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## ▶ Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses.

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*Can one of the UK's most notorious 'club drugs' help alcoholic patients withdraw from and stay away from alcohol? The answer from this authoritative review is that probably it can, but not well enough to displace safer and less abuse-prone alternatives.*

**SUMMARY** The main goals for clinical management of alcohol withdrawal are to minimise the severity of symptoms and to facilitate treatment entry to promote longer-term remission from dependence. Medications to aid withdrawal include benzodiazepines, anticonvulsants and gamma-hydroxybutyrate (GHB). Similarity of GHB's psychoactive effects to alcohol was first described in the 1970s and subsequently confirmed, and represents the rationale for its use in alcohol addiction treatment. Clinical trials have shown it can prevent and suppress withdrawal symptoms, and improve abstinence rates in the medium term.

The drug was used in Europe for decades without reports of severe side effects and incidents of abuse. When during the 1980s it became widely available in the USA as a health food and body-building supplement, reports of adverse events increased to the point that the US Food and Drug Administration ordered its removal from the market in 1990. Adverse effects included mild hypothermia, dizziness, nausea, vomiting, weakness, loss of peripheral vision, confusion, agitation, hallucination, decreased respiratory effort, unconsciousness and coma. Some deaths have been reported, usually when GHB has been mixed with other drugs, though one has been ascribed to GHB alone. The drug is licensed and approved for medical use with alcoholics only in Italy and Austria.

At the time of this review, clear estimates of the beneficial and harmful effects of GHB in the treatment of alcohol dependence, and the balance between these, had yet to be established. The review aimed to assess the evidence for the drug both as an aid to withdrawal and as a continuing medication to help prevent relapse, drawing on trials which randomly allocated patients either to GHB or to a placebo or other medication.

Analysts found 13 randomised trials which tested the drug's effectiveness and safety in the treatment of alcohol problems, involving 648 participants. All but two of the trials had been conducted in Italy; one was from Germany and another Austria.

### Main findings

Six trials with a total of 286 participants evaluated GHB's effectiveness in ameliorating withdrawal symptoms. One study found the drug did reduce symptoms significantly better than a placebo, but there were just 23 patients. Seven of the 11 GHB patients developed transitory vertigo; none of the 13 placebo patients developed any side-effects. Other trials featured a variety of other medications and doses. No strong differences were observed between GHB and either the benzodiazepine tranquilliser diazepam or clomethiazole, a drug used to help induce sleep in cases of severe insomnia. There were, however, some statistically significant differences in symptom reduction favouring GHB, though in one study high doses caused more side-effects (not severe enough to prompt termination of treatment) than clomethiazole. More side effects from high doses were also apparent in a comparison between higher and lower doses of GHB.

Seven trials involving 362 participants tested GHB as a mid-term treatment to prevent relapse in patients already detoxified from alcohol. These made several different comparisons, so each analysis was able to include only one or two trials, and the trials were generally small, with 17 to 98 participants. Two trials compared the drug with an inactive placebo over respectively three and six months. Retention, craving, abstinence, amount drunk, and measures of heavy or controlled drinking, all favoured GHB, and sometimes to a statistically significant degree after three months but not six months of treatment. However, the drug may (the finding was not statistically significant) have caused more side-effects than the inactive placebo.

When compared to other anti-relapse medications, based on three trials and one trial respectively, GHB appeared superior to both naltrexone and disulfiram in reducing craving and supporting abstinence, but not in respect of relapse to heavy drinking or the intensity of consumption. In both cases it may (the findings were not statistically significant) have caused fewer side effects than the other medications.

Some anti-relapse studies tried combining GHB with other medications. Compared to naltrexone alone, adding GHB improved numbers abstinent, but possibly caused more adverse effects. The combination of GHB, naltrexone and escitalopram also improved abstinence rates after up to six months of treatment compared to escitalopram alone. Without naltrexone in the mix, results were similar but not statistically significant.

The number of patients developing side-effects from GHB was low. Most consistently reported (nearly a fifth of patients at normal 50mg doses) were dizziness or vertigo. Side-effects were more common at higher doses; at 100mg per day, just over half of patients experienced vertigo, but none so severely that they left treatment.

### The authors' conclusions

Evidence was insufficient and too inconsistent to be confident that GHB had been proved preferable to an inactive placebo or to other drugs for the treatment of alcohol withdrawal or the prevention of relapses. However, there were indications that it is more effective than naltrexone and disulfiram in reducing craving and in maintaining abstinence, possibly signs of the drug's potential which should be explored in larger and rigorous independent trials.

Studies were few and small, and selected their patients on the basis of long lists of inclusion or exclusion criteria. Only one was judged a good quality study. The finding from these randomised trials that at 50mg doses about a fifth of patients experience dizziness or vertigo is in line with observations on more than 1000 patients in other kinds of studies. However, in anti-relapse studies, side-effects tended to be fewer from GHB than from naltrexone or disulfiram. It should be noted that the reviewed studies did not permit an assessment of the risk of dependence on GHB as a result of treatment, and nor are such trials well suited to identifying rare adverse effects.

Set alongside concerns about addiction to GHB and the misuse or abuse of the drug, the findings of this review suggest it be used only under strict medical surveillance. In many countries GHB is an illegal drug but available over the internet or through the illicit market. In these circumstances, it is used for its purported anabolic effect or for weight loss or sleep induction, but also as a euphoria-inducing recreational drug, especially when taken with other illicit substances. When used as an illegal drug, several cases of dependence based on the development of withdrawal symptoms have been described but (when known) only after the consumption

of five times the therapeutic dose. Problems with abuse of the drug appear confined primarily to polydrug abusers and use outside a medical context. When administered under continuous medical surveillance at therapeutic doses and with supervision by a designated family member, cases of abuse and withdrawal are rare. Since abuse and toxicity are more frequent in polydrug abusers or previous drug abusers, GHB should not be used for these patients.

**FINDINGS COMMENTARY** Due to the potential for it to be misused, UK clinical guidelines in which it is described as a "club drug" unequivocally advise: "Do not use gammahydroxybutyrate (GHB) for the treatment of alcohol misuse." An update to those guidelines cited the featured review in confirmation of this stance, though the review reserved this degree of caution only for patients with a history of drug misuse, and found GHB no more side-effect prone than naltrexone and disulfiram. However, these medications have virtually zero abuse potential and are authorised in the UK for the treatment of alcohol problems, as is acamprosate. Generally too these drugs are safe. With no convincing advantages in preventing relapse, there seems little case for considering GHB as an aid to treatment for alcohol dependence.

In the UK benzodiazepines are the preferred way to ease withdrawal from alcohol and prevent complications. Possible extra amelioration from using GHB instead does not seem enough to outweigh other considerations.

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