

**Project title:** Improving GHB withdrawal with baclofen

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### **Plain English language**

Background: GHB (gamma-hydroxybutyrate) and its pro-drugs GBL (gamma-butyrolactone) and 1,4-butanediol are central nervous system depressants (hereafter GHB). Regular use of GHB can lead to dependent use, with use every 1-4 hours to prevent withdrawal. GHB withdrawal or detoxification may be challenging to clinicians and dependent users as it is unpredictable and potentially life-threatening due to delirium and behavioural problems. Whilst benzodiazepines can treat GHB withdrawal, very high doses may be insufficient to reduce such complications. Our clinical experience was that in addition to benzodiazepines, baclofen, which is a medication that targets the same system in the brain as GHB, the GABA-B system, may be beneficial in improving GHB detoxification and that starting baclofen 2 days prior to stopping GHB may help further.

This was a feasibility double-blind placebo controlled trial of baclofen in managing GHB withdrawal in those dependent on GHB requiring planned outpatient or unplanned inpatient detoxification to provide information about recruitment and characteristics of the proposed outcome measure (symptom severity, complications, treatment escalation) to inform a definitive RCT of the role of baclofen in addition to benzodiazepines for GHB detoxification.

Findings: In the outpatient planned arm, the recruitment rate was developing though slower than that originally stated with 6 completed from 21 initial contacts within 5 months (target 60). Most were ineligible due to lack of appropriate support at home. One person required admission to hospital ie treatment escalation. In the unplanned arm, only one person completed detoxification (target 28) with two not proceeding due to staffing issues. The sponsor stopped the study after 6 months due to concerns about recruitment rate. Due to the small amount of data, we are unable to undertake statistical analyses.

Conclusions: We are cautious in drawing any conclusions due to small participant numbers however it was evident that participants welcomed the opportunity to take part in the trial due to expertise of study team, that there is limited expertise outside specialist centres to access, and that service reconfigurations and changes in GHB use contributed to the challenge of recruiting and conducting the study. We advise that outpatient GHB detoxification is a challenging clinical situation to manage and expert advice and inpatient facilities must be available.

### **Keywords**

Baclofen

Gamma-Hydroxybutyrate (GHB)

Withdrawal

Dependence

Detoxification

Feasibility  
RCT  
Qualitative

## **Summary of research findings**

### **Background:**

GHB (gamma-hydroxybutyrate) is a CNS depressant used recreationally. Dependence on GHB is associated with withdrawal symptoms that are similar to alcohol withdrawal but generally more severe. Benzodiazepines have been the pharmacotherapeutic mainstay for GHB withdrawal. However, adjunctive baclofen may be beneficial in improving GHB detoxification and starting baclofen 2 days prior to stopping GHB may help further.

### **Aims and objectives:**

The main objective was to investigate the feasibility of recruiting participants and characterising the impact of adding baclofen to a standard benzodiazepine regimen for management of GHB withdrawal in the community and hospital.

### **The secondary objectives included:**

1) withdrawal symptoms and complications such as delirium and requirement for treatment escalation during detoxification (detox) in a planned and unplanned detox setting (Club Drug Clinic (CDC), CNWL NHS Foundation Trust & St Thomas's Hospital, Guy's & St Thomas' NHS Foundation Trust (GSTT); 2) did starting baclofen 2 days prior to stopping GHB conferred additional benefits; 3) recruitment rate; 4) secondary outcome measures (anxiety, depression, sleep); 5) GHB, other drug/alcohol use 1mo post-randomisation; 6) participant and staff views about the acceptability of the study design; 7) information to develop full economic analysis in definitive trial.

### **Methods:**

This was a feasibility double-blind placebo controlled trial of baclofen in managing GHB withdrawal in those dependent on GHB requiring planned outpatient (CDC) or unplanned inpatient detox (GSTT) to provide information about recruitment and characteristics of the proposed outcome measure (symptom severity, complications, treatment escalation) to inform a definitive RCT of the role of baclofen in addition to benzodiazepines for GHB detox.

Key inclusion criteria: anyone (>18 yrs old) who i) either in active withdrawal or ii) has underlying GHB dependence and wishes to undergo GHB detox or iii) is thought to have underlying dependence and is at risk of acute withdrawal. Key exclusion criteria: medication is not required for management of GHB withdrawal, lacks capacity to consent, unable to take oral medication or baclofen.

Randomisation and groups. The planned outpatient group (hereafter CDC) received 2 days preload then detox: a) baclofen 10mg tds for 2 days then: benzodiazepine+baclofen 10mg tds or b) placebo tds for 2 days then: benzodiazepine+baclofen 10mg tds or c) placebo tds for 2 days then: benzodiazepine+placebo tds. For the unplanned inpatient group (hereafter GSTT): a) benzodiazepine+baclofen 10mg tds or b) benzodiazepine+placebo tds. The benzodiazepine reducing regimen was determined by the prescribing clinician.

## Key Findings.

### Recruitment.

The study was active for five months from September 2016 to January 2017. In CDC group, 6 participants were randomised from 21 referrals; 2 were deemed clinically inappropriate (eg did not want abstinence), 4 failed to engage after initial telephone screening, 1 sought detox from their local service and 8 were being assessed when the sponsor brought the study to an end. For those that did not proceed, their clinical details including GHB use was similar to those who were randomised. A major issue for many potential participants was to meet the requirement that someone had to be at home to support their early days of GHB detox. In the GSTT arm, 1 person completed the detox with 2 not enrolled due to staffing issues (eg lack of pharmacy availability).

The trial failed to meet its initial projected recruitment rate (4.2/mo) despite being widely and regularly promoted to colleagues and via social media and CDC website. On 24/01/2017 the sponsor closed the study.

### Reasons for study closure:

In closing the study, the sponsor sought independent advice and considered the following in addition to the fact that the expiry of medication could not be extended: A] There are no safety concerns with regards to this trial. For the 7 participants recruited 1 participant has had an SAE reported, this SAE demonstrated that the safety monitoring and reporting systems established for the trial worked well. B] expected recruitment 4.9/month vs actual recruitment 1.3/month. This is a feasibility trial of recruitment to inform a main RCT and so not powered to detect meaningful differences in clinically important endpoints. After 6 months of recruitment, it is clear that the trial is not feasible. As participants are not being recruited at a reasonable rate, to continue the trial to recruit a few more participants will not add any value or important scientific information. C] Staffing: The project manager's role as trial manager is essential in respect to monitoring compliance to the protocol, GCP, regulations and sponsor procedures. The project manager has been trained extensively and has the working knowledge of the trial, the sites and is responsible for data management and monitoring activities. She has a good working relationship with us and understands the sponsor's requirements/procedures. When she goes on maternity leave, unfortunately it doesn't make sense to appoint a replacement for her at the very end of the trial with all the training that would be involved. From a sponsor perspective this would bring only risks in regards to compliance. The sponsor concluded on the basis of the risk-benefit assessment to terminate the study early.

### From the data collected:

Key information: CDC group: only 2 completed their detox on day 10, one was admitted on day 1 of detox to a general hospital due to delirium, individuals dropped out on day 2, day 8 and detox was stopped for the other on day 8 due to continuing drug use. This range of outcomes is commensurate with our clinical experience. The GSTT participant was discharged on day 3 and completed their detox on day 10.

There were no insurmountable difficulties in collecting data during detox using CRFs and clinical records. Of note, the sedation assessment tool was added to the Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA) to see if it provided additional useful

information but all participants scored 0. This included the one who was admitted with delirium, who also scored low on the CIWA. This suggests the sedation tool is not useful and that CIWA scale may not be sensitive enough to pick up developing delirium. Sleep data was also highly variable making it hard to interpret.

Concerning qualitative interviews, 3 CDC participants completed their interview before study closure; GSTT participant declined. Of note, the CDC participants particularly welcomed the expertise available at CDC compared with their local services and was commensurate with client satisfaction forms revealing generally very high levels of satisfaction with their experiences. The staff were all highly committed to the trial and were frustrated that it was unable to continue to deliver evidence for this important clinical question. They raised issues about the burden of regulatory processes, challenges about how difficult to do the trial with current clinical pressures and 'risk averse' position, delays with the starting but also enjoyed contributing.

30 days follow-up was only possible from 3 CDC & the GSTT participant of which 2 were still abstinent from all drugs and alcohol on day 30. Our level of follow-up was not unexpected in this client group.

#### **Conclusions and Impact.**

This feasibility study did not achieve its projected rate of recruitment however currently less people are presenting with GHB dependence for detox. The appreciation of expertise available by participants and local services supports the need for accessible specialist treatment. This is particularly pertinent given one challenge faced was the changes in addiction service configuration. The CIWA and sedation tool did not appear to capture all aspects of GHB withdrawal adequately. The role of baclofen as an adjunct to benzodiazepines in managing GHB withdrawal remains unclear. Based on our experience we advise that outpatient GHB detox should be undertaken with expert advice and that inpatient facilities must be available.

#### **Patient and public involvement**

As part of our recruitment strategy, presentations about the trial were given to: 1. Public Health England (PHE) London-wide providers; 2. PHE commissioners forum; 3. London Drug Consultants meeting; 4. Commissioners in triboro (Westminster, Hammersmith & Fulham, Kensington & Chelsea); 5. our partnership providers eg Antidote have supported our participants and advertised the study to their clients.

We established greater links with User organisations outside CNWL

As study terminated early the opportunities for PPI dissemination are limited. We have discussed the limited data within clinical teams which includes a peer mentor at CDC.

#### **Data sharing statement**

See link [\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which

contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

**Disclaimer**

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This project was carried out between August 2015 and May 2017. This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.