**Protocol for “A randomised controlled trial of Cognitive Bias Modification training during early recovery from alcohol dependence”**

**BACKGROUND**

One in five Australians will develop alcohol abuse or dependence (i.e. an alcohol use disorder) during their lifetime (Teesson *et al*., 2010). Consumption of alcohol accounted for 4.7% of male and 3% of female deaths in Australia in 2010 (Gao *et al*., 2014). Alcohol use disorders are associated with over 60 diseases and conditions and the associated social costs in Australia are estimated to exceed $15 billion per annum (Collins & Lapsley, 2008). Given the costs of alcohol use disorders and increasing resource constraints in public healthcare, research into effective treatment is a priority investment.

Treatment for alcohol-dependent persons often commences with costly and intensive inpatient detoxification, followed by several weeks or months of outpatient counselling (AIHW, 2014). Yet despite decades of research on psychosocial and pharmacological treatments for alcohol use disorders, relapse unfortunately remains ‘the norm’. Research suggests that 80-90% of alcohol-dependent patients relapse after detoxification (Boothby & Doering, 2005; Sanghani *et al*., 2015), often in the first few weeks or even days following detoxification (Miller & Kavanagh, 2011). Alcohol-dependent individuals typically undergo multiple episodes of inpatient withdrawal before achieving sustained recovery. Relapsing individuals therefore place considerable burden on an already overstretched healthcare system in their demand for subsequent costly inpatient detoxification treatments, their disproportionately higher use of acute health services due to alcohol-related injuries and illnesses, and extended periods of unemployment and related welfare support (Manning *et al*., 2013). Hence there is an urgent need for novel and effective methods to reduce relapse following inpatient detoxification, as such interventions are likely to benefit those directly and indirectly affected by alcohol use disorders and generate substantial economic savings in terms of public spending.

According to contemporary “dual process” models of addiction, alcohol use disorders are maintained by an imbalance between two independent but interacting information processing systems (Bechara, 2005), of which one operates at least partly outside conscious control, rendering the drinker persistently vulnerable to relapse. One system, the impulsive/automated system, becomes sensitised towards alcohol-related stimuli in the environment (Strack & Deutsch, 2004). The other is the reflective/executive control system, which becomes less proficient at suppressing automated impulsive behaviours in favour of alternative/healthier responses (Wiers *et al*., 2013). The interplay between these two interconnected systems is influenced (or unbalanced) by cognitive motivational biases. One such cognitive bias is termed ‘attentional bias’; the tendency for alcohol-related cues in the environment to selectively capture attention because of their increased incentive salience. Another relevant cognitive bias is ‘approach bias’; the automatically activated action tendencies to approach alcohol due to the motivational significance that is attributed to alcohol-related cues (Wiers *et al*., 2009). These cognitive biases have been proposed to result in an individual’s behaviour becoming increasingly governed by alcohol-related cues in their environment, triggering the desire to consume alcohol (Wiers *et al*., 2007). The resulting automatic approach tendency is then harder to inhibit because of a compromised executive control system that is impaired in its ability to steer the individual towards an alternative behavioural response (Czapla *et al*., 2013; Stavro *et al*., 2013).

Chronic alcohol use affects multiple brain circuits including those that underpin decision-making, reward and stress (Cui *et al*., 2013). However there is mounting evidence of structural, functional and neurocognitive recovery and reorganisation during early withdrawal from alcohol (Bartsch *et al*., 2007; van Eijk *et al*., 2013; Willoughby *et al*., 2015). This includes recovery in brain regions that underpin the motivational system and associated cognitive biases. Significant improvements in neurocognitive functioning have also been observed within the initial week (Manning *et al*., 2008) and even days (Mann *et al*., 1999) of detoxification. It is therefore possible that cognitive biases are also amenable to change at this time.

Cognitive-bias modification is an umbrella term used to describe computerised training programs designed to target and change maladaptive cognitive biases. To address approach bias towards alcohol, Wiers *et al*. (2010) developed the alcohol approach/avoidance task (alcohol-AAT). In this task, participants are presented with pictures of alcohol-related stimuli and neutral stimuli and are instructed to respond with an approach behaviour (pulling a joystick) or an avoidance behaviour (pushing a joystick). Pulling increases the size of the picture, while pushing decreases the size of the picture, essentially generating the sensation of approaching or avoiding alcohol-related stimuli. In a sample of social drinkers, those who were trained to avoid (push away) pictures of alcohol showed a reduced approach bias to untrained pictures in the same task, and consumed less alcohol in a subsequent taste test than those who were trained to approach (pull towards them) pictures of alcohol. Participants in clinical studies of the alcohol-AAT undergo numerous trials of the approach bias training delivered over multiple sessions (days), so that the automatic approach bias is weakened, and avoidance bias strengthened, in response to alcohol cues. Approach bias modification has been tested in outpatient alcohol-dependent samples, with promising results (Wiers *et al*., 2011; Eberl *et al*., 2013).

Surprisingly, despite evidence that CBM is efficacious in re-training cognitive biases and reducing relapse, and that early withdrawal is a time of neural recovery relevant to these biases, no published study has examined the impact of re-training approach biases during the acute detoxification phase. With respect to the dual process model of addiction, psychosocial treatments such as CBT, motivational interviewing etc. that typically follow detoxification address the faulty reflective processes by augmenting cognitive control to inhibit drinking behaviour. However, they fail to address the other faulty system, (i.e., the impulsive/automatic information processing system). We anticipate that by weakening approach bias during detoxification, their behaviour will become less driven by immediate alcohol-related representations. This should allow greater capacity to consider future consequences of their behaviour, thereby reducing the likelihood of relapse in those vulnerable days after leaving the supportive environment offered by inpatient settings.

**Participants and recruitment:**

Participants will be 300 alcohol-dependent patients (aged 18-65) admitted for inpatient detoxification at De Paul House (St. Vincent’s Hospital Melbourne), Wellington House (Eastern Health) or Windana Drug and Alcohol Reovery. Inclusion criteria are:

1. Current moderate or severe DSM-5 alcohol use disorder (i.e. at least 4 alcohol use disorder criteria met within the past year, according to the Structured Clinical Interview for DSM-5 Disorders – Research Version (SCID-5-RV; First, Williams, Karg, & Spitzer, 2015)).

2. Report at least weekly use of alcohol in the past month.

3. Be able to understand English.

Exclusion criteria are:

1. History of neurological illness or injury or brain trauma involving loss of consciousness for longer than 30 minutes.

2. Intellectual disability.

3. Acutely unwell, as judged by clinical staff.

Clinicians at De Paul House, Wellington House, and Windana will be advised of the inclusion and exclusion criteria. They will advise eligible patients of the opportunity to participate in research and seek their permission for a researcher to contact the patient for further explanation if interested in participation. If a patient agrees to be approached, clinical staff will identify them to a researcher who will approach the patient on day 3 or 4 of detoxification to provide further information about the study. If a patient expresses a desire to participate and appears to have understood the information provided, they will be asked to sign a consent form. After providing informed consent, the researcher will administer the SCID-5-RV and the time-line follow-back (TLFB; Sobell & Sobell, 1996) to confirm that the participant meets alcohol use disorder and frequency of use criteria. Signing the consent form will also provide permission for the researcher to view the participant’s clinical intake notes to confirm other inclusion and exclusion criteria.

**Procedure:**

Following provision of informed consent, the researcher will conduct a baseline questionnaire assessment. In addition to the SCID-5-RV (which will also be used to index the number of alcohol use disorder criteria met, in addition to eligibility) and the TLFB (which will also index tobacco, medication, and other drug use during the past 30 days, as well as alcohol use), this questionnaire will also include:

1. A demographic/clinical history questionnaire assessing date of birth, gender, country of birth, Aboriginal/Torres Strait Islander status, highest level of completed education, relationship status, employment status, housing status, age of onset of alcohol use, history of prior withdrawal treatment, other drugs of concern, family history of substance use disorders, psychiatric diagnoses, and any brain injuries, neurological disorders or other mental disorders.

2. The Alcohol Craving Questionnaire – Short Form – Revised (ACQ-SF-R; Singleton, Tiffany, & Henningfield, 2014) to assess craving for alcohol at the time of assessment.

Following this, a baseline battery of computerised tests will be administered including:

1. A modified neutral version of the Alcohol-AAT (Wiers, Rinck, Kordts, Houben, & Strack, 2010) to measure approach bias towards alcohol. Participants are required to react to the format of pictures using a joystick (e.g. push landscape pictures, pull portrait pictures), irrespective of the content of the pictures. There are two categories of pictures; 10 different alcoholic beverages and 10 different non-alcoholic beverages (images will differ from those used in the training task). Each image type is repeated 4 times, for a total of 80 trials. Every picture type appears in landscape and in portrait format 50% of the time. For both categories of pictures (alcohol, non-alcohol), the median reaction time (RT) for pull responses is subtracted from the median RT for pull responses to produce a measure of approach bias. A positive score indicating that a participant more readily approached that category of picture than avoided it, while a negative score indicates the opposite.

2. A picture rating task designed to measure subjective desire elicited by beverage images. Participants will view 20 computerised images, 10 of alcoholic beverages and 10 of non-alcoholic beverages. Participants rate ‘wanting’ of images by marking a point along an accompanying 100 mm line with end caps either side indicating “I do not want this at all” to “I really want this”. Scores range from 0-100, based on the ‘mm’ distance between the participant’s mark and the lower end point (i.e. a score of 0 indicates no wanting at all; a score of 100 indicates maximal wanting). Within each of the two beverage categories (alcoholic; non-alcoholic), 5 of the 10 images are identical to images to be used in the training task (see below) and the other 5 are novel images not used in other study tasks. Thus, by repeating this task after the final session of training, we will therefore not only be able to measure whether the training task reduces cue-induced alcohol desire, but also whether this generalises to alcohol images that participants haven’t been trained to avoid.

Following these assessments, participants will commence either the cognitive bias modification (CBM) training task, or a sham-training version of this task, according to a randomisation sequence programmed into the laptop used for the training task.

1. In the intervention CBM task, participants will be exposed to 240 computerised images of 40 different alcoholic and 40 different non-alcoholic drinks and instructed to respond as quickly and accurately as possible with an approach or avoidance movement according to their orientation (landscape or portrait). While instructions are based on picture orientation, one orientation will contain alcoholic beverages 95% of the time (and non-alcoholic beverages 5% of the time) and will require an avoidance movement (pushing of a joystick, which decreases image size). The other orientation will contain non-alcoholic beverages 95% of the time and alcoholic beverages 5% of the time and will require an approach movement (pulling the joystick, which increases image size). The requirement to push away nearly all (95%) of alcohol images is intended to train participants to over-ride their pre-existing tendency to approach alcohol, and we hope that this will generalise to a reduced tendency to approach alcohol and its related cues following discharge from detoxification. This requirement will be reversed on 5% of trials to reduce the likelihood of participants being unblinded to the nature of the training. In each session, the 240 training trials will be preceded by 8 practice trials in which participants will be asked to respond to blank rectangles (4 in landscape orientation and 4 in portrait orientation) to familiarise participants with (or remind them of) the task demands. In both practice and training trials, a red ‘X’ will be displayed if a participant makes an incorrect response, and they will be unable to proceed to the next trial until they respond correctly.

2. In the control sham-training task, 150 participants will be exposed to 240 computerised images 40 different alcoholic and 40 different non-alcoholic drinks and instructed to respond as quickly and accurately as possible by using the joystick to move the images to the left or right according to their orientation (landscape or portrait). Each orientation will contain images of alcohol beverages 50% of the time and non-alcoholic beverages 50% of the time. Thus, there will be an equal frequency of requirement to move alcoholic images to the left and to the right, and neither motion expands or shrinks the images, meaning participants in this condition are not systematically trained to either approach or avoid alcoholic images, though this training is matched to the CBM task in terms of exposure to images and requirement to respond to each one. Each session will begin with 12 practice trials, as in the CBM condition. As in the CBM condition, a red ‘X’ will be displayed if a participant makes an incorrect response, and they will be unable to proceed to the next trial until they respond correctly.

The training will be repeated on each of the three following days, such that the participant receives four consecutive days of training. Additional baseline questionnaire measures will be administered after training on days 2 and 3. These will not be administered on day 1 to avoid the initial session being too time-consuming, burdensome, or fatiguing. On day 2, the researcher will administer excerpts from a modified version of the Lifetime Drug Use History Questionnaire (LDUH) to record past-year use of acute health service and substance withdrawal treatment services. On day 3, the researcher will administer the Severity of Alcohol Dependence Questionnaire (SADQ; Stockwell, Sitharthan, McGrath, & Lang, 1994) to assess symptoms of physical dependence on alcohol.

Immediately before and following each CBM training session, participants will complete a single-item visual analogue scale measure of the current intensity of their craving for alcohol (ranging from “not at all” to “extreme”), to allow researchers to monitor whether the task has triggered increased cravings. If participants indicate high cravings at the end of the session (i.e. marking within the quarter of the scale closest to the “extreme” end), the researcher will offer the participant the SOBER intervention guide-sheet (a mindfulness-based set of activities, such as breathing exercises, designed to reduce cravings) and will ask the participant whether they feel they are at risk of relapse and whether they would like further support from clinical staff. If necessary, the researcher will alert withdrawal unit clinical staff to provide further support. The researcher will also remind the participant of their right to withdraw from the study without any consequences for their treatment if there are any indications that the task is distressing to the participant (e.g. a high score on the post-session craving measure or signs of tearfulness or agitation). If such signs of distress are severe or sustained, or if the participant expresses fears that they are highly likely to relapse due to uncontrollable cravings or distress, the researcher will terminate the session and seek immediate support from clinical staff. The researcher must document any time that additional support is sought from clinical staff, regardless of whether the participant withdraws from the study or not.

If a session must be terminated due to distress, the researcher will discuss with clinical staff the following day to check whether the participant still qualifies as not meeting exclusion criterion 3 (“acutely unwell, as judged by clinical staff”). If clinical staff feel the participant now meets this exclusion criterion, they will be withdrawn from the study. Otherwise, the researcher will approach the participant to discuss whether they would like to continue with the study, while reminding them of their right to withdraw from the study without any consequences for their treatment.

Following the final training session, the ACQ-SF-R will be re-administered, as will the alcohol-AAT and picture rating tasks to measure possible changes in alcohol cravings, approach bias, and cue reactivity, respectively. All participants will also be asked to provide contact details to be used for follow-up assessments. To minimise loss to follow-up, we will request that the participant provide multiple points of contact (e.g. family, friends, agencies involves in ongoing treatment) in addition to the participants’ contact details, if they are willing to do so. Participants’ treatment agency, family and friends will only be contacted if participants are un-contactable at follow-up. In addition, participants will be asked to rate the following statements on a 5-point scale (ranging from “strongly disagree” to “strongly agree”): “I found the task improved my attention”; “I found the task decreased my craving for alcohol”, and “I found the task interesting”. At the conclusion of these assessments the participant will be given a $30 supermarket voucher.

A researcher will also collect medication information (i.e. medications prescribed at admission and discharge, and doses of medications adminsitered on each day of inpatient treatment), date of admission, and date of discharge from the participant’s clinical notes. Demographic and clinical information in the participant’s medical record will also be collected to confirm the participant’s self-report, including: date of birth, country of birth, Aboriginal or Torres Strait Islander status, gender, education level, relationship status, employment status, housing status, substance dependence and psychiatric diagnoses, age of onset of alcohol use, presence of family history of substance use disorder, and history of brain injury or mental disability. Identifying information will be removed from any copies made of clinical notes, and replaced with the participant’s assigned number to maintain participants’ anonymity. All computerised information collected from participants will be stored on a password protected computer. Paper documents will be stored in a locked filing cabinet at the detoxification unit during until a participant is discharged, and these documents will then be moved to a locked filing cabinet at Turning Point following the participant’s discharge. Locator forms, which contain identifiable information, will be stored in a separate locked filing cabinet to that used to store de-identifed paper records and a Microsoft Excel file summarising re-identification information will be protected with a password different to that used to access the drives containing de-identified data.

A researcher will contact the participant to administer the TLFB, ACQ-SF-R, and LDUH two weeks, three months, six months and 12 months post-discharge. At the 2-week follow-up, the TLFB will only measure substance use during the time since discharge while, at further follow-ups, it will measure the previous 30 days. To index basic relapse-relevant information in periods missed by the TLFB at the 3-, 6-, and 12-month follow-ups (e.g. 3-5 months after discharge at the 6-month follow-up), participants who had still maintained continuous abstinence at the previous follow-up will be asked additional brief questions assessing whether they consumed any alcohol since the previous follow-up and, if so, the date of the first consumption of alcohol, whether they drank on more than 3 consecutive days at any time and, if so, the date of the first consumption of alcohol exceeding 3 consecutive days. For each follow-up that the participant completes, they will be sent a $10 supermarket voucher by post.

**Data analysis:**

The primary endpoint is abstinence/relapse assessed at each follow-up. In the ITT analysis of the primary endpoint, the divisor for the proportion of abstinent participants in an arm will be the number randomized to that arm and individuals lost to follow-up will be deemed to have relapsed. These proportions will be compared using a two-sample binomial test (two-sided α=0.05) and a 95% confidence interval for the difference in the proportions will also be reported. In a supportive analysis of the primary endpoint, participants who complete fewer than 4 training sessions or who miss the follow-up, will be excluded from the denominator (and the numerator) when the proportion of abstinent patients is calculated in each arm. This “per-protocol” analysis will use the same statistical methods as the ITT analysis. In a supplementary analysis of all available assessments (from 2-weeks to 12-months) a logistic regression analysis, using the method of generalized estimating equations (GEE), will be used to compare the arms, and changes over time in the arms, adjusting, if need be, for sites. Additional exploratory analyses will also investigate adjusting the estimated difference between the arms for such covariates as pre-admission drinking days, mean drinks per drinking day and severity of alcohol dependence score. Full details will be given in the statistical analysis plan (SAP) that will be documented prior to the first analysis of the primary endpoint.

Logistic regression analyses (GEE method) will also be used to investigate the moderating effect of baseline approach bias score by including baseline scores as covariates in the model and testing the significance of all two-way interactions, as well as the three-way interaction, of treatment arm, time and the covariate. To determine the economic feasibility of CBM, in terms of savings to the treatment system (evidenced by fewer repeat inpatient detoxifications and episodes of acute health service use at the 12-month follow-up), we will compare net spending (cost of CBM intervention + cost of further detoxification/acute health service use for each participant) in the CBM group to net spending (cost of further detoxification/acute health service use) in the control group. The statistical significance of the difference between the groups will be assessed with a t-test and a variance-stabilising transformation, such as the logarithm, will likely be required. For cue-induced wanting, outcomes will be assessed with a repeated measures ANOVA assessing within-subjects variables of ‘time’ (pre-training/post-training), ‘picture-type’ (alcohol/non-alcohol), and ‘novelty’ (used in training/not used in training), with the between-subjects conditions of ‘group’ (CBM/Control). This will be followed up by separately testing effects of time, picture, type, and group at each level of novelty, i.e. conducting separate analyses for those images that were used in training and for those images that weren’t, to examine generalisability.

**Hypotheses:**

We hypothesise that:

H1 - Compared to those receiving sham training, participants receiving CBM training will show significantly higher rates of abstinence from alcohol at each follow-up.

H2 - Stronger baseline approach bias will be associated with a larger effect of CBM (i.e., baseline approach biases will moderate CBM’s effect on abstinence).

H3 - Significant net cost saving in the CBM group compared to controls in terms of reduced cost of repeated inpatient detoxification treatment and acute health care use during the year following discharge (after accounting for the costs of implementing CBM training in the CBM group).

H4 - Compared to those receiving sham training, participants receiving CBM training will show significantly reduced cue-induced desire to alcohol images (but not to images of non-alcoholic beverages). We expect that this interaction will remain, with similar effect size, when analyses are restricted to images not included in the training task, demonstrating generalisation of reduced cue-induced desire beyond the specific stimuli that participants were trained to avoid.

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