Adjunctive Medication Management and Contingency Management to enhance adherence to acamprosate for alcohol dependence: the ADAM trial RCT

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/DQKL6124.

Primary conflicts of interest: Sadie Boniface was joint PI on an NIHR Policy Research Programme award in 2021 (NIHR202711) and works at the Institute of Alcohol Studies the Alliance House Foundation, and other academic and civil society organisations.

Anne Lingford-Hughes has received Honoraria paid into her Institutional funds for speaking and Chairing engagements from Lundbeck, Janssen-Cilag; received research grants or support from Lundbeck, GSK; unrestricted funds support from Alcarelle for a PhD, consultancy for Silence (paid) and Dobin, Britannia Pharmaceuticals and AstraZeneca (all unpaid); delivered training for British Association for Psychopharmacology about alcoholism treatment.

John Marsden declares research grants from the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM; randomised controlled trial of novel cognitive therapy for cocaine use disorder). John Marsden is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network and he was Senior Academic Advisor for the Alcohol, Drug, Tobacco, Justice Division, Health Improvement, Public Health England (to September 2021). He received honoraria and travel support from PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2018 and 2021).

John Strang is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. John Strang has been in receipt of an NIHR Senior Investigator Award.

Joanne Neale is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

Colin Drummond is supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. CD is in receipt of an NIHR Senior Investigator Award. CD was part funded by the NIHR Collaboration for Leadership in Applied Health Research and Care South London (NIHR CLAHRC South London) now recommissioned as NIHR Applied Research Collaboration South London at King's College Hospital NHS Foundation Trust. CD has also received research funding from the NIHR and the Medical Research Council.

Eileen Brobbin is completing a PhD funded by the NIHR Applied Research Collaboration South London at King's College Hospital NHS Foundation Trust.

Laura Hermann is in receipt of an NIHR Pre-doctoral Fellowship.

Published October 2023
DOI: 10.3310/DQKL6124

Scientific summary

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Health Technology Assessment 2023; Vol. 27: No. 22
DOI: 10.3310/DQKL6124

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Alcohol is a significant risk factor for morbidity and mortality. In the UK there has been an increase in harm related to alcohol while also a reduction in funding to public health budgets, including alcohol services. While some individuals do successfully complete alcohol treatment, the majority will undergo frequent episodes of relapse. Providing effective treatment can reduce relapse rates and associated harms thus having a positive impact on cost-effectiveness.

The National Institute for Health and Care Excellence (NICE) recommends acamprosate in combination with psychological intervention as a first-line treatment for relapse prevention in alcohol dependence, however, acamprosate adherence poses a problem for its effectiveness in clinical practice. The reasons for non-adherence are complex and often due to multiple influences. Currently there is insufficient evidence as to which forms of intervention are effective in increasing adherence. Psychosocial interventions to support medication adherence have the potential to promote positive beliefs about medication and any concerns. Medication Management (MM) is a psychosocial intervention which aims to improve medication and treatment adherence by providing education, support, and practical advice about drinking behaviour and medication. There has also been an increasing focus on extending the role of the community pharmacist and the delivery of MM to improve medication adherence compliments this expanding role. Engagement in psychological interventions and retention in treatment is often poor in alcohol dependence but there is evidence that Contingency Management (CM) improves engagement and retention in substance use disorder treatment. There is currently limited evidence of its effectiveness within alcohol treatment but if shown to be effective it has the potential to also be adopted within the NHS and community pharmacies.

Objectives

Our aim was to evaluate the effectiveness and cost-effectiveness of adjunctive MM with and without CM in improving adherence to acamprosate for relapse prevention in alcohol dependence.

1. To conduct a definitive three-arm, randomised controlled trial (RCT) of the effectiveness of MM with and without CM compared to Standard Support (SS) alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.
2. To estimate the cost-effectiveness of MM with and without CM compared to SS alone in enhancing adherence to acamprosate in alcohol dependence relapse prevention.
3. To assess the impact of adherence to acamprosate for alcohol dependence relapse prevention on abstinence and reduced alcohol consumption.

Methods

Trial design

This was a three-arm, parallel-group, pragmatic RCT, which began with an internal pilot phase to demonstrate recruitment, randomisation and interventions could be implemented as planned.

Eligibility and recruitment

Participants presenting to alcohol services in one of the trial sites (London, Southampton, Birmingham, Yorkshire and Humber) who met the trial inclusion criteria were recruited via service staff.

Participants

Inclusion criteria were: (1) adults, aged 18 years and over; (2) an *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis of alcohol dependence; (3) abstinent from alcohol at baseline assessment; (4) in receipt of a prescription of acamprosate; and (5) willing and able to provide informed consent. Exclusion criteria were: (1) a diagnosis of a severe physical/mental illness likely to preclude active participation in treatment or follow-up, (2) unable to understand verbal English at a level necessary to engage in the intervention and follow-up and (3) concurrent dependence on an illicit substance (other than cannabis).

Randomisation and interventions

Participants were randomised in a 2 : 1 : 1 ratio to SS, SS + MM or SS + MM + CM using a stratified random permuted block method using a remote system. Participants and researchers were not blind to treatment allocation. SS typically comprised of monthly dispensing of prescribed acamprosate, monthly monitoring of the service user for 3 months by the specialist alcohol service, and then returned to the care of their GP for monthly monitoring in accordance with NICE guidelines and current clinical NHS clinical practice.

SS + MM participants followed the same care pathway as those in SS, with the addition of MM delivered by a central telephone support service by trained pharmacists. MM was delivered once a week for the first 6 weeks, reducing to once a fortnight for the following 6 weeks, and then monthly for 3 months.

SS + MM + CM participants followed the same care pathway as those in the SS + MM arm but with the addition of CM. Incentives in the form of vouchers were provided to reinforce attendance at MM sessions, up to a total of £120.

Outcomes

The primary outcome measure was the self-reported per cent of medication taken as prescribed during the 6-month target phase of prescribing, post randomisation.

Data collection

Data were collected at baseline, 2, 4, 6 and 12 months. Following an amendment, the 12-month follow-up was removed to maximise participant recruitment, and the recruitment period was extended without extending the trial end date. Data that had been collected at the 12-month follow-up were still included in the trial analysis plan. The primary outcome was collected at the 6-month follow-up.

Sample size

The sample size aimed to detect a clinically important effect size difference of 0.3, about 13% difference in per cent adherence. In order to make the study cost-efficient, we proposed to allocate twice as many to the SS group than to the SS + MM and SS + MM + CM groups. With power at 80%, alpha of 0.05 and a two-sided test, this required 524 to be followed up at the primary end point, 262 in the SS group and 131 in each of the other groups. We anticipated a loss to follow-up at month 6 of 30% and inflated the required sample at baseline to 748 to account for this. Sample sizes were calculated using Stata 12 (StataCorp LP, College Station, TX, USA).

Statistical methods

The primary analysis was an analysis by treatment allocated (ATA) and was based on all available data for participants who were randomised, irrespective of whether they complied with their allocation or not.

The primary analysis was based on the ATA. Secondary analyses examined treatment effects under different scenarios for compliance with allocation/treatment: complier average causal effects (CACE). Two scenarios of compliance were defined in this trial. The first compliance for those in the SS + MM and SS + MM + CM group was defined as adhering to at least 50% of the MM calls. In the second, the

threshold was increased to 100%. Both scenarios are modelled in the analysis. We considered missing data as being missing at random (MAR) or missing not at random (MNAR). We conducted a multiple imputation to address MAR and a sensitivity analysis to address MNAR.

Fractional regression was conducted to model the relationship between pre-randomisation factors and per cent adherence to acamprosate and per cent days abstinent from alcohol at month 6. Interaction terms with treatment allocation were included in the model and a significance level of 0.1 was used as a threshold to determine which variables were maintained in the final model reported. Baseline variables included initially in the model include age, gender, marital status, ethnicity, employment status, number of children, age of first drink, weekly and daily drinking, frequency and quantity of alcohol consumption, severity of alcohol dependence, alcohol urges and alcohol-related problems. This analysis was augmented with an additional analysis for the SS + MM and SS + MM + CM groups where the same dependent variable was assessed with the same independent variables with the addition of therapeutic alliance.

Method of economic evaluation

The primary economic analysis was a cost-utility analysis where outcomes were expressed as quality-adjusted life-years (QALYs), as recommended by NICE. A secondary analysis explored cost-effectiveness in terms of the primary clinical outcome which was adherence to relapse prevention medication. The primary economic perspective was the NHS and personal social services (NHS/PSS) perspective preferred by NICE.

The primary time horizon of the economic analyses using both QALYs and relapse medication adherence was the 6-month follow-up, consistent with the primary clinical analysis. A secondary analysis was carried out at the 12-month follow-up using QALYs. The primary economic outcome was QALYs calculated using the EuroQol-5 Dimensions, a five-level version measure of health-related quality-of-life scores at baseline, 6- and 12-month follow-ups.

The primary economic analysis was composed of two separate comparisons: (1) SS + MM + CM versus SS alone; and (2) SS + MM versus SS alone, both at 6 months post randomisation, and assessed cost-effectiveness in terms of cost per QALY using the EuroQol-5 Dimensions measure of quality of life. Two secondary economic evaluations were carried out, a cost-utility analysis at 12 months post randomisation and a cost-effectiveness analysis using adherence to relapse medication which was the primary clinical outcome. Cost-effectiveness was explored using incremental cost-effectiveness ratios (difference in mean cost divided by difference in mean effect) and cost-effectiveness acceptability curves (CEACs), which show the probability that SS + MM + CM or SS + MM are cost-effective compared to SS alone for different levels of willingness to pay for improvements in outcome.

Sensitivity analyses were carried out to test the impact of varying methods and assumptions on the relative cost-effectiveness of the interventions being compared. We planned three sensitivity analyses: (1) a broader analytical perspective to include the cost of crime (which was not completed as no crimes were reported), (2) a complete case analysis for comparison with the results that used multiple imputation for missing data and (3) a cost-utility analysis using QALYs calculated from EuroQol-5 Dimensions, three-level version tariffs.

Results

A total of 1459 potential participants were approached of whom 1019 (70%) were assessed. Of these 739 (73%) were eligible and consented to participate in the study. Allocation was in the ratio of 2 : 1 : 1, 372 (50%) were allocated to SS, 182 (25%) to SS + MM and 185 (25%) to SS + MM + CM. At the primary end point, 6 months post randomisation, 518 (70%) were successfully followed up with 255 (68.5%)

allocated to SS, 122 (67.0%) to SS + MM and 141 (76.2%) to SS + MM + CM. There were no serious adverse events related to the trial interventions reported.

The mean difference in per cent adherence to acamprosate at month 6 between those allocated to SS and SS + MM + CM versus SS was 10.6% [95% confidence interval (CI) 19.6% to 1.6%]; this difference was statistically significant. When the SS + MM group was compared to SS alone, the SS + MM group had a lower per cent days adherent than the SS group, mean difference 3.1% (95% CI 12.8% to −6.5%); this was not significant. A similar non-significant finding was seen when we compared the SS + MM and SS + MM + CM groups, mean difference 7.9% (95% CI 18.7% to −2.8%).

Our secondary analysis included per cent days abstinent from alcohol at month 6. The ATA found differences favouring both intervention groups over SS alone but neither of these was significant. When a CACE analysis was conducted using scenario 2, both intervention groups had a significantly greater per cent days abstinent than SS alone. This analysis also highlighted the relationship between adherence to acamprosate and better outcomes, something additionally highlighted by a significant correlation between adherence to acamprosate and increased per cent days abstinent at month 6. CACE analysis: Under scenario 1, 50% adherence, the mean difference in per cent adherence increases from 10.6% (95% CI 19.6 to 1.62) to 12.4% (95% CI 17.8% to 7.1%) in the SS + MM + CM versus SS comparison, indicating that at 50% compliance those allocated to SS + MM + CM have a mean of 12.44% more adherence to acamprosate at month 6 than those allocated to SS alone. When comparing the SS + MM versus the SS group, a previous non-significant difference 3.14% (95% CI 12.8% to −6.5%) becomes a significant difference of 13.2% (25.4–1.15%). Under scenario 2, the differences are larger in magnitude, the SS + MM + CM group having 22.2% (95% CI 29.7% to 14.7%) more adherent days than the SS group alone. At the same time, the magnitude of difference is larger for the SS + MM versus SS comparison 31.8% (95–60.5% vs. 3.10%), although this comparison is based on a small number of participants, 20, and should be interpreted with caution.

For SS + MM + CM versus SS, the primary economic analysis at 6-month follow-up using QALYs, the secondary economic analysis at 6-month follow-up using medication adherence and the economic modelling over a 20-year time horizon using QALYs all found SS + MM + CM to dominate SS (better outcomes at lower cost). At 12-month follow-up, although SS + MM + CM was not dominant, it generated more QALYs at an additional cost that was below the NICE cost per QALY threshold. CEACs also showed there was a higher probability of SS + MM + CM being cost-effective compared to SS alone in all analyses and at all time points.

For SS + MM versus SS, at 6- and 12-month follow-up and when modelled over 20 years, SS + MM achieved better outcomes at higher cost compared to SS. In terms of cost-effectiveness, SS + MM was not found to be cost-effective at 6-month follow-up but had a higher probability of being cost-effective compared to SS at both the 12-month follow-up (using the higher £30,000 per QALY NICE threshold) and when modelled over 20 years (over the full £20,000–30,0000 cost per QALY threshold).

Conclusions

When comparing SS + MM + CM versus SS alone, we observed a significantly higher per cent adherence to acamprosate in the SS + MM + CM group, and the differences were of the magnitude that would indicate a clinically important difference. Differences were also observed when comparing SS + MM versus SS and SS + MM + CM versus SS + MM, but these were not significant. We explored how robust these findings were to assumptions about the nature of any missing data and we explored a missing data imputation model to explore the impact of data that may be MAR and a sensitivity analysis to explore data that may not be MAR. Neither of these analyses found any significant deviation from the analysis based on observed values, we can be confident that our findings from the ATA analysis are robust. To explore the effect of compliance to MM we conducted a CACE analysis using two scenarios of

compliance, 50% and 100%. In both scenarios, we found greater benefits associated with SS + MM + CM and SS + MM versus SS alone and these benefits were significant and clinically important.

There were several limitations to the current trial that should be taken into consideration. The trial's primary outcome measure changed substantially due to data collection difficulties and therefore relied on a measure of self-reported adherence. A lower than anticipated follow-up rate at 12 months may have lowered the statistical power to detect differences in the secondary analyses, although the primary analysis was not impacted.

The results of the primary economic analysis at the 6-month follow-up point suggest that MM was only cost-effective when supported by incentives to encourage support session uptake. This finding was heavily influenced by lower total costs in the SS + MM + CM group as a result of lower use of residential rehabilitation facilities compared to both SS + MM and SS alone, which may be related to the significantly higher medication adherence seen in the CM group. Over the medium (12 months) and longer term (20 years), SS + MM + CM remained cost-effective compared to SS and there was a higher probability of SS + MM being cost-effective compared to SS. These results support the addition of MM to SS for alcohol dependence, with or without CM. However, the economic benefit was stronger when CM was included.

Trial registration

This trial is registered as ISRCTN17083622 https://doi.org/10.1186/ISRCTN17083622.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 22. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.6

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/86/03. The contractual start date was in December 2014. The draft report began editorial review in December 2021 and was accepted for publication in August 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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