). As benzodiazepines are also drugs of abuse, the abuse potential of GHB should not preclude its development as a treatment for alcohol withdrawal, as it appeared to have slight advantage in controlling withdrawal symptoms compared with diazepam (although this may have been due to the relative doses used). However, the development of other medications without abuse potential, such as the anticonvulsants, would seem preferable.

More interesting—and potentially more difficult clinically to implement—is GHB’s potential role as a relapse-prevention agent. The review included 13 RCTs comprising 648 participants, extracted from a larger pool of 39 published trials, which reported the efficacy of GHB on a number of alcohol-related outcomes. GHB outperformed placebo on measures of controlled drinking, number of daily drinks, relapse rate and complete abstinence. For maintenance of abstinence, GHB outperformed both naltrexone and disulfiram, and improved the efficacy of naltrexone when used in combination. GHB and acamprosate were not compared. The authors note a number of limitations in their review. Because of the low number of enrolled patients and the poor quality of many the studies, the authors rated the overall quality of the evidence as low in general, but moderate for treatment of withdrawal and prevention of relapse; for a variety of reasons (outlined fully in the Review), they could have overestimated the efficacy of GHB in relapse prevention. Nonetheless, the authors recommended forging ahead with larger trials that can determine optimal dose and schedule, and also evaluating the use of GHB for treating unexpected withdrawal.

Does GHB’s status as a ‘club drug’ preclude its use for alcoholism? During the 1980s, easy access to GHB-containing products led to its use for weight loss, sleep induction and bodybuilding. Unapproved and unregulated, GHB became notorious for serious adverse effects such as dependence, overdose (including in combination with alcohol) and death, and was vilified in the media as a ‘date rape’ drug (Weiss and Colyer, 2010). It was eventually prohibited (split scheduled) in the USA in 2000. That being said, initial concerns about the potential of GHB for abuse and diversion when prescribed for narcolepsy have proved to be unfounded, largely because of the implementation of strict controls in the form of the Xyrem Risk Management Program (Carter et al., 2009; Fuller et al., 2004).

Components of the Xyrem program include a physician and patient registry, compulsory educational materials for
patients and physicians, a specially trained pharmacy staff, a method for tracking prescription shipments, an initial post-marketing surveillance program and a centralized distribution and dispensing facility. This specialized facility has security features far in excess of most pharmacies: medication holding, dispensing and shipping areas are secured by locked, steel-reinforced concrete holding areas and 24-h security includes motion detectors and closed-circuit television surveillance of all areas. As of March 2008, 26,000 patients had been prescribed 600,000 bottles of GHB, but only 5 cases of diversion (0.001%), 10 cases of DSM-IV abuse (0.04%), and 4 cases of DSM-IV dependence (0.016%) had been reported (Wang et al., 2009).

Will such stringent controls be sufficient to allow safe prescription of GHB for alcoholism, or are they feasible only for a comparatively rare disorder (narcolepsy) that does not hijack patients’ motivational system? While we do not have the answer to those questions, the experience with other controlled substances like the opioid pain medications suggests that despite controlled prescribing and other precautions, increased availability can have unintended consequences for the community at large, such as the recent upsurge of opiate dependence, particularly among young people. Despite its potential benefits, the adoption of GHB as a treatment for alcoholism faces considerable obstacles that cannot be overcome simply through larger clinical trials.

Finally, the acceptability of any proposed treatment by the community of individuals with alcohol use disorders, their families, the providers who treat them and the self-help community is an important consideration. Self-help groups such as Alcoholics Anonymous (AA) have played an important role in recovery. Despite the official position of AA that medically necessary treatments are acceptable, a recent survey of members of AA found that almost one-third of the members had experienced some pressure to stop taking medications of any type (Rychtarik et al., 2000). The use of medications contradicts a historical emphasis on complete abstinence and also the experience of many addiction treatment counselors, whose own personal recovery was achieved by working the 12 steps. GHB’s pleasant subjective effects will doubtless assist compliance relative to a medication such as naltrexone, but will also increase diversion risk, perception of diversion risk and consequently clinicians’ and other community members’ resistance to its use. The use of GHB can be justified for use in a controlled setting, such as a detoxification center or an inpatient unit, where medications are administered or dispensed on a daily basis; its outpatient use for relapse prevention, less so.

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**REFERENCES**


