Double-blind, 36 month, placebo-controlled trial of mifepristone on cognition in alcoholics

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Introduction

Cognitive deficits are seen in 50 to 80 % of those dependent on alcohol currently there is no effective treatment. Depression is a major symptom in many people who are dependent on alcohol, and is associated with greater tendency to relapse drinking. High levels of release of glucocorticoids (cortisol) during and after the acute alcohol withdrawal period may contribute to symptoms of depression and cognitive deficits following alcohol detoxification.

Aim

To examine the extent to which the Type II glucocorticoid receptor antagonist, mifepristone, when given to alcohol-dependent persons during the acute phase of alcohol withdrawal, protects against the subsequent memory loss and depressive symptoms during abstinence from alcohol. The results will provide information about the extent of the contribution of glucocorticoids to these problems, which will aid future development of treatment for alcohol dependence.

Hypotheses:

1. Those who receive mifepristone will have superior cognitive function, measured using the CANTAB cognitive battery, compared to those who receive placebo.
2. Those who receive mifepristone will show significant improvement in symptoms of depression from baseline, measured using the Beck Depression Inventory, compared to those who receive placebo during the first 4 weeks of treatment.

Method

Double blind randomised controlled proof of principle clinical trial. Participants were alcohol dependent males completing an alcohol detoxification. Participants were randomised to receive 600mg of mifepristone or placebo (one 200mg tablet three times a day) for 7 days starting on the first day of detoxification and 400mg for the following 7 days (one 200mg tablet twice a day). The primary outcome measures were cognitive ability measured by the Cambridge Neuropsychological Test Automated Battery (CANTAB), depressive symptomatology measured using the Beck Depression Inventory (BDI-II). Secondary outcomes included severity of the acute phase of alcohol withdrawal, alcohol craving and symptoms of protracted withdrawal Participants completed follow-up visits at 3, 6 and 12 months post randomisation to examine abstinence form alcohol, levels of relapse drinking and depressive symptomatology.

Statistical analysis

All data was checked for distributional assumptions. The primary outcome, CANTAB battery was assessed using parametric models controlling for pre-assessment variables using analysis of covariance. Depression was assessed at 4 weeks using non-parametric models adjusted for baseline values. Secondary outcomes were assessed in a similar manner. As the number of participants was low no imputation of missing data was undertaken, as the parameters this is based on would be

unreliable. The mean and 95% significance value is presented for normally distributed variables and the median and inter-quartile range for non-normally distributed variables. Outcomes were interpreted taking account the multiple number of tests contained in the primary outcome CANTAB battery by employing Bonferroni corrections where required.

Results

A total of 57 people were screened to take part in the trial and 27 (47%) were randomised (figure 1). Table 1 presents the participant demographics, which were similar for those randomised and not randomised. There were no differences between those who were allocated placebo and those who were allocated mifepristone for measures of drinking (table 2). Table 3 presents the results of the neurocognitive testing, placebo and mifepristone groups performed similarly across all tests. A decrease on score on the Beck Depression Inventory was seen over the first three weeks of treatment, with no statistically significant differences between the placebo and mifepristone groups (table 4).

Table 1: participant demographics:

	Randomised (n = 27)	**Not randomised (n=30)**
Age, mean (SE)		
White, n (%)	26 (96.3)	18 (85.7)
Married or cohabiting, n (%)	2 (7.4)	1 (4.8)
In employment, n (%)	1 (3.7)	2 (9.5)
Professional or skilled, n (%)	9 (33.3)	10 (47.6)
Home owner, n (%)	1 (3.7)	0
Years of education, mean (SE)	11.14 (0.48)	13.08 (0.88)
Number of children, mean (SE)	2.19 (0.32)	2.42 (0.29)
Age of first drink, mean (SE)	12.50 (0.48)	14.17 (0.52)
Age drinking weekly, mean (SE)	16.36 (0.72)	20.00 (2.12)
Age drinking daily, mean (SE)	24.64 (2.71)	25.83 (2.81)

Figure 1: Trial consort diagram

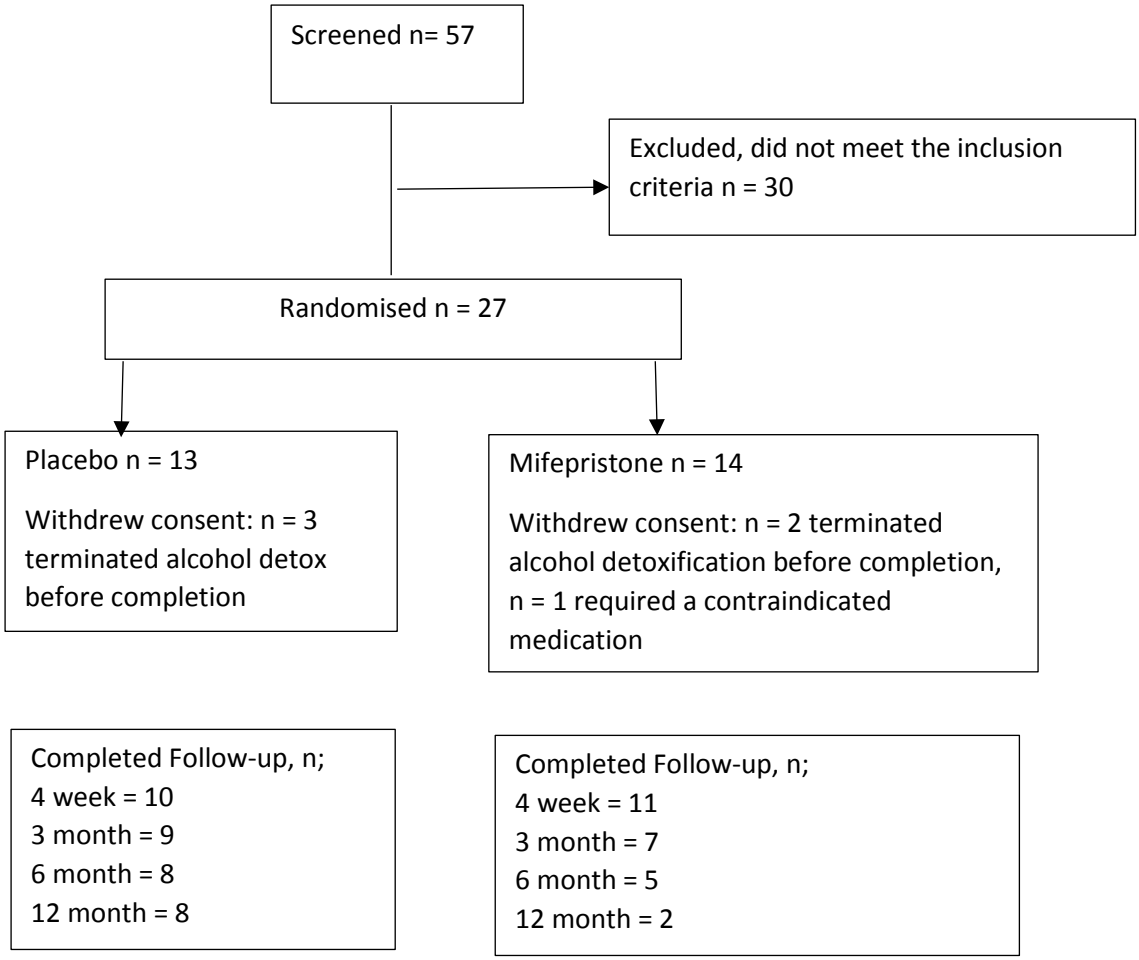

Table 2: Participant alcohol consumption, problems experienced and craving prior at baseline assessment, prior to detoxification

	Placebo (n=13), median (IQR)	**Mifepristone (n=14), median (IQR)**	**P value**
Timeline Follow-back, drinks per drinking day	27.24 (24.27)	29.53 (18.13)	0.99
Alcohol Problems Questionnaire	13 (6.5)	13.5 (6.75)	0.99
Alcohol Urge Questionnaire	51 (31.5)	47.5 (16.75)	0.71

Table 3: Neuropsychological function at 4 weeks post commencement of detoxification, placebo versus mifepristone

Test	**Placebo (n=10), mean (95% CI)**	**Mifepristone (n=11), mean (95% CI)**	**P value**
Memory			
Paired Associates Learning (number of trials)	13.00 (10.50; 15.50)	14.00 (9.49; 18.51)	0.99
Pattern Recognition Memory (% correct)	90.00 (80.35; 99.65)	91.67 (86.66; 96.67)	0.39
Spatial Recognition Memory (% correct)	66.50 (53.99; 79.01)	73.64 (64.99; 82.28)	0.39
Executive Function			
Stockings of Cambridge (number of problems solved)	8.10 (6.69; 9.51)	7.55 (5.84; 9.25)	0.99
Intra-Extra Dimensional Set Shift (number of trials)	117.60 (69.67; 165.53)	164.82 (87.31; 242.33)	0.67
Spatial Working Memory (between errors)	39.00 (23.83; 54.17)	53.09 (41.12; 65.06)	0.20
Attention and psychomotor speed			
Reaction Time, reaction (milliseconds)	330.51 (282.88; 378.13	350.44 (290.09; 410.78)	0.67
Reaction Time, movement (milliseconds)	460.66 (382.12; 539.19)	489.92 (431.43; 548.42)	0.39
Rapid Visual Information Processing latency (milliseconds)	432.45 (325.38;539.51)	473.69 (391.54; 555.84)	0.18
Match to Sample Visual Search (% correct)	96.11 (91.50; 100)	95.95 (92.19; 99.72)	0.99

Table 4: Symptoms of depression measured using the Beck Depression Inventory over 4 weeks of treatment, placebo versus mifepristone

	Placebo, median (IQR) [n]	**Mifepristone, median (IQR) [n]**	**P value**
Baseline	17 (24) [11]	23 (23) [13]	0.99
Week 2	10 (15.5) [10]	17 (23) [10]	0.18
Week 3	8.5 (16) [10]	13.5 (16.5) [10]	0.66
Week 4	7 (11.75) [10]	14 (12) [11]	0.20

Conclusions

Based on the data that is available, we can conclude that the current trial has found no evidence to suggest that mifepristone is superior to placebo in preventing problems with memory and depression in those completing a detoxification for alcohol dependence. However, it was not possible to recruit the numbers of participants required, primarly because of the closure of all the inpatient alcohol detoxification units.

Challenges and protocol changes

There were many challenges faced during the completion of this research, which resulted in an underpowered trial. The challenges faced are summarised below;

1. March 2009 - August 2009, delay waiting for the risk assessment from SLaM/IoP R&D office.
2. September 2009 – November 2010 problem due to withdrawal of medication supplier.
3. February 2011 – December 2011 Changes in NHS commissioning of Alcohol Detoxification Units resulting in:-

February 2011 withdrawal of Capio Hospital site from trial
May 2011 withdrawal of Surrey and Borders hospital site from trial
September 2011 closure of North East London Hospital ward
October 2011 closure of Bethlem Royal Hospital ward
December 2011 closure of Springfield hospital ward

4. January 2010 – December 2012 Necessity for Ethics Committee approval for Protocol changes, owing to replacement of hospital sites and reduction of four week inpatient stays in NHS Alcohol Detoxification wards to a maximum of two weeks.
5. September 2011 - July 2012 Delays in site contract preparation by King's College Joint Clinical Trial Office
6. June 2013 – September 2013 Delay in delivery of second batch of medication.
7. June 2013 - November 2013 Delay in Sussex hospital site initiation owing to closure of West Park pathology laboratory.
8. Whilst the formal decision to include outpatients was taken at a Trial Management meeting in September 2014, it took until November 2014 to complete all the negotiations and arrangements for outpatient recruitment at the different hospital sites and to obtain Ethics approval for this.
9. March 2015 to April 2015 Delay in recruitment at Hull site, owing to lack of chlordiazepoxide availability for inpatients

10. October 2014 to April 2015 Delay in recruitment at Hull site due to the recommissioning of Hull Alcohol Service.
11. November 2014 - February 2015 Delay in recruitment at Hull site, owing to changes in clinical staff.
12. April 2015 onwards. Inpatient recruitment at Hull site had to cease, owing to decommissioning of alcohol detoxification inpatient beds.
13. April 2015 - Recruitment had to cease at the Barnsley site due to their inpatient unit undergoing review, they did not have sufficient staff to continue recruitment for the trial
14. May 2015 - Recruitment had to cease at the Sussex site as the site did not have the resources to support the trial.
15. July 2014 onwards - lack of availability of clinical input at the Kent site, owing to maternity and sick leave.

Following advice from the Trial Steering Committee, a protocol amendment to recruit participants completing their detoxification as outpatients was completed in September 2014. However, due to the withdrawal of support from two of the sites and the constant re-commissioning of addiction services, recruitment to the trial continued to be difficult.

Arrangements for publication and dissemination

The results of the trial will be submitted to a peer reviewed journal and further disseminated via an academic conference.