PSYCHOLOGICAL TREATMENT FOR ALCOHOL-RELATED LIVER DISEASE

Universal Trial Number: U1111-1230-4489

Trial Registration: ANZCTR Registration Number: ACTRN12619000710123p

SUMMARY

This project is primarily a quality assurance activity intended of determine non-inferiority or superiority of a new treatment protocol for patients with Alcoholic Hepatitis (AH) referred to the Alcohol and Drug Assessment Unit by the Department of Gastroenterology and Hepatology. In addition, we seek to collect saliva samples from these patients to replicate recent research which has identified an association between PNPLA3 gene and AH. Early evidence suggests that the risk of AH is doubled among G allele carriers of PNPLA3 (Liangpunsakul et al. 2016).

PROJECT TEAM ROLES & RESPONSIBILITIES

PROJECT TEAM SUMMARY

	Name	Health Profession	Organisation
PI	Prof Jason Connor	Allied Health	MSH
CI1	Dr Paul Clark	Medical	MSH
CI2	A/Prof Gerald Feeney	Medical	MSH
CI3	Dr Matthew Gullo	Allied Health	MSH
CI4	Prof Gerald Holtman	Medical	MSH
AI1	A/Prof Graeme Macdonald	Medical	MSH
AI1	Dr Jason Coates	Allied Health	MSH

PROF JASON CONNOR (PI)

Position: Senior Visiting Clinical Psychologist

Organisational department: Alcohol and Drug Assessment Unit, Division of Medicine, PAH

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Academic Qualifications: BA, BSocSci(Hons), PhD, FAPS, FCCLP, FCHP

Academic Appointments: Director, Centre for Youth Substance Abuse Research, The University of Queensland

Professor, Discipline of Psychiatry, The University of Queensland

Project Responsibilities:	Overall project coordination.
	Clinical supervision of the psychological interventions.
	Ethics applications.

DR PAUL CLARK (CI)

Position:	Staff Specialist (Hepatologists/Gastroenterologist) and NHMRC Fellow
Organisational department:	Department of Gastroenterology and Hepatology, PAH
Phone number(s):	Primary: +61 7 3176 6530
Email address:	paul.j.clark@uq.edu.au
Academic Qualifications:	Bachelor of Arts
	Master of Natural Resources and Environment Agricultural Economics
	Bachelor of Medicine, Bachelor of Surgery with 1st Class Honours
	Fellow, RACP
	Master of Public Health and Tropical Medicine
	Doctor of Philosophy
Academic Appointments:	Senior Lecturer at The University of Queensland
	NHMRC Fellow
Project Responsibilities:	Direct medical management of patients.

DR MATTHEW GULLO (CI)

Position:	Visiting Clinical Psychologist
Organisational department:	Alcohol and Drug Assessment Unit, PAH
Phone number(s):	Primary: 07 3176 5191
Email address:	matthew.gullo@health.qld.gov.au
Academic Qualifications:	B.Psych (Hons), PhD (ClinPsych), MAPS, FCCLP
Academic Appointments:	Senior Lecturer at The University of Queensland
Project Responsibilities:	Supervision of psychological interventions.

Statistical support.

PROF GERALD HOLTMAN (CI)

Position:	Director, Gastroenterology & Hepatology
Organisational department:	Gastroenterology & Hepatology, PAH
Phone number(s):	Primary: +61 7 3176 6530
Email address:	Gerald.Holtmann@health.qld.gov.au
Academic Qualifications:	Staatsexamen Medizin (equivalent to MB BS)
	Doctoral Thesis
	Habilitation (PhD)
	FRACP
	FRCP (London)
	MBA
Academic Appointments:	Associate Dean Clinical at The University of Queensland
Project Responsibilities:	Coordination of patient referrals to ADAU.

A/PROF GERALD FEENEY (CI)

Position:	Medical Director
Organisational department:	Alcohol and Drug Assessment Unit, PAH
Phone number(s):	Primary: 07 3176 5191
Email address:	Gerald.Feeney@health.qld.gov.au
Academic Qualifications:	MB. BCh., BAO (NUI)
	Fellow of the Royal Australasian College of Physicians
	Foundation Fellow of the Australasian Chapter of Addiction Medicine
	MD (UQ)
Academic Appointments:	Adjunct Associate Professor at The University of Queensland
Project Responsibilities:	Overall project coordination.
	Supervision of ADAU clinical staff.

Supervision of medical officers.

A/PROF GRAEME MACDONALD (AI)

Position:	Senior Staff Specialist
Organisational department:	Gastroenterology & Hepatology, PAH
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Academic Qualifications:	PhD, MBBS, FRACP
Academic Appointments:	Associate Professor at The University of Queensland
Project Responsibilities:	Assist in the assessment of AH patients and their medical management.
	Co-Coordinate the recruitment and referral of AH patients to ADAU.

DR JASON COATES (AI)

Position:	Psychologist
Organisational department:	Alcohol and Drug Assessment Unit, PAH
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Email address:	jason.coates@health.qld.gov.au
Academic Qualifications:	B.Psych(Hons), MPsych(Clin), PhD, MAPS
Academic Appointments:	Nil
Project Responsibilities:	Coordinate the project under supervision of PI/CIs.
	Treat all AH patients with tailored CBT.
	Establish and manage databases.
	Input clinical data.
	Draft ethics applications.
	Run statistical analyses.
	Assist in preparation of research manuscript.

RESOURCES

RESOURCES NECESSARY FOR THE PROJECT TO BE CONDUCTED

- Office space at the Alcohol and Drug Assessment Unit.
- Oragene saliva collection kits.
- Research Manager/Clinical Psychologist to coordinate the project under supervision of PI/CIs, treat all of the AH patients with tailored CBT, establish and manage databases, input clinical data, draft ethics applications, run statistical analyses and assist in preparation of research manuscript.

FUNDING/SUPPORT BEING SOUGHT OR SECURED

Secured 2019 Metro South Health Research Support Scheme Project Grant for the study entitled "When Drugs Don't Work: Tailored Behavioural Intervention for Alcoholic Hepatitis" (2019-2020). The grant is funded by the Metro South Study, Education and Research Trust Account (SERTA).

BACKGROUND

OVERVIEW

Alcoholic hepatitis (AH) poses a significant burden on public tertiary hospitals. Medication for AH has recently been demonstrated to be ineffective in a large high-quality study. Sustained alcohol abstinence is the strongest predictor of long-term survival. Behavioural interventions to promote abstinence in AH have not been systematically assessed. We propose to trial an early and intense Cognitive Behavioural Therapy (CBT) program for patients at high risk of poor outcome of alcohol-related liver disease/severe AH and evaluate treatment outcome as a matter of quality assurance.

REVIEW AND RATIONALE

Three-month mortality from AH is 30%, with over half of AH patients dead within a year (Thursz, et al. 2015; Torok, 2015). Although specialist society guidelines recommend glucocorticoids (prednisolone) and/or nonselective phosphodiesterase inhibitors (pentoxifylline) in appropriate patients (Euro. Liver, 2012; O'Shea, et. al., 2010), a recent high quality, multi-centre, double blind randomised controlled trial (RCT) published in the New England Journal of Medicine showed no benefit from prednisolone or pentoxifylline (Thursz, et al., 2015). No new pharmacological agents are imminent (Saberi et al., 2016).

Abstinence is the only independent predictor of survival in AH (Potts et al. 2013). No research on behavioural approaches for AH patients to maintain alcohol abstinence is available. An effective, scalable, geographically unrestricted, cost-effective intervention is urgently required.

Meta-analyses report CBT is effective in achieving alcohol abstinence for about 25% of alcohol dependent patients (Connor, et. al., 2016, Lancet). Approximately half (45%) of AH patients referred to ADAU withdraw prior to commencing treatment. AH patients represent a more medically unwell group, often with established alcohol dependence, and typically featuring neuro-psychiatric and nutritional deficits of alcohol-related disease, in addition to liver failure. AH patients admitted to the PAH report an average 150g of alcohol (15 standard drinks) on each drinking occasion. Their mean WHO Alcohol Use Disorders Identification Test score is 29 (range 0-40), where > 20 indicates severe alcohol dependence. Effective early intervention and more intensive ongoing management and retention strategies are essential for this population group. A tailored CBT intervention targeting unique components of the AH disease process, psychological sequelae, and treatment accessibility is critical. No such intervention has been empirically evaluated.

The research team has significant experience in developing behavioural interventions for alcohol dependence (Young, Connor, Feeney, 2011; Connor NHMRC APP1031909, APP455926; APP553059; Connor, Gullo APP1099400). There is evidence that more frequent, brief behavioural interventions are more effective than longer, less frequent appointments (O'Donnell et al. 2014). A further treatment compliance challenge is mode of delivery. AH patients are often too medically unwell to attend clinics and therefore traditional face-to-face

appointments are difficult to achieve. Critical to a tailored CBT AH intervention is a simple approach allowing flexibility in adoption across the inpatient and outpatient environments, that is cost-effective, scalable and effective. These novel efficacy data have the capacity to inform a large multi-site RCT NHMRC application.

Only a minority of heavy alcohol users develop significant liver disease. Genetic susceptibility likely contributes (Yeluru et al. 2016). The PNPLA3 gene has been reliably associated with non-alcoholic steatohepatitis and hepatitis C induced steatohepatitis (meta-analyses Chamorro et al. 2014; Clark, PhD thesis). Recently, the risk (G) allele for PNPLA3 has been associated with AH, with almost double the risk for G allele carriers (Liangpunsakul et al. 2016). Existing studies characterising AH poorly identify alcohol exposure and fail to comprehensively incorporate known or suspected etiological and prognostic factors. Replication and development of this research will inform understanding of risk, treatment prognosis, and tailored behavioural treatment for AH.

AIMS

1. Examine non-inferiority or superiority of a new treatment protocol for patients with Alcoholic Hepatitis (AH) referred to the Alcohol and Drug Assessment Unit by the Department of Gastroenterology and Hepatology.
2. Replicate recent research which has found risk of AH among G allele carriers of PNPLA3.

HYPOTHESES / EXPECTED OUTCOMES

1. We expect that AH patients treated with an updated treatment protocol will have superior outcomes to historical controls of AH patients (Treatment as Usual, TAU).
   - The primary outcome will be treatment engagement and retention.
   - Secondary outcomes will include treatment initiation and drinking behaviours over treatment.
2. Genetic data will better characterize alcohol dependent patients that develop AH, compared to those that do not. The proportion of patients with risk (G) allele for PNPLA3 will be significantly higher among patients with alcoholic hepatitis than historical controls without liver disease.

PROJECT DESIGN

RESEARCH PROJECT SETTING

The research site will be based at the PAH Alcohol and Drug and Alcohol Assessment Unit (ADAU) in the Division of Medicine and Department of Gastroenterology & Hepatology (Dept. G&H).

PARTICIPANTS

RECRUITMENT

Patients are referred to the Dept. G&H for AH from the PAH Emergency Department, other medical/surgical units from other hospitals within and beyond the Metro-South District. Approximately one per week is managed for AH. All consenting patients will be offered the AH CBT program (see Procedure) and comprehensive assessment (see Measures).

ELIGIBILITY CRITERIA

All PAH AH patients will be diagnosed and medically managed by liver disease specialists (Hepatologists CI Clark and CI Macdonald) and Addiction specialist (CI Feeney). Liver biopsy remains the gold standard for diagnosis (Clark, et al., 2011), however indications for physician practice varies. While biopsy is the preferred inclusion criterion, absence will not be an exclusion criterion. For patients without liver biopsy, inclusion requires 1). Consistent alcohol risk history, 2). Absence of other acute liver injury risk; 3) at least 2/3 of:

jaundice < 8 weeks, AST/ALT ratio > 2; neutrophilia. Further characterised on AH severity (Maddrey Discriminant Function 32) and the presence of cirrhosis.

SAMPLE SIZE AND STATISTICAL OR POWER ISSUES

To determine non-inferiority or superiority of the new treatment protocol when the primary outcome is patient retention non-inferiority requirements were calculated in R version 3.5.0. Holding power level at 80% and alpha at 0.05, with a present response rate for patients with AH completing treatment at 30% and a modest protocol goal of 40%, a sample size of 70 patients is required to support non-inferiority within a 10% equivalence margin. Given that we have historical data for N ~130 patients, we only require 35 (70 / 2 = 35) patients to commence the new protocol for this study to be sufficiently powered.

METHODOLOGICAL APPROACH

AIM 1: ASSESSMENT OF TREATMENT PROTOCOL

Tailored CBT Intervention: Shepard et al. (2016) demonstrate that adjunctive telephone-based therapy is a cost-effective modality with good long-term treatment outcomes. As noted, it also meets all of the requirements for a medically unwell, and frequently socially, geographically or mobility challenged AH population. Critical to AH patient abstinence is development of drinking refusal self-efficacy skills, alternative coping strategies, non-pharmacological pain management, modification of situational triggers, nutrition, psychoeducation and management of alcohol craving. The Tailored Alcoholic Hepatitis Intervention will match for the existing generic face-to-face CBT Intervention historical benchmark for length of treatment (3 months) and therapist contact (8 hours). The generic alcohol CBT program has ADAU physician consult plus 8 x 1 hour face-to-face outpatient sessions over 3 months with a clinical psychologist. The Tailored Alcoholic Hepatitis intervention will have a rapid inpatient assessment to enhance treatment engagement consisting of 2 x 20 min sessions while an inpatient, including 1) ADAU Physician assessment and 2) Clinical Psychologist treatment plan. Post discharge, the same clinical psychologist will deliver the intense 2 x weekly 20 min 'booster' telephone sessions for 3 months (totaling 8 hours). Where feasible- based on patient health and geographical location- face-to-face sessions are preferred and can be substituted for telephone sessions.

AIM 2: ASSESSING GENETIC SUSCEPTABILITY TO AH.

We will genotype PNPLA3 in AH patients via saliva sample in the current study. Saliva will be collected from patients via self-collection kit. Patient's spit approximately 2ml saliva into a funnel. Saliva is mixed with a stabilization solution making it suitable for storage. The ADAU maintains a genetically informed database of > 250 treatment seeking, alcohol dependent patients without AH, who will act as our alcohol-exposure adjusted control. Ethics approval for collection and analysis of genetic data of patients attending ADAU has previously been obtained (HREC/14/QPAH/664).

ASSESSMENT AND MEASURES

Assessments are embedded within ADAU routine protocol. They are outlined below:

Assessment of alcohol use and dependence severity include the following comprehensively validated self-report measures: Brief Michigan Alcoholism Screening Test (bMAST), Alcohol Use Disorders Identification Test (AUDIT), Timeline Follow-back Procedure (TLFB), Severity of Alcohol Dependence Questionnaire (SADQ), and the Mini Alcohol Craving Experience scale (MACE). Alcohol related psychological constructs are assessed by the Drinking Expectancy Profile (DEP; outcome expectancies and refusal self-efficacy), Motivation Thought Frequency Scale (MTF; abstinence motivation), and Dysfunctional Impulsivity Scale (DIS). Social factors are examined by the Perceived Support Scale and routine assessment of demographic information. Liver disease severity will determined by MELD score. Neurocognitive functioning are assessed by the Trails A&B. Quality of Life are assessed by the Chronic Liver Disease Questionnaire (CLDQ), Short Form-6D, Depression Anxiety,

Stress Scale (DASS-21) and General Health Questionnaire (GHQ). Blood samples are taken for full medical work up as part of routine care.

RATIONALE FOR CHOICES OF METHOD/S (TIED TO PROJECT AIMS/OBJECTIVES)

As this is foremost a service improvement and quality assurance exercise, data collected will be compared to historical controls to ensure all patients receive the best available care.

TIMEFRAMES

Based on historical trends recruitment and treatment of the required 50 AH patients will take approximately 2-years from commencement of the study. Analysis of the available data and any publication is expected to be completed within 2-years following patient intervention.

PATIENT CONSENT

In standard care each patient signs a consent form agreeing that "I understand that deidentified data (anonymous data) collected may be used for program evaluation" as well as consent to participate in the program. Consistent with recent National Statement on Ethical Conduct in Human Research updates we include an 'opt-out' option at multiple points of the program.

Regarding the updated protocol and collection of genetic material, patients are verbally informed of the protocols and purpose surrounding saliva collection and provided an information sheet and consent form specifically outlining this information (attached). Patients are provided time to read the consent form and invited to ask any questions. Patients may provide or withdraw consent at any time. Provision of consent does not alter patient care in any way.

We include an additional consent provision for DNA to be available for up to 15 years and further research much be first approved by ethics committee. Patients can choose not to consent to this option. Consents will be obtained by Dr Jason Coates (Project manager and treating psychologist).

DATA MANAGEMENT

All data will be kept on secure, password protected, Queensland Health servers. Further access to the specific drive requires Metro South Health administration permissions and approval from the head of this department. Data will be kept consistent with ADAU (and Queensland Health) clinical guidelines, but not less than 7 years. Data used in research will be re-identifiable (coded). The coding "key" will be a password protected excel document stored within the same drive. Management practices will conform to ADAU (and Queensland Health) clinical guidelines, but not less than 7 years. Data will be destroyed via deletion of deidentified electronic file when required. Access to this deidentified data will only be granted to people approved under this application or extension to this application.

Salvia and extracted DNA samples will be stored in a locked freezer in a secure PC2 laboratory at the Queensland University of Technology (QUT). All samples will be de-identified. Laboratory protocol ensures samples are checked for viability routinely. Should a participant withdraw their consent after provision of the saliva sample their sample will be destroyed as per protocol of the PC2 laboratory at the QUT. Any electronic data generated from their sample will be deleted.

DATA ANALYSIS

Aim 1: The primary outcome will be assessed via logistic regression, where the outcome is completed treatment (0 = no, 1 = yes) and the independent variable is treatment group (0 = old protocol, 1 = new protocol). Potential confounding variables will be included as covariates (e.g. dependence severity). As the mechanism of the PNPLA3 gene is unknown it will be included as a covariate. Depending on the distribution of the number of sessions attended, parametric or non-parametric statistics may be employed to determine whether more sessions were attended on average. Again, potential confounding variables will be included as covariates.

Analysis of secondary outcomes (drinking behaviour) will be analysed using non-parametric longitudinal mixed effects models (Multilevel Modelling). LME models are considered the gold standard in psychotherapy research as they have the advantage of modelling the trajectory of longitudinal outcomes. Missing data may therefore be imputed based on individual trajectories. See above for power analysis.

Aim 2: The primary outcome will be assessed via logistic regression, where the outcome is completed G Allele of PNPLA3 (0 = no, 1 = yes) and the independent variable is AH status (0 = control, 1 = AH). Potential confounding variables will be included as covariates (e.g. dependence severity).

ANTICIPATED RISKS AND BENEFITS

The primary concern for studies utilising historical controls is that the active condition may cause harm. Given that the active condition in this study is the addition of psychological support via enhanced personalised care, no adverse effects are expected. In contrast we expect improved therapeutic outcomes, reduced social costs, and improved patient quality of life as a result of this study.

RESULTS, OUTCOMES AND FUTURE PLANS

PLANS FOR RETURN OF RESULTS OF RESEARCH TO PARTICIPANTS

Patients will be provided the results of their psychometric assessments and blood tests as a matter of routine care. As outcomes from genetic data is not clinically meaningful the results will not be fed back to patients. Research outcomes will be made available to participants upon request; in which case a research summary will emailed to patients upon completion.

PLANS FOR DISSEMINATION AND PUBLICATION OF PROJECT OUTCOMES

Summary statistics (e.g. descriptive and inferential statistics) of deidentified data are intended to be published within peer reviewed journals and may be presented at academic conferences. The outcomes of this study may also provide grounds for future grant applications to fund more robust clinical RCTs.

OTHER POTENTIAL USES OF THE DATA AT THE END OF THE PROJECT

Any further use of the data collected will be requested via ethics application. The most likely use is for identification of prognostic markers and intervention targets as a matter of quality assurance, program evaluation, and program development.

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