CEASAR (Computerized Exercise to Alter Stimulant Approach Responses):

Piloting a novel intervention to improve outcome in individuals suffering from cocaine or methamphetamine use disorder: A randomized controlled study

1 RATIONALE

The pilot study will test the feasibility and efficacy of a novel computerized intervention. The intervention will be an add-on to the current 'treatment as usual' at the Burnaby Centre for Mental Health & Addiction (BCMHA) in Burnaby, BC, Canada. 'Treatment as usual' encompasses the full array of evidence-based treatments (Knapp 2015). But, there is still ample need to improve treatment, specifically stimulant (cocaine and methamphetamine) use disorder treatment (Newton 2013). BCMHA serves the hardest-to-treat clients with severe concurrent disorders by providing a six-month inpatient recovery program (Schütz 2013). The program focuses on clients who have not been treated successfully by locally available services. The study will be randomized and double blinded by design, but may turn out to be single-blinded, as interviewers will be exposed to both active and placebo trials and may be able to differentiate active from inactive interventions. The intervention is an adaptation of the recently developed "retraining of automatic approach" intervention, which has been shown to reduce relapses in alcohol dependent persons (Wiers 2013) and seems to be currently successfully tested in smokers (Woud 2016).

BACKGROUND

Stimulant use disorders are among the most challenging disorders, specifically in individuals suffering from concurrent disorders or also identified as dual diagnosis (Banlieu 2012). While medication is available to support the treatment of other substance use disorders (alcohol, opioids, tobacco), currently there is none to treat stimulant use disorders, such as cocaine use disorder and methamphetamine use disorder (Newton 2013). Current interventions are mainly based on education, motivational interviewing and cognitive behavioural approaches. The cognitive behavioural approach has limits in the population treated at the BCMHA, as they often suffer from mild to moderate cognitive problems, and thus may have issues in understanding complex behaviours (Homer 2008, Depp 2015). Contingency management is another evidence-based approach (Knapp 2015). All interventions are provided concurrently at BCMHA. Treatments can be combined with CEASAR. In fact, they appear to be complementary approaches.

Recently a group in Europe developed the "retraining of automatic approach" intervention, which is not based on conscious learning, the need of the client, or the client's understanding of her or his behaviour, but constitutes a more mechanistic training. This method was successfully applied to change drinking behaviour in a sample of alcoholic inpatients (Wiers 2010). The intervention—based on cognitive-bias modification—is straightforward, uncomplicated, and does not require "active learning based on an understanding of complex behaviours" (Wiers 2011). The intervention itself is a simple targeted computer based training for "avoidance of substances". As opposed to the more regularly used explicit or declarative learning, an implicit non-declarative procedural learning approach is used. This approach is less dependent on an

individual's ability to understand their own situation-dependent behaviours, but is more of a procedural type of training such as learning to ride a bike. Participants respond to cues by initiating a distancing activity (pushing a joystick away). Positive activities in contrast, are pulled in. This differential activity trains participants to alter initial responses and "cognitive biases" (Wiers 2013).

OBJECTIVES

1.1 RESEARCH QUESTION:

1.1.1 Can the CEASAR intervention (Computerized Exercise to Alter Stimulant Approach Responses) be successfully integrated into treatment at the BCMHA?

1.1.2 Does the approach show any effectivity in improving treatment outcomes when applied to a population of complex concurrent disorder clients at an in-patient recovery program?

1.2 HYPOTHESIS

1.2.1 The intervention will be easy to integrate into the existing program.

1.2.2 Participation in the experimental (stimulant-avoidance) condition will reduce craving (as assessed by the stimulant craving questionnaire brief version), show reduction in an automatic association of activities with stimulant use and stimulant relapses (as assessed by behaviour association questionnaires) and have reduced relapses as assessed by urine drug screens in 12 weeks following initiation of the intervention.

1.3 OBJECTIVE

Test the hypothesis and evaluate whether or not the Computerized Exercise to Alter Stimulant Approach Responses (CEASAR) can improve stimulant use disorder outcomes in a population with concurrent disorders that are difficult to treat.

2 METHODS

2.1 RESEARCH METHODS:

2.1.1 Patients

The inclusion criteria for participants are:

- Adult: Must be 19 years or older
- "Current" stimulant use disorder (cocaine, crack cocaine, amphetamine, methamphetamine, crystal meth), active before intake at BCMHA (assessed by MINI)
- Competent to consent: Must understand the consent form and give informed consent
- Proficient in English

This study will enrol both male and female subjects, and requires proficiency to read and write in English in order to understand the consent form. Additionally, patients must have been diagnosed with a stimulant use disorder (mainly cocaine use disorder, methamphetamine use disorder). Patients will be recruited at the centre using flyers and through active recruitment of clinic clients by interviewers. Once a client has indicated interest in the study, an interviewer will provide the potential participant with the consent form, review the consent form and if possible, gain informed consent from all participants. Participants will be given enough time to decide whether or not they wish to participate. They may decide to participate in the study at any time,

given that the study is still being conducted and that the participants will still be at the BCMHA for 12 weeks once they agree to begin the study.
Interested clients will be screened during the consent process for eligibility. In addition, participants may be excluded during the study in the case of acute crises not allowing them to regularly participate. This will be determined by the treating psychiatrist, and could arise from situations such as psychotic decompensation, an acute depressive episode, or a manic or hypomanic episode.

2.2 MEASURES

The information and consent form will include information regarding access to clinical documentation to complete the characterization of individuals including socio-demographic data, clinical diagnoses, use history, medication, and cognitive characterization. All participant clients are well characterized within the treatment program at BCMHA. We will access data from the treatment provider, complement missing data and add assessments, such as a cognitive assessment component (including working memory, motor inhibition, and spatial memory). Access to clinical information will be limited to the client's current treatment program. We are thus in a position to identify factors (socio-demographics, mental disorders, substance use disorders, cognitive characteristics, smoking history, etc.) associated with treatment outcome.

During the appointment, participants will complete a battery of questionnaires as listed in the study protocol. Participants will complete questionnaires using a tablet, unless they request a paper survey. The Qualtrics system contracted through UBC and approved by UBC for ethical privacy and data storage practices, will be used for completing questionnaires and chart reviews. This will reduce the need for double data entry, reducing the overall cost and assuring data quality.

Outcome measures are:

- *Craving as assessed by the stimulant craving questionnaire-brief (Paliwal 2008).*
- *Behavioural association as assessed by the behaviour association scale, which measures the degree to which substance use is associated with a number of different situations (Krank 2010).*
- *Relapse to use as identified by self-report and regular urine drug screen.*

2.3 INTERVENTION

Consenting patients will be randomized into 2 conditions: the active, CEASAR intervention (experimental condition) and a placebo intervention (control condition). Assessment of the outcome will be done blind to the randomization.
A randomization monitor will generate and maintain a list of random numbers. A randomization list will be run to assign either experimental or placebo intervention. The investigators will contact the randomization monitor after enrolling a participant, and the randomization monitor will generate a randomization number and communicate this number to the investigator.

In both cases, individuals will use joysticks to train "approaching" or "avoiding or distancing". In the placebo condition, the stimulant cues and neutral cues will be randomized. In the treatment condition, individuals will be trained to "avoid" cues associated with stimulant use and approach "alternative" cues. Individuals will be asked to cue their activity (approach=pull versus avoid=push) based on the framing of the cue (landscape versus portrait). Alternative cues will contain a variety of objects, which will range from small articles such as a pen, to food items. Previous studies have demonstrated that outcome is independent from mode of presentation – whether it is implicit (participant not aware of what they are doing) or explicit (participant knows what they are doing).
Similar to the alcohol cues and the tobacco cue based studies, which have been established, we will use a mix of validated standard cues and locally relevant cues to cover a range of potential cues associated with crystal meth and crack cocaine use. The cues will be partially visual (e.g. pictures of rocks, pipes, needles, etc.) and partially textual (e.g. eight ball, rock, etc.). For the approach condition, we will use the neutral and positive cues (e.g, an apple or a pencil) applied in previous studies. Patients will sit comfortably with a joystick while pictures are presented on a computer screen. Patients will be presented with pictures, pulling pictures in a portrait format and pushing pictures in a landscape format. In the experimental condition, pushed pictures will exclusively be stimulant use-related pictures. In the control condition, stimulant use-related pictures will be equally divided into push and pull conditions. Previous studies have used this format, and we have already implemented two workstations with this specific joystick-driven program.

2.4 DURATION

A CEASAR session will last 15 minutes. Study participants will take part in three sessions per week in the first two weeks, then two sessions per week in the following 2 weeks, and then one session per week thereafter. Each patient will participate in a total of 14 sessions over a period of 8 weeks. The outcome assessment will cover 12 weeks after the initiation of the intervention (4 weeks after the last CEASAR session). While a six month follow up would be preferred, given the pilot character of the study and the average length of stay of 4 months, we decided to focus on the three-month period as a pilot.

2.5 SAMPLE SIZE

For the pilot study we plan to recruit a minimum of 60 participants to complete 12 weeks of the pilot study. A recent review on pilot sample data suggested a sample size of 10-40 per group (Herzog 2008)[3]; with 30 completers at each group, we will be on the upper end of the suggested sample size.
If we recruit 10 individuals every month, we will complete recruitment in approximately 6-8 months (depending on non-completion). The plan is to complete the study in approximately one year.

2.6. COMPENSATION

Participants will be compensated with $10 for every assessment (lasting less than one hour) and $5 for participation in the intervention (lasting 15 min) independent of study completion, in the form of a gift card or voucher. Thus, the client can accumulate an upper limit of $110. As clients will be compensated using the contingency management program at BCMHA, funding will support this program, allowing the client to receive "rewards" of his or her choice, but not monetary compensation. If preferred by the participant, we will alternatively compensate in the

form of a gift card.

3 ANALYSIS AND OUTCOMES

3.1 OUTCOME

Stimulant use will be assessed by the ASI, clinical history, and the UDS starting at intake. The MINI module completed by the treating psychiatrist will determine stimulant use disorder. A stimulant use disorder is necessary to be eligible to participate.
Primary outcome will be the number of relapse days between week 2 and 12. We assume relative small number of relapses, but stimulant use (specifically crystal meth use) is the biggest concern for relapse in the centre and individual relapses occur most commonly with stimulants.
We further measure craving and implicit association as potential mediators of relapse and they may help explain individuals' tendencies to relapse to stimulant use.

Week:	**Base**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Intervention:													
Sessions		***	***	**	**	*	*	*	*				
Outcome:													
UDS	^			^	^	^	^	^	^	^	^	^	^
Craving Questionnaire	**X**				**X**				**X**				**X**
Behaviour Association Questionnaire	**BA**				**BA**				**BA**				**BA**

3.2 STATISTICAL ANALYSIS

Relapses: Cumulative relapses will be compared using simple t-tests. Further analysis using linear regression models will account for potential baseline differences (due to randomization). The clinical urine drug screens will provide the basis for calculating relapses.
Craving: Stimulant craving reduction (baseline versus week 12) will be compared to the placebo group, as assessed by the Stimulant Craving Questionnaire-Brief (SCQ-B) (Paliwal 2008). Statistical analysis will be similar to the primary outcome with t-test and linear regression models.
Behaviour Association scale: The scale has four dimensions, which will be analyzed separately (see above).
The study will have to be approved by the ethics committee and the PHSA research board before initiation. It will be registered with Clinical Trial at NIH.

3.3 POTENTIAL APPLICATIONS

Once completed, this pilot study will be used to leverage support for a full clinical trial—both in terms of clinical support and funding. A computerized intervention could be made available to

clients throughout the province for little cost. The intervention is simple, associated with low cost, and can easily be used as an add-on complementary treatment component.

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5 BUDGET

		Project Total
Personnel		
Graduate Research Assistant	20 hours/week at $16.00/hour	$16,640.00
Graduate Research Assistant (Benefits)		$1,996.80
Subtotal:		**$19,636.80**
Patient Costs		
Participant Incentive	70 max participants x $110.00 max payout	$7,700.00
Subtotal:		**$7,700.00**
Other		
Computer and tablets	Cost of 1 study computer and 3 tablets	$3,500.00
Inquisit software	First license at $450, 3 additional at $150 each	$900.00
Printing, Mailing, and Communications	General administrative costs	$250.00
Open access article publication	1 submission	$1,500.00
Subtotal:		**$6,150.00**
Total:		**$33,486.80**