Remote Treatment of Alcohol Withdrawal: A Pilot Study

Principal Investigator: Matthew Sloan, MD, MSc[1,2]

Co-Investigators (CAMH): Nikki Bozinoff, MD[1,3]

Bernard Le Foll, MD, PhD[2,3]

Christian Hendershot, PhD[1,2]

Lena Quilty, PhD[1,2]

Francesca Di Paola, MD[2,3]

Leslie Buckley, MD[1,2]

Consultant (Internal): Marcos Sanchez, MSc[3]

Consultant (External): Meldon Kahan, MD[3,5]

Jennifer Wyman, MD, MSc[3, 5]

Kate Hardy, PhD[5]

Bryce Barker, PhD[6]

Sandra LaFleur[7]

[1]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[2]Addictions Division, Centre for Addiction and Mental Health, Toronto, ON, Canada

[3]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada

[4]Biostatistical Consulting Unit, Centre for Addiction and Mental Health, Toronto, ON, Canada

[5]Substance Use Service, Women's College Hospital, Toronto, ON, Canada

[6]Canadian Centre on Substance Use and Addiction, Ottawa, ON, Canada

[7]Patient Advisory Committee, Centre for Addiction and Mental Health

Address of Trial Site:

Centre for Addiction and Mental Health (CAMH), COMPASS Clinic, 100 Stokes Street, 3rd Floor, Toronto, Ontario, M6J 1H4

Table of Contents

Introduction

During the COVID-19 pandemic, an increasing number of medical services have been offered remotely. Despite this, no systematic effort has been made to determine whether alcohol withdrawal management can be managed using telemedicine. Remote alcohol withdrawal management could have several advantages for patients including: 1) improved convenience and ease of access to treatment, 2) decreased exposure to SARS-CoV-2, 3) ability to provide withdrawal management in remote settings that lack ambulatory withdrawal management facilities (e.g. hospital beds and dedicated nursing). The goal of this pilot study is to assess the feasibility of remote alcohol withdrawal management and determine whether remote withdrawal management is satisfactory to patients.

Background

Alcohol use disorder (AUD) is one of the most prevalent substance use disorders in Canada (1) and is associated with high rates of death and disability (2). Many patients require withdrawal management as a first step in treatment. However, accessing medically managed withdrawal services can be difficult. For example, patients in need of priority care for substance use disorders (SUDs) in Ontario typically wait around three weeks for treatment initiation and the majority of institutions do not reserve beds or space for these individuals (3). For alcohol detoxification, this problem has been compounded by the COVID-19 pandemic, as several addiction treatment centres have closed (4) and patients may be reluctant to seek in-person care due to fears of SARS-CoV-2 transmission. This creates a dangerous barrier to treatment as both untreated alcohol withdrawal and untreated AUD can be fatal.

Alcohol withdrawal is typically managed with benzodiazepines in an inpatient or outpatient setting. Outpatient management is safe for mild to moderate withdrawal, costs less than inpatient treatment (5-9), and is the preferred treatment setting as it minimizes disruptions to family life and employment (10). Symptom-triggered withdrawal management, in which a clinician repeatedly assesses the patient using a standardized withdrawal measurement tool and only administers benzodiazepines when patients are symptomatic, improves treatment safety and efficacy. Symptom-triggered approaches have been shown to reduce treatment duration and decrease the quantity of benzodiazepines needed to manage withdrawal symptoms (11-13), which is valuable as benzodiazepines may cause adverse side effects (14). However, symptom-triggered outpatient withdrawal management requires multiple in- person assessments, which is problematic due to the risk of SARS-CoV-2 transmission.

One way to improve treatment access and mitigate the risk of SARS-CoV-2 transmission is through the use of telemedicine. Telemedicine-delivered treatment shows comparable outcomes to in-person treatment across a range of mental illnesses including depression, post-traumatic stress disorder, and schizophrenia (15-18). Telemedicine is also an effective way to treat certain SUDs. For example, telemedicine is as effective as in person care for the treatment of opioid use disorder with buprenorphine and methadone (19-21). In the treatment of AUD, telemedicine has been used to deliver psychotherapy (22, 23), brief interventions (24-26), and manage anticraving medications (22), with similar retention and patient satisfaction as usual care (22-24, 27). However, to the best of our knowledge, no studies have examined the use of telemedicine to manage alcohol withdrawal.

Using telemedicine to provide remote symptom-triggered alcohol detoxification could significantly decrease the need for in-person monitoring and reduce SARS-CoV-2 transmission in both patients and hospital staff. The goal of this pilot study will be to assess the feasibility of remote alcohol withdrawal management and determine whether it is satisfactory to patients. Our telemedicine intervention will provide rigorous monitoring by experienced clinicians. Based on the effectiveness of telehealth interventions for other mental illnesses, we hypothesize that remote withdrawal management will be safe and feasible in the majority of patients and demonstrate a high patient satisfaction rate. It could then be scaled up rapidly to treat patients throughout Ontario and in other parts of Canada. There would likely be considerable interest in adopting this approach internationally if it is found to be feasible, especially in countries with high rates of SARS-CoV-2 infection and limited access to detoxification facilities and specialized AUD treatment.

Research Question and Hypothesis

Is remote withdrawal management feasible and satisfactory to patients? Based on studies of telemedicine interventions across other psychiatric conditions, we hypothesize that remote withdrawal management will be both feasible and satisfactory.

Objectives

Objective 1**:** Our main objective is to determine the feasibility of remote alcohol withdrawal management. The following indicators will be used:

(1) Retention in treatment (primary objective): Proportion of study participants that complete the entire 3-day remote withdrawal management protocol. We will consider a completion rate of ≥ 70% as strong evidence of feasibility.

(2) Transfer to a higher level of care (primary objective): Percentage of participants sent to the emergency room due to complications, need for intensive monitoring, or acute intoxication. If ≤ 20%, of participants require transfer to a higher level of care, we will consider this as additional evidence of feasibility.

(3) Development of withdrawal- or treatment-related complications: Percentage of participants who develop withdrawal complications or treatment-related complications.

(4) Longer-term retention: Percentage of patients who have dropped out of the study before the final study visit (30 days after treatment initiation).

Objective 2: The secondary objective of this study is to determine patient satisfaction with remote alcohol withdrawal management. The following indicators will be used:

(1) Satisfaction with the overall treatment protocol, measured with the Client Satisfaction Questionnaire-8 (28).

(2) Satisfaction with the telemedicine platform (e.g. visual quality) and service delivery over telemedicine will be measured using a modified version of the Telehealth Satisfaction Scale (29).

Objective 3: The third objective of this study is to examine treatment duration, benzodiazepine requirements, and withdrawal severity. The following indicators will be used:

(1) Percentage of participants requiring benzodiazepine treatment.

(2) Average duration of active withdrawal treatment (i.e. number of days that patients received diazepam among patients that received benzodiazepines).

(3) Average dose of diazepam required to control symptoms among patients that received diazepam.

(4) Peak withdrawal severity score measured over the treatment period

Objective 4: The fourth objective of this study is to examine predictors of relapse (i.e. time to first drink, time to first heavy drinking day, time to first three consecutive heavy drinking days) following remote alcohol withdrawal management. Outcomes will include:

(1) Percentage of participants who relapse using each of the above outcomes and mean or median time to relapse.

(2) Whether measures of executive dysfunction (e.g. impulsiveness), negative emotionality (e.g. depressive symptoms, anxiety), and incentive salience (e.g. craving) predict relapse following treatment and the effect size of each of these domains on propensity to relapse.

Study Design

Overview: This pragmatic single-arm pilot study will recruit actively drinking participants with a history of alcohol withdrawal in order to provide remotely monitored alcohol withdrawal treatment using telemedicine. Potential participants will be patients who are registered at CAMH prior to screening. They will initially present for a screening and eligibility assessment, at which point written informed consent will be obtained, initial data collection will be completed, and it will be determined whether the participant is eligible for the study. In conjunction with the study team, the participant will select a date to begin the remote withdrawal procedure. Remote withdrawal management will take place over a 3-day period. During this 3-day period, participants will receive symptom-triggered diazepam treatment using a modified version of the Clinical Institute Withdrawal Assessment for Alcohol Scale, revised (CIWA-Ar) (30) administered by a trained study clinician. In the unlikely event that the participant's withdrawal symptoms have not resolved after 3-days of symptom-triggered treatment, the procedure will be extended by an additional 1-2 days. Within one week following termination of withdrawal treatment, participants will complete a remote follow up visit in which they will be offered weekly counselling sessions and anticraving medication (if they are not already prescribed anticraving medication) to prevent relapse to alcohol use. They will also complete patient satisfaction questionnaires at this time. On day 30 (+/- 7 days) following treatment initiation, there will be an in-person follow up visit to assess relapse to alcohol use. At this visit, participants will return all study materials to the research team. If the participant is given a study tablet, follow up phone calls may be placed to remind the patient to return the tablet.

Participants: We aim to enroll participants until we have initiated withdrawal management in 30 participants seeking treatment for alcohol withdrawal. This sample size was selected due to its feasibility as a recruitment target for a one-year study timeline. Recruitment will occur through The Centre for Addiction and Mental Health (CAMH) Concurrent Outpatient Medical & Psychosocial Addiction Support Services (COMPASS) clinic. All participants will undergo a urine drug screen

(UDS) and an eligibility assessment with a trained study clinician. Patients 18 years of age or older with active alcohol use and a history of alcohol withdrawal based on DSM-5 criteria will be eligible. Only individuals capable of providing informed consent in English will be permitted to enroll. Participants will have their capacity to consent assessed by a trained clinician or research staff.

Inclusion Criteria

Adults (≥18 years of age) will be enrolled until the required number of 30 participants has completed at least day 1 of detox. Individuals will be included if they:

(1) Are actively using alcohol
(2) Previously met DSM-5 criteria B for alcohol withdrawal
(3) Aim to achieve at least 30 days of abstinence as a treatment goal following initiation of remote alcohol withdrawal management
(4) Are able to provide informed consent in English.
(5) Reside or are able to stay at an address within 2-hours travelling distance from CAMH for the entire duration of the remote withdrawal procedure.
(6) Are enrolled in the Ontario Health Insurance Plan (OHIP)

Exclusion Criteria: Participants will be excluded for the following reasons:

(1) History of complicated withdrawal including withdrawal seizures, hallucinosis, or delirium
(2) Positive UDS for sedatives or opioids, currently prescribed sedatives or opioids, or diagnosis of sedative-hypnotic or opioid use disorder within the past year (based on assessment)
    a. Individuals prescribed low doses of benzodiazepines (e.g. lorazepam 1mg PO daily) or a positive urine benzodiazepine screen that is not thought to be due to benzodiazepine misuse may be permitted to proceed with the study at the discretion of the study physician
(3) Severe medical or psychiatric comorbidity that would prevent safe participation in the study
(4) Contraindications to the safe use of diazepam including: known hypersensitivity to diazepam severe respiratory insufficiency, severe hepatic insufficiency, sleep apnea syndrome, acute narrow-angle glaucoma, and myasthenia gravis.
    a. Individuals with sleep apnea may be permitted to proceed with the study at the discretion of the study physician
(5) Active withdrawal symptoms (CIWA-Ar > 12) at the time of the eligibility assessment
(6) Active suicidal ideation at the time of eligibility assessment
(7) Positive urine pregnancy test, actively breastfeeding, or planning to become pregnant or breastfeed during the study period
(8) Lack of stable housing.
(9) Enrollment in another study that conflicts with the procedures or scientific integrity of this study

Recruitment: COMPASS staff will be informed of the study and will discuss the project with potentially eligible patients, who will be referred to research staff if they are interested in participating. A member of the research team will attend regularly scheduled clinical meetings to inform clinicians of this studies ongoing recruitment. CLEARR will also be used as one of the recruitment methods. All new referrals to COMPASS will be reviewed by the CLEARR coordinator and CLEARR physician for eligibility to participate using minimal

inclusion/exclusion criteria. Once a patient is identified, the attending physician/clinician will be notified via outlook calendar invite or email that their patient may be eligible for the study. The attending physician/clinician will decide whether research is appropriate for the patient and if so, they will ask the patient for consent to be contacted regarding the research study. If the patient provides verbal consent to be contacted to receive more information about the study, the physician will connect the patient with the CLEARR coordinator or study research team who will further explain the study. No PHI will be given to the study research team prior to the patient's consent. Interested participants can be recruited in several different ways: (1) they will be given the contact information to reach research staff and can reach out directly, (2) research staff will reach out to potential participants if they verbally assent to being contacted, (3) if potentially eligible participants are already in the clinic and are interested in the study, they can be directly assessed for eligibility (i.e. participate in in-person visit 1). An effort will be made to identify and contact eligible female patients as we aim to recruit at least 10 female participants. Ads and flyers may be placed on REB approved research boards near the clinic to facilitate recruitment; these will be approved by the REB prior to use.

CAMH ER staff will be informed of the study and will discuss the project with potentially eligible patients, who will be referred to research staff if they are interested in participating. We will also post flyers and leave brochures in the ER. This study may also recruit through the CAMH Research registry (an internal hospital system for recruiting research participants). The CAMH research registry may also be used to recruit participants for this research project. Upon REB approval, authorized research personnel may search and contact potential research participants included within the research registry for study participation. This research project will also be posted on the research registry website, as well as the public CAMH website. Once posted, interested participants can use the "Find a CAMH study" feature to explore research projects that they are of interest to them.

CAMH clinic staff or CLEARR coordinators would ask these patients for their interest in participating in the study using an REB approved script, specific for this strategy. If the patient agrees, their contact information will be provided to the research team. The research team would then contact the patient about participating in the research study.

External recruitment methods may also used. Specifically, advertisement flyers may be posted in locations around the community, including in the Toronto Transit Commission (TTC) as well as different websites (i.e., Kijiji, Facebook, CAMH website). The research team may also reach out to clinicians and support staff at different institutions so that they can pass along the study brochure and/or flyers to potentially eligible participants who can then contact the research team if they are interested in the study. If individuals are not found be eligible for the study but are still seeking medical treatment or withdrawal management, they will be encouraged to go to present to the RAAM clinic at the COMPASS clinic or the ER where a physician can assess them.

Participant Consent:

Prior to the consent discussion: Research personnel will contact participants by telephone using a telephone script. During the telephone call, participants will undergo a telephone pre-screen, using the Eligibility Checklist Phone Screen, to determine initial eligibility prior to in-person screening. Research personnel will obtain consent to send a copy of the informed consent form (ICF) to the

participant prior to the consent discussion; this may occur over REDCap, email, mail, or secure file transfer, according to participant preference.

Consent Discussion and Documentation: The consent discussion will occur either by WebEx or in-person, at the participant's preference. However, given the COVID-19 pandemic, preference will be given to remote consent discussions over WebEx. The consent discussion will be conducted by research personnel who are not the PI and do not have a clinical relationship with the participant and the Informed Consent Checklist will be used to track the consent discussion.

Informed consent will be documented in one of two ways, according to participant preference:

1. *REDCap e-Consent*: Participants will be provided with a read-only copy of the ICF via REDCap prior to conducting the consent discussion. The link may be used by participants as many times as they wish (it is not single-use). Upon clicking the link, participants will review the landing page, and continue on to the ICF text. The entire contents of the ICF will be displayed according to the current REB approved consent form, minus the signature/attestation page(s). Informed consent will be documented using the REDCap e-Consent Framework. Following the consent discussion, the prospective participant will be sent a link to the e-consent via chat feature in WebEx. The participant will complete the e-consent and be provided with the option to download and/or email themselves the signed ICF. If email is chosen, the email will only be used for this purpose (it is not retained by REDCap). Following the participant signature, the person conducting the consent discussion will complete the Person Conducting Consent Discussion Attestation Page. PDF copies of the signed ICFs and Attestation pages will be retained in the REDCap File Repository. The research team will provide the participant with a copy of the fully signed ICF via mail and/or email, in accordance with the participant's wishes.
2. *In-Person Written Paper Consent*: Following the consent discussion, the participant and the person conducting the consent discussion will each personally sign and date the ICF. This will occur in person.

Participants will have their capacity to consent assessed using a consent quiz. Participants will be able to take the quiz until they achieve a score of > 9 out of 10 or until it becomes evident that they lack capacity to provide consent (in which case they will not be permitted to enroll). In between quiz attempts, a member of the research team will review relevant aspects of the study with the participant to ensure adequate comprehension.

Following informed consent: A complete (fully signed) copy of the ICF will be provided to participants by email, mail, or secure file transfer, according to their preference.

Following the consent discussion participants will undergo a WebEx or in-person educational session with a study clinician or research staff who will educate them about the risks of alcohol withdrawal and diazepam treatment. They will also be emailed and given a handout, the Participant Decision Tree, which they can refer to if they are unsure of what to do after hours during the remote withdrawal. This meeting will take place prior to the first remote withdrawal session and can occur during the eligibility visit if necessary.

Screening and Eligibility Assessment: Patients interested in participating will complete a detailed eligibility assessment. Parts of this assessment may be done remotely, but the Eligibility Update Form, Previous DSM-5 Alcohol Withdrawal Assessment, breathalyzer test, urine drug screen, the initial CIWA-Ar with vital signs, the clinical questions for the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), and blood tests will be done in person. The Eligibility Update Form will be used to confirm key details following the telephone pre-screen. Patients will provide urine for a urine drug screen (UDS) and pregnancy test (for female participants), a breathalyzer test, and blood work to determine liver and kidney function. We will not repeat blood work if liver function tests and kidney function tests have already been performed within the past two weeks. The patient will be asked about newly diagnosed medical and psychiatric conditions and which medications they are taking. Medications will be reviewed on I-CARE to ensure that the participant is not actively prescribed sedatives or opioids. Active pregnancy, breastfeeding, or intention to become pregnant or breastfeed, lack of stable housing, residence within two hours commute to CAMH, contraindications to diazepam treatment, English proficiency, enrollment in OHIP, and enrollment in other studies will have been assessed by one or more of our eligibility questionnaires. History of DSM-5 alcohol withdrawal will also be assessed with a questionnaire. The Columbia Suicide Severity Scale (28) will be administered to verify that there is no active suicidal ideation and the study clinician will use the Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-Ar) (30), the most commonly used withdrawal assessment tool, to verify that the patient is not in active withdrawal (CIWA-Ar score > 12) at the time of enrollment. If the participant is in alcohol withdrawal (CIWA > 12), study staff will notify the study physician. The participant will be offered treatment at day detox (if there is capacity) or in the ER or may be rebooked to complete the eligibility assessment on another day. The risks of delaying or refusing care will be explained to the patient if they are not interested in receiving immediate treatment.

As part of this assessment, vital signs will be measured. Eligible participants will provide their address and phone number. Participants will complete additional assessments on a tablet or another device. These assessments will include a 30-day version of the Timeline Followback Interview (TLFB) (31), Alcohol Use Disorder Identification Test (AUDIT) (32), SCID-5: Lifetime Alcohol and Drug Use section of the Overview, Alcohol Use Disorder module, and if indication of current drug use, the past-12 month Substance Use Disorder Module (33), Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (34), Penn Alcohol Craving Scale (PACS) (35), Patient Health Questionnaire-9 (PHQ-9) (36), General Anxiety Disorder-7 (GAD-7) (37), the Short form of the Bem Sex Role Inventory (BSRI) (38), the Cannabis Use Disorder Identification Test – Revised (CUDIT-R) (39), the Fagerstrom Test for Nicotine Dependence (FTND) (40), the Barratt Impulsiveness Scale (BIS-11) (41), the short version of the UPPS-P Impulsive Behavior Scale (42), the Speilberger Trait Anxiety Inventory (STAI) (43), the Obsessive-Compulsive Drinking Scale (OCDS) (44), Difficulties in Emotion Regulation Scale (DERS) (49), Prior Detoxification Questionnaire, Perceived Stress Scale (50), Social Readjustment Rating Scale (51), Impaired Control Scale (52), Pittsburgh Sleep Quality Index (53), and Emotion Regulation Questionnaire (ERQ) (54). If participants are eligible, a start date for remote withdrawal management will be agreed upon. A preference will be given to earlier days of the week (i.e. Monday and Tuesday) to prevent the remote withdrawal procedure from extending into the weekend. Participants will be instructed to abstain from alcohol for roughly 6 hours prior to their initial withdrawal management assessment and to remove all alcohol from their residence if possible. We will also remind participants that if we are not able to contact them during the study period, we may call their

emergency contact. Participants who do not have access to a smartphone, tablet, or computer at home with adequate internet access will be given a tablet with or without a data plan (depending on participant need) to take home for the duration of the study. A test of the telemedicine platform may be performed in advance if possible to ensure that there will be no technical problem the day of the scheduled withdrawal. Prior to entering the clinic, participants may be screened for COVID-19 symptoms, recent travel, and known contacts with COVID-19 or symptoms of COVID-19. During this in-person visit, participants will be required to wear a mask (except during breathalyzer testing) and research staff will be required to wear a mask and face shield to reduce the risk of SARS-CoV-2 transmission. Research staff will also try to maintain a distance of at least 2 meters from participants whenever possible.

Remote Alcohol Withdrawal Management: Patients will undergo initiation of withdrawal management on the day selected in conjunction with the research team. Patients will be instructed to remove any alcohol from their home if possible prior to the initiation of the remote withdrawal management process. Participants will be treated for a period of 3 days. On each day, a supply of diazepam determined by the clinician (typically a maximum of 80mg on day one) will be delivered by the treating pharmacy or picked up by the participant or one of their family members if this is deemed necessary (e.g. participants may have a sufficient supply of diazepam remaining from the previous day, in which case they would not need to pick up additional medication). Participants will be contacted the day before the first remote alcohol withdrawal management day to remind them to pick up their diazepam prescription and log into the telemedicine platform the following morning. At around 9:00 AM on each treatment day, participants will be asked to log on to a CAMH-approved telemedicine platform (i.e. WebEx or the Ontario Telemedicine Network [OTN]). Patients will provide identification (name, date of birth, and/or photo ID) to the treating clinician and confirm the address and phone number where they can be reached. They will also be asked to confirm their emergency contact's name and phone number. A study clinician will confirm when the patient last consumed alcohol, ask about any new medications since the patient was last assessed, and confirm that they have not used any benzodiazepines (other than the diazepam prescribed for this study, except in the case of study participants who takes low dose benzodiazepines and have been approved for inclusion by the study physician at eligibility – these participants will be permitted to continue to take their usual medication) or opioids within the last 24 hours. I-CARE will be checked when possible during each day of remote detoxification for new medication prescriptions. The CIWA-Ar (adapted for telemedicine use) will then be administered by a trained study clinician over the video telemedicine platform. Participants will be asked to log in to the telemedicine platform through their device or the study tablet. Participants who score 10 and above on the modified CIWA-Ar will be advised to take a specific dose of diazepam (either 10 or 20mg, at the clinician's discretion). Participants will be reassessed every hour and receive diazepam until their CIWA-Ar score falls below 10. If a participant is not able to take the dose at the time of the assessment (e.g. they ran out of medication and need to go to the pharmacy to pick up additional diazepam), the next dose of diazepam may be held or the next CIWA-Ar may be delayed to the hour after the most recent dose of diazepam was taken (at the discretion of the study clinician). After CIWA-Ar scores fall below 10, participants will be intermittently reassessed every 1-4 hours at the clinician's discretion. Participants will be monitored until around 4:00 PM each day through these serial assessments and will have access to as needed doses of diazepam should they develop withdrawal symptoms overnight. At the end of the day, the study physician will direct the patient to take additional doses of diazepam overnight on an as needed basis depending on the clinical context. The amount of

diazepam taken by the participant overnight will be recorded the following day. In the event that the clinician is not able to reach the client via WebEx or OTN, they will call the patient by phone.. If the participant is not able to be reached, research staff will continue to contact the participant for up to 3 hours, with calls approximately every 30 minutes. If research staff cannot reach the participant after 3 hours or it is past 4:00 PM, research staff will leave a detailed voicemail message for the participant using the Unable to Contact script, asking them to resume treatment and reminding them to go to the emergency if there are any adverse events. In the event that the clinician is able to reach the study participant but the telemedicine platform is not working, the clinician will try using another platform (e.g. switching from the Ontario Telemedicine Network to WebEx). Participants may also be given the opportunity to try logging into the telemedicine platform(s) on another device. If the telemedicine platforms are still not working despite these attempts to fix the problem, the clinician will try to connect again within the next 10-20 minutes. If there are continued technical problems with the telemedicine network, the clinician may contact the patient by phone or the patient may be instructed to come to the clinic for the remainder of that day's withdrawal management procedure (at the clinician's discretion, depending on the patient's clinical status). If the patient comes to the clinic, an effort will be made to troubleshoot the telemedicine connection while the patient is at CAMH (including potentially giving the participant a study tablet with a data plan) so that the participant can resume remote withdrawal management the next day.

The treatment protocol will continue for 3 days. If a participant does not have three consecutive CIWA-Ar scores < 10 at this time, the treatment protocol will be extended for an additional two days. A minority of patients should require this extension as average treatment duration in symptom-triggered withdrawal studies is less than 2 days (12). Throughout the remote withdrawal procedure, diazepam-related adverse events will be assessed by a clinician using the Research Adverse Events Log. Participants will be sent to (or asked to go to) the emergency room (ER) if they develop any severe withdrawal complications, display evidence of severe alcohol intoxication, severe sedation, require excessively high doses of diazepam, or at clinician discretion (e.g. CIWA-Ar not coming down). Participants sent to the ER will be contacted by phone to document adverse outcomes and ensure appropriate clinical follow up. Patients refusing to go to the ER will have the risks of refusing treatment explained at length by a member of the treating team.

Follow Up Visits: Participants will be scheduled for one remote follow up visit within one week following completion of remote detoxification (this will be targeted for the day after remote withdrawal treatment completion). At this time, participants will be reassessed by a study clinician via telemedicine. The Research Adverse Events Log will be completed to determine if there are any residual adverse effects from diazepam treatment. Participants will be offered an anticraving medication (e.g. naltrexone) to reduce alcohol cravings and likelihood of relapse if they are not already taking one. They will also be offered weekly psychosocial support from a clinician at the COMPASS clinic for a period of 4 weeks following treatment. They will be instructed to return any unused doses of diazepam to the pharmacy. Participants will also be asked to complete the Client Satisfaction Questionnaire-8 (28) in order to determine overall satisfaction with treatment and a modified version of the Telehealth Satisfaction Scale (29) in order to determine satisfaction with the telemedicine platform. A final in-person study visit will occur on day 30 (+/- 7 days) following treatment initiation. At this follow up visit, the participant's drinking status will be assessed using a 30-day version of

the TLFB and their anxiety, depression and craving levels will be reassessed using the GAD-7, PHQ-9, and PACS. The participant will also complete the DERS and ERQ to measure difficulties in emotion regulation. A urine drug screen will also be performed (including a urine ETG) to assess for relapse to alcohol use and use of other drugs. During the final follow up visit, if the participants was given a tablet they will be asked to return the study tablet. They will also be compensated for their participation. Prior to entering the clinic, as per CAMH policy, all participants will be screened for COVID-19 symptoms, recent travel, and known contacts with COVID-19 or symptoms. During this in-person visit, participants will be required to wear a mask at all times and research staff will be required to wear a mask and face shield to reduce the risk of SARS-CoV-2 transmission. Research staff will also try to maintain a distance of at least 2 meters from participants to the extent possible. In between the first and second follow up visits, participants may continue their usual medical follow up with their physician(s) to adjust their medications and ensure medical and psychiatric stability as per usual practice in the clinic. During the study period, if a participant is unable to schedule a meeting with their physician, the study physician will also be permitted to adjust the participant's medication as clinically indicated (and at their discretion).

Data Capture: Study data will be collected using REDCap (Research Electronic Data Capture) whenever feasible. When direct collection with REDCap is not feasible, data collected via paper forms will be transferred to REDCap when deemed appropriate by the research team. REDCap is a secure, web-based application for collecting electronic data via online data entry forms and surveys. It is built and distributed by Vanderbilt University, with a local instance installed on a central CAMH server overseen by the CAMH REDCap Operations Committee. All data are stored on site and backed up daily. Hard copies of paper forms with personal identifying information will be stored in a locked filing cabinet in a locked office at CAMH

Data Sharing: After the primary findings of the study are accepted for publication, de-identified data may be made available for internal and external data sharing upon request. Data sharing may also be initiated by the PI. We will ask participants to consent to this in the Informed Consent Form.

Remote Assessments and Remote Informed Consent for In-Person Visits: Due to the COVID-19 pandemic, elements of the in-person screening and eligibility assessment (in-person visit 1) as well as the final follow up visit (in-person visit 2) may be administered remotely to reduce the risk of SARS-CoV-2 transmission. For in-person visit 1, the Eligibility Update Form, Previous DSM-5 Alcohol Withdrawal Assessment, breathalyzer test, urine drug screen, initial CIWA-Ar with vital signs, the clinical questions for PAWSS, and bloodwork will still need to be administered in-person. For in-person visit 2, the urine drug screen and return of the study tablet (when applicable, for patients lacking access to a smartphone, tablet, or computer at home and/or adequate internet access) will need to occur in-person.

Community Advisory Board

Sandra LaFleur is an Indigenous woman with personal and professional experience related to alcohol withdrawal and is a collaborator on this grant. We will recruit an additional 1-2 people with lived experience or their family members through the Patient and Family Engagement in Research Office at CAMH to serve on a community-advisory board (CAB) for this project. The

CAB will be engaged around specific topics including obtaining meaningful consent, and preparation of plain language summaries for participants. The CAB will meet with the research team at the outset of the project and thereafter for feedback and preparation of knowledge translation activities.

Memorandum of Understanding: It has been recommended that a minimum requirement for projects involving CABs include a memorandum of understanding (41). Together with our community advisory board, we will draft a memorandum of understanding which we will ask all team members to adhere to.

Decision Making: The community advisory board will provide valuable input into decision making. Members who are unable to attend a meeting will have the opportunity to contribute questions and ideas in advance by telephone or e-mail.

Capacity-Building For Community Members: Community Advisory Board members will learn about clinical research and methodology and will be actively involved throughout the project.

Compensation: The community advisory board (CAB) will be comprised of 2-3 members or family members with lived experience. They will be involved in refining the study protocol, providing input on obtaining meaningful consent in the context of alcohol withdrawal, bridging from detoxification to other treatment services, and preparation of patient-facing knowledge translation materials. They will receive honoraria for up to 6 half-days (please see budget).

Privacy and Confidentiality CAB members agree as part of the memoranda of understanding that members' individual stories would not be shared outside of the group.

Ownership of Data: The Investigators are entitled to publication and presentation of the methods and results of the study. In the event that the Investigators and CAB co-author a publication or presentation, CAB members may be stated as authors or credited in the publication, commensurate with the level of participation. CAB members will not be permitted to publish material about the research project without the consent of the principal investigator.

Study Visits

	In-Person Visit 1	Detox Day 1 (Telemedicine)	Detox Day 2 (Telemedicine)	Detox Day 3 (Telemedicine)	Remote Follow Up (Day 4*) (Telemedicine)	In-Person Visit 2 (Day 30 +/- 7 days)
Breathalyzer Test	x					
Demographic Form	x					
Urine Drug Screen	x					**x**
Urine Pregnancy Test	x					

Blood Test	x					
CIWA-Ar (30)	x					
Modified Remote CIWA-Ar		**x**	**x**	**x**		
Previous DSM-5 Alcohol Withdrawal Assessment	x					
Eligibility Update Form	x					
Prior Detoxification Questionnaire	x					
Final Eligibility Form	x					
30-day TLFB (31)	x					**x**
AUDIT (32)	x					
Lifetime Alcohol and Drug Use section of the Overview of SCID-5	x					
AUD module of SCID-5	x					
Past-12 month SUD module of SCID-5 (if necessary)	x					
PAWSS (34)	x					
PHQ-9 (36)	x					**x**
GAD-7 (37)	x					**x**
STAI	X					
PSS (50)	x					
SRRS (51)	x					
BIS-11	X					
UPPS-P	X					
CUDIT-R (39)	X					
FTND (40)	X					
PACS (35)	X					**x**
OCDS	x					
Short Form of the Bem Sex Role Inventory (38)	x					
DERS (49)	x					**x**

ICS (52)	x					
PSQI (53)	x					
ERQ	x					**x**
Client Satisfaction Questionnaire-8 (28)					**x**	
Columbia Suicide Severity Scale (27)	x					
Telehealth Satisfaction Scale (29)					**x**	
Research Adverse Events Log		**x**	**x**	**x**	**x**	

Notes: A minority of participants may need up to two extra days of withdrawal monitoring and management. Extra withdrawal management days will consist of remote CIWA-Ar monitoring and will have the same procedure as for Detox Day 1, 2 and 3. In cases where individuals require extra days of detoxification, the remote follow up visit will be pushed to after detox is completed. So, if a participant required 5 days of detoxification, we would try to schedule the remote follow up visit on day 6 but the visit can occur up to one week following detox completion. Assessments may be collected by paper or using electronic data capture platform REDCap.

*Remote follow up visits will ideally be scheduled the day following detoxification but can take place up to a week following the completion of remote withdrawal management.

TLFB: 30-day Time Line Follow Back
AUDIT: Alcohol Use Disorder Identification Test
Lifetime Alcohol and Drug Use section of the Overview of SCID-5: Overview of Structured Clinical Interview-DSM5
AUD module of SCID-5: Alcohol Use Disorder module of Structured Clinical Interview-DSM5
Past-12 month SUD module of SCID-5: Substance Use Disorder module of Structured Clinical Interview-DSM5
CIWA-AR: Clinical Institute Withdrawal Assessment for Alcohol-Revised
CUDIT-R: Cannabis Use Disorder Identification Test-Revised
FTND: Fagerstrom Test for Nicotine Dependence
GAD-7: General Anxiety Disorder-7
PACS: Penn Alcohol Craving Scale
PAWSS: Prediction of Alcohol Withdrawal Severity Scale
PHQ-9: Patient Health Questionnaire-9
STAI: State Trait Anxiety Inventory
BIS-11: Barratt Impulsiveness Scale
UPPS-P: UPPS-P Impulsive Behavior Scale
OCDS: Obsessive-Compulsive Drinking Scale

DERS: Difficulties in Emotion Regulation Scale
PSS: Perceived Stress Scale
SRRS: Social Readjustment Rating Scale
ICS: Impaired Control Scale
PSQI: Pittsburgh Sleep Quality Index
ERQ: Emotion Regulation Questionnaire

Study Timeline From October 1, 2020

	Time (months)											
Activity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Project Launch	■	■	■	■								
Community Advisory Board Meetings	■	■			■			■			■	■
Recruitment and data collection					■	■	■	■	■			
Data analysis										■		
Knowledge Translation Activities											■	■

Data Analysis

As this is a pilot study to determine the feasibility of the proposed intervention, the recruitment target was based on feasibility and no power calculations were conducted. All data will be analyzed in aggregate and stratified by sex. Average or median values will be used as measures of central tendency depending on the distribution of the data. Measures of variability (e.g. standard deviation, interquartile range) will be reported. When feasible, logistic regression will be used to examine demographic and clinical predictors of binary outcomes (e.g. completion of detoxification protocol, need for a higher level of care) and linear regression will be used to examine associations with continuous outcomes (e.g. total dose of benzodiazepines received, highest CIWA-Ar score measured). Predictors examined will include age, sex, gender role scores, race, household income, and presence of psychiatric or SUD comorbidities. Survival analyses will be used to examine time to relapse. Other types of statistical analyses may also be used to examine the data. Marcos Sanches (Collaborator) is a biostatistician at CAMH and will assist with planning and conducting analyses.

Main Outcome Measures

(1) Retention in treatment: Proportion of study participants that complete the entire 3-day remote withdrawal management protocol.
(2) Transfer to a higher level of care: Percentage of participants sent to the emergency room due to complications, need for intensive monitoring, or acute intoxication.

Managing and Reporting Side Effects

Side effects will be documented by a study clinician throughout the remote withdrawal procedure using the Research Adverse Events Log. Participants will be instructed not to take any additional doses of diazepam if they appear oversedated. If suspected respiratory depression is present, the study clinician will contact 911 and request that an ambulance be sent to the participant's location for urgent emergency medical technician evaluation.

Management of Co-Occurring Conditions and Additional Withdrawal Complications

The patient's physician will be permitted to prescribe any medications required during the withdrawal procedure to manage co-occurring conditions or side effects of withdrawal as determined by their medical judgement. Examples of this may include nicotine replacement therapy if the participant desires to quit smoking at the same time as abstaining from alcohol or PRN medication to manage withdrawal-related nausea or vomiting.

Medical Costs Resulting from Complications

In the event of complications, healthcare costs are expected to be covered by the Ontario Health Insurance Plan (OHIP). All participants will be required to have OHIP coverage.

Ethical issues:

A. Confidentiality: Confidentiality will be strictly adhered to. Information collected for the treatment of the patient will be documented in the I-CARE medical records system and will be accessible to the treating team, study nurse, research team, and PI for the duration of the study. Clinically-relevant information obtained during the protocol (including laboratory tests) will also be shared with the participant's clinical treatment team. Participants will be assigned participant codes for data collection. A list linking participant codes to their names, MRN, date of birth, and contact information will be password protected on CAMH computers and will only be accessible to the PI, co-investigators, study nurse, and research team (e.g. research analyst, graduate student). No personally identifiable information (e.g. name, date of birth, MRN, email address, phone number) will be kept in the master data file used for analysis. Participants and their family members will only be contacted by email if they consent to the privacy risks either verbally or in writing.

   All paper forms with personally identifiable information will be stored in a locked filing cabinet in a locked office at CAMH. All electronic documents with personally identifiable

information will be stored on password protected encrypted CAMH devices. The PI, co-investigators, statistical consultant, study nurse, and research team (e.g. research analyst, graduate student) will have access to the data for data sorting and analysis.

If a privacy breach occurs we will follow appropriate CAMH process including notifying the CAMH Information and Privacy office and CAMH REB. We will obtain REB approval of the notification script prior to informing participants of the privacy breach.

B. Consent: All participants will be required to provide written, informed consent before participating in any study-related procedures. Participants will be given the opportunity to ask any questions about study design and procedures during the consent process. Participants will be informed that they can withdrawal their consent at any time and for any reason. Capacity to consent will be assessed using a consent quiz following a full review of the informed consent form. Participants will need to score > 9/11 on this quiz, they may attempt the quiz multiple times.

C. Risks to participants: As with in-person withdrawal treatment, there are important risks that the participants will need to be aware of prior to providing consent.

(1) Withdrawal complications: Alcohol withdrawal can lead to important complications, including but not limited to: (a) withdrawal seizures, (b) alcohol withdrawal delirium, (c) alcoholic hallucinosis (hallucinations with a clear sensorium), (d) and rarely, death. If participants develop any severe withdrawal complications, such as seizure or delirium, 911 will be contacted so that the participant can be sent to the emergency room for urgent evaluation and treatment.

(2) Medication complications: Treatment with diazepam can lead to side effects including but not limited to drowsiness, fatigue, muscle weakness, ataxia, anterograde amnesia, confusion, falls, and respiratory depression (which can lead to death in severe cases). Diazepam most often causes drowsiness with some sources indicating that almost a quarter of people who take this medication (23%) experience this side effect. Deaths from respiratory depression due to benzodiazepines are rare. For example, in a study looking at all illicit drug overdoses in British Columbia from 2015-2017, only 6% had benzodiazepine or so-called Z-drug (a type of sleeping medication) use that was deemed relevant to death (42). Deaths from benzodiazepines most commonly occur when they are used together with opioids such as heroin, morphine, or hydromorphone (Dilaudid) (43). Participants will be advised that they should not take this medication while using respiratory depressants (e.g. opioids, alcohol, other benzodiazepines). They will also be advised not to use diazepam when pregnant or breastfeeding or intending to become pregnant or breastfeed. Diazepam should not be used in individuals who are pregnant since it can increase the risk of congenital malformations and premature birth. It should also not be used when breastfeeding since it is released in breast milk. A study clinician will monitor for side effects on each day of withdrawal treatment and during the follow up visit. If patients are experiencing severe side effects identified by study staff (e.g. suspected respiratory depression), 911 will be contacted so they can be taken to the emergency room for urgent evaluation and treatment. Participants will also be advised

that diazepam is an addictive substance and there is a potential for drug abuse. Participants will only be given a limited supply of diazepam per day to reduce the possibility of abuse. Diazepam is contraindicated in individuals with known hypersensitivity to diazepam and in patients with severe respiratory insufficiency, severe hepatic insufficiency, sleep apnea syndrome, acute narrow-angle glaucoma, and myasthenia gravis. Participants with any of these conditions will be excluded from participation. Participants will also be informed that they should not use diazepam while driving or operating heavy machinery. There is no need to taper diazepam during withdrawal management as the medication effectively self-tapers due to its long half-life (44).

(3) Relapse to alcohol use: Following withdrawal treatment, individuals may resume using alcohol. This has many potential risks including higher risk of motor vehicle accidents, other types of accidents, development of liver disease, and death due to intoxication. Participants may need repeat medical withdrawal management should they relapse to alcohol use. Efforts will be made to decrease relapse rates, including offering participants weekly counselling sessions and anticraving medication (e.g. naltrexone, acamprosate), both of which have been shown to reduce the likelihood of relapse.

(4) SARS-CoV-2 Transmission: This study involves two in-person visits, during which time SARS-CoV-2 transmission could occur. SARS-CoV-2 transmission could also occur during transit to the hospital or visits to the pharmacy. Efforts made to prevent SARS-CoV-2 transmission may include standardized screening of participants prior to entering CAMH for COVID-19 symptoms, recent travel, and contact with individuals who displayed COVID-19 symptoms. Participants will be required to wear a mask at all times (except during breathalyzer testing) and research staff will be required to wear a mask and face shield to reduce the risk of SARS-CoV-2 transmission. Research staff will also try to maintain a distance of at least 2 meters from participants whenever possible. Study tablets will be sanitized in between participants.

(5) Blood Draws: Blood collection can cause bruising and discomfort at the injection site. There is a small risk of fainting. Infection can also rarely occur, but the risks are minimized by using proper sterile technique.

(6) Questionnaires: Questionnaires about alcohol can sometimes trigger cravings. Should this occur, participants will be encouraged to discuss their cravings with the research or clinical team. Questionnaires may also cause fatigue. Questionnaires should not pose any other risks to participants. Participants who are filling out questionnaires will be granted breaks when necessary.

D. Benefits to participants: If remote withdrawal management is successful, benefits to participants may include increased convenience of treatment (e.g. not having to be monitored in hospital for treatment response) and decreased exposure to SARS-CoV-2 during withdrawal management since participants will be at home.

A wallet card with the contact number(s) will be given to the participant. Participants will be instructed not to call this number in the event of an emergency (e.g. a withdrawal seizure), instead they should call 911. Participants will also be given the phone number of the study clinician; they can call there during the day if they are having technical problems. Participants will also be given a handout (either by email or in-person), the Participant Decision tree, which they can refer to if they are unsure how to handle specific situations after hours during the remote withdrawal procedure.

Study Documentation and Archiving

Investigators will retain a participant list should they need to contact participants after study completion. This list will contain complete name, date of birth, MRN, study identification number, address, phone number, and email address of participants. This list will be password protected on a CAMH computer and will only be accessible to the PI, co-investigators, study nurse, and research team (e.g. research analyst, graduate student). Study data and documents will be retained in a secure setting by the research team for a period of 25 years after the termination of the study.

Termination of the Study

Participants may be withdrawn for the following reasons:

1) Participant does not meet inclusion criteria or meets one of the exclusion criteria
2) Participant is prescribed a medication or begins abusing a drug which would could cause a severe adverse reaction if combined with a benzodiazepine (e.g. an opioid)
3) Participant develops severe withdrawal complications, such as a seizure or delirium tremens
4) Pregnancy
5) Withdrawal of consent
6) Loss to follow up
7) Major protocol violation

Participants may also be withdrawn at the discretion of the principal investigator if it is deemed to be in the best interest of the participant. If a participant is withdrawn, they will be replaced with a new participant until recruitment targets are met or the study is terminated. Data collected up to the participant's withdrawal from the study may be used in data analysis.

Criteria for the Termination of the Trial

The study will be terminated when recruitment targets have been met. The study may also be terminated at the discretion of the PI or due to adverse events.

Funding

This study is funded by CIHR's COVID-19 Mental Health & Substance Use Service Needs and Delivery Grant. Funding will be provided by both CIHR and the Ontario Ministry of Health.

Participant Compensation

Visit	Compensation	Time	Description
In-Person Screening and Eligibility	$ 20	Approximately 3 hours	Determination of eligibility for the study, urine drug screen, blood test, and questionnaires/assessments.
Remote Withdrawal Assessment and Treatment	$40/day (total for 3 days = $120)	Several short assessments throughout the day (approx. 9:00 AM – 4:00 PM)	Withdrawal management over a 3-day period using telemedicine.
Remote Follow-up Session	$40	Approximately 1.5 hours	Participant will be offered the opportunity to receive anticraving medication and counselling. They will complete satisfaction questionnaires
Final In-Person Visit	$ 50	Approximately 2 hours	Final study visit in which the participant will bring back the study tablet, complete a urine drug screen, and complete questionnaires & assessments.
Total	**$230**		

Notes: A minority of participants may need up to two extra days of withdrawal monitoring. Extra days will be compensated at a lower rate ($10 per day) to avoid incentivizing false reporting of withdrawal symptoms. Maximum compensation for participants is therefore $250 total. Taxi vouchers will be provided if necessary.

Participants will be reimbursed at the time of completion of the study. If participation ends early for whatever reason, compensation will occur on a pro-rated basis as described above.

Project Team:

Our research team consists of experts in addiction medicine and the implementation of technological interventions to optimize addiction treatment. Matthew Sloan (Principal Investigator) is an Addiction Psychiatrist, Assistant Professor at the University of Toronto, and Clinician Scientist at CAMH, with experience investigating determinants of alcohol consumption. He has spent five years working at a detoxification clinic and has extensive experience managing alcohol withdrawal. He also has experience using telemedicine to treat addiction, including working at a telebuprenorphine clinic which provided opioid agonist therapy to patients living in rural Connecticut. Nikki Bozinoff (Co-Investigator) is an addiction medicine specialist with a research background focused on improving service delivery to individuals with substance use disorders. Bernard Le Foll (Co-Investigator) is an addiction medicine specialist and senior Clinician Scientist focused on investigating novel treatments for substance use disorders. Lena Quilty and Christian Hendershot (Co-Investigators) are clinical psychologists with experience studying mobile health and computerized interventions for SUDs. Leslie Buckley (Co-Investigator) is the Chief of the Addictions Division at CAMH and Francesca Di Paola (Co-Investigator) is the Medical Head of CAMH's COMPASS Clinic. Marcos Sanches (Internal Consultant) is a biostatistician and will serve as a statistical consultant on the project. Meldon Kahan, Jennifer Wyman, and Kate Hardy (External Consultants) form the leadership team for Mentoring, Education and Clinical Tools for Addiction: Primary Care-Hospital Integration (META:PHI), a network of Rapid Access Addiction Medicine clinics delivering low-barrier, evidence-based interventions in over 60 locations across Ontario. META:PHI has a strong interest in disseminating this intervention across its network should it prove feasible through its yearly conference, best practice documents, and continuing education listserv. Bryce Barker (External Consultant) is a knowledge broker at the Canadian Centre on Substance Use and Addiction (CCSA), an organization that seeks to disseminate evidence-based treatment for substance use disorders at the national level. CCSA can leverage its national forums and practitioner networks to promote the adoption of this intervention.

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