The association between loneliness and substance use

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1. PURPOSE OF STUDY

The proposed study will be the first to assess these cognitive, affective, and behavioral pathways by which loneliness impacts opioid use. Individuals with an opioid use disorder (OUD) reporting loneliness ($N = 125$) will be randomized to either a 6-session Cognitive-Behavioral Therapy for loneliness (CBT-L; $n = 63$) or a 6-session education control condition ($n = 62$), both delivered via telehealth. Telehealth delivery can be easily implemented and can increase reach and access to individuals not engaged in treatment. We will use an established brief CBT manual to address loneliness. We will assess loneliness, negative affect (i.e., depression and anxiety), and the quality and quantity of social interactions prior to, during, and after the intervention to evaluate the subsequent impact on opioid use trajectories. Participant will complete questionnaires pre-treatment, post-treatment, and at 1- and 2-months post-treatment. Given the need to elucidate mechanisms of opioid use and to test novel treatment approaches to reducing opioid use, we propose the following specific aims in this pilot study:

Aim 1: To assess the efficacy of CBT-L's impact on loneliness, negative affect and the quality and quantity of social interactions among individuals with OUDs
Hypothesis: CBT-L will reduce loneliness and negative affect (i.e., depression and anxiety) and will increase the quality and quantity of social interactions compared to the education control.

Aim 2: To assess the cognitive, affective, and behavioral mechanisms of the impact of CBT-L on opioid use trajectories
Hypothesis: CBT-L will reduce opioid use relative to the education control and these reductions will occur due to reduced loneliness, negative affect, and increased quality and quantity of social interactions.

2. BACKGROUND AND RATIONALE

Premature deaths from opioids have devastated U.S. communities, with nearly 50,000 opioid-related overdose deaths in 2017.[1] The declining U.S. life expectancy has been largely attributed to opioid-related deaths.[2] The multi-faceted public health response to this epidemic includes increasing access to evidence-based treatments, decreasing prescription opioid availability, and guidelines that promote non-pharmacological pain treatments.[3-5] Understanding and addressing psychosocial stressors represents an essential area to reduce the demand for opioids.[6] Through the use of adaptive coping strategies for psychosocial stressors, desire to use opioids might decrease thereby increasing engagement in social support.

Loneliness—a subjective emotional state characterized by the *perception* of social isolation[7]—is a critical psychosocial stressor that can significantly impact opioid use. Loneliness is distinct from social isolation in that people with relatively few social contacts may not feel lonely, while individuals with rich social experiences may feel lonely.[8] Loneliness impairs one's ability to effectively engage social support.[9] Loneliness is evident across the lifespan and can be experienced by anyone, although it occurs at higher rates among those with psychiatric disorders, people who are objectively isolated, and people with chronic illnesses.[7] A national study of

adults ages 45+ found that over one-third reported loneliness[10] and in 1,200 primary care patients, 20% reported being lonely.[11] Loneliness can have deleterious effects on physical and mental health, increasing the risk for a constellation of chronic diseases and the development and exacerbation of psychiatric disorders and suicidal behavior.[8,12] A meta-analysis of 70 studies found that loneliness increases odds of mortality by 29% in adjusted analyses accounting for the largest number of covariates.[13]

Substance use is among the several unhealthy behaviors through which loneliness relates to increased premature mortality. Loneliness has been linked to tobacco and alcohol use in numerous studies,[14-17] including a national 10-year longitudinal study of over 3,000 people, where greater loneliness was associated with a 70% decreased likelihood of smoking cessation.[16] In cross-sectional data with 18-39 year olds, loneliness was associated with problematic drinking after accounting for depression, alcohol consumption, and coping style.[15]

Bohnert and Ilgen[18] postulate that large-scale social factors (e.g., lack of employment opportunities, socioeconomic inequities) increase opioid use leading to depression and social isolation. The opioid epidemic further impacts communities through harmful effects on social networks and social cohesion emphasizing a need to increase meaningful social interactions.[6] Opioid use can be reinforced through coping with social isolation that occurred as a result of finding social contact less rewarding and being concerned with the stigma attached to opioid use.[19] Indeed, loneliness increases opioid use, is associated with a variety of negative consequences among individuals using opioids[20-25] and is a critical factor that needs to be addressed in response to the opioid epidemic

Prevalence of loneliness among individuals with OUDs is very common. A study among a sample receiving methadone maintenance for OUD found that nearly three-fourths of women and over two-thirds of men reported *moderate to severe* loneliness.[26] Prior studies among heroin-dependent individuals maintained on methadone found greater loneliness was associated with non-suicidal self-injury, sleep disturbance, greater pain intensity, and poorer quality of life[22-25] key risk factors for relapse.[27,28] Loneliness and difficulty meeting abstinent friends is more commonly cited as a reason for craving among heroin users who relapse compared to those who remain abstinent.[29] In a longitudinal study, the greatest reduction in heroin use was not just in people who were married, but those who reported a close personal relationship with his/her spouse.[30] Accounts among individuals with an OUD indicate they often lack purpose largely driven by a sense of loneliness.[31] Social isolation is both a motivation for heroin use and a risk factor for suicidal behavior among individuals addicted to heroin.[32-34] Addressing loneliness can affect treatment seeking. Those injecting drugs were 3 times less likely to seek OUD medications (e.g., methadone, buprenorphine) if they live alone.[35] Additionally, treatment retention is associated with a perception of strong social support from one's family.[36] A qualitative study revealed that there appears to be a subtype of people using heroin characterized as being more socially disconnected and these individuals have more cognitive barriers to engaging in methadone maintenance (e.g., harms of treatment outweigh the benefits) compared to other subtypes.[37] Addressing loneliness in people using opioids can reduce risk factors for relapse or continued use and have a significant positive impact on how a person develops, maintains, and utilizes social support, including treatment seeking—all of which are essential factors in reducing opioid use.[38-41]

To effectively reduce opioid use and related mortality, individual-level longitudinal data is needed to further understand the mechanisms by which loneliness impacts opioid use. The current proposal addresses this need by assessing hypothesized cognitive, affective, and

behavioral mechanisms by which loneliness is associated with opioid use.

3. ADMINISTRATIVE ORGANIZATION

The study telehealth sessions will be conducted at the UR Medical Center in the Psychiatry Department. Participating sites include Medical University of South Carolina's School of Nursing and The Ohio State University's Department of Psychology.

4. STUDY DESIGN

The proposed study will be the first to assess these cognitive, affective, and behavioral pathways by which loneliness impacts opioid use. Individuals with an OUD reporting loneliness ($N = 125$) will be randomized to either a 6-session Cognitive-Behavioral Therapy for loneliness (CBT-L; $n = 63$) or a 6-session education control condition ($n = 62$), both delivered via telehealth. We will assess loneliness, negative affect (i.e., depression and anxiety), and the quality and quantity of social interactions at baseline, during the intervention sessions, post-treatment, and at 1-month and 2-month follow-ups.

5. SUBJECT POPULATION

We will nationally recruit 125 adults with OUD for this randomized clinical trial. We estimate that our screen failure rate will be approximately 10-30%. We estimate attrition from the consent and baseline assessment to the end of the 2-month follow-up to be approximately 20%.

Inclusion of Vulnerable Populations:
We will not purposefully recruit pregnant women, but neither will we exclude such participants from participating. The research activities are not expected to affect the pregnancy as it is a psychosocial intervention.

6. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: To be eligible, participants must be ages 18+, understand English, have internet access, screen positive for an active OUD on the OUD Module of the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV),[42] and screen positive for loneliness by scoring at least a T-score > 60 on the NIH Toolbox Loneliness Scale.[43]

Exclusion criteria: Consistent with previously used telehealth-delivered assessments, we will exclude any participant who does not understand consent. Potential participants who are in the process of detoxifying as measured by the Subjective Opiate Withdrawal Scale will also be excluded.

7. RECRUITMENT METHODS

Participants will be recruited using Internet social media websites (e.g., Facebook, craigslist) and select print/web portals. Advertisements will target adults 18+ across the United States. Social media advertising (e.g., through Facebook, Reddit, Instagram) will be used to inform potential participants of the study and direct them to a University of Rochester landing page (see **Advertising** appendix) contact the project coordinators by phone or email for additional information. Paid searches will be used to potential participants through online keyword searches (e.g., opioids, alone) with a secondary tactic of finding people who are looking for

paid research studies. Digital banner advertising will be used targeting individuals based on behaviors and search history. See **Phone screen script, information sheet, and verbal consent Appendix**.

8. CONSENT PROCESS

The consent document will be created using a REDCap-based electronic consent form. The IRB-approved consent form will be developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. We will contact UR IT support to create the REDCap eConsent. Potential subjects will participate in the consent process by eConsent obtained remotely with required remote consent process via Zoom (including toll-free phone option) or phone. **Verification with an Established Passcode:** In this approach, an agreed passcode is communicated via phone or email between the subject/subject's legally authorized representative and the study team. This passcode is saved as part of the subject's record for verification use later. The subject/subject's legally authorized representative at the time of accessing the survey/eConsent must then enter the passcode which is compared with the stored version entered by the study staff. eConsents accessed on personal electronic devices (e.g., computers, portable tablets, smart phones). During the remote consent process, research staff will thoroughly go over the consent form with the participant while clarifying any points as needed and answering all questions the subject may have. The informed consent form will contain a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. It will be explained to participants in easy-to-understand language. The limits of confidentiality will also be explained, including the potential to break confidentiality in the acute risk of suicidal behavior or violence, or disclosures of unreported physical or sexual abuse of a child. This will occur prior to any data collection and the consent form will include text regarding the retention and use of that data.

Research staff (Tamara Bilinski or Jonathan Umansky) will sign their name at the bottom of the form to show that they have explained the research, answered all questions to the subject's satisfaction, that the subject has demonstrated comprehension of the information, and the participant will sign the eConsent. Subject signatures will be obtained using a typed signature. Once the consent form is signed and submitted, subjects will be able to receive a print-out of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form. Study procedures will continue once research staff receive the signed consent.

Certificate of Confidentiality:
The Certificate of Confidentiality is automatically included as part of the notice of award.

With this Certificate, the investigators cannot be forced to disclose or use research information, documents, or samples that may identify the subject in any Federal, State, or local civil, criminal, administrative, legislative, other proceedings, or be used as evidence.

Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes, or to other government agencies related to communicable diseases.

The investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of child abuse and neglect, or serious harm to the subject or others.

9. STUDY PROCEDURES

Screening: The project coordinator will screen by phone following a script. Potential participants will provide verbal consent to complete the screening measures. Those individuals meeting eligibility who are interested in participating will be scheduled for a telehealth-based appointment to go over Consent, complete eConsent, and conduct a baseline assessment.
Assessments and Intervention: Participants will be enrolled following consent and will complete the baseline assessment. Following the baseline assessment, participants will be randomized to condition (control or experimental) by a computer-generated algorithm. Participants will schedule a convenient time for their telehealth-based intervention sessions. Mid-treatment, post-treatment, and 30- and 60-day post-treatment follow-up assessments will also be conducted by telehealth. Participants will be paid $40 each for the baseline and post-treatment assessment, $20 for the mid-treatment assessment and $30 each for the 30-day and 60-day follow-up assessments. Participants will also be paid $20 for completing the first 3 sessions within 4 weeks. The post-treatment assessment will also include an exit interview for participants to describe acceptability of the intervention. All assessments and interventions will be conducted via Zoom (including toll-free phone option) or phone. If requested, participants will be sent a letter indicating study activities completed.
Randomization: We will randomize at the participant level using block randomization in groups of 4. All demographic and outcome variables will be assessed for baseline equivalency. Any between-group baseline differences will be controlled for statistically in all subsequent analyses with baseline differences being defined here as any absolute standardized mean difference (Cohen's d) greater than or equal to .15.
Interventions

CBT for Loneliness (CBT-L): CBT is effective for treating a wide variety of disorders.[45-48] The mechanism behind CBT's efficacy comes from its ability to change an individual's beliefs/thoughts, which serves to change behavior (in the case of the current study, increasing meaningful social interactions and reducing opioid use).[46,49-53] CBT has been shown to be efficacious in both computer and telephone formats,[54-56] as well as when administered by individuals other than highly trained mental health professionals.[57-59] Additionally, CBT was chosen over other formats such (e.g., social skills training, enhanced social support) because CBT has shown the strongest effects in reducing loneliness.[60] CBT-L is a brief, patient-centered, tailored, one-on-one, 6-session intervention. Each weekly session is ~45 minutes via telehealth. We will use Cully and Teten's *Brief Cognitive Behavioral Therapy* manual[61] (see **CBT-L Appendix**) which was originally designed for specificity to a limited number of topics to reduce the number of CBT sessions to 6. This CBT protocol was developed to be adaptive in terms of treatment length and topic areas and is helpful for targeting symptoms or lifestyles that are not part of a formal diagnosis (e.g., loneliness). CBT-L seeks to improve emotional functioning and enact behavior change through addressing maladaptive thinking and behaviors in 6 sessions:

- Session 1: Case history (e.g., onset of feeling alone, when was it most prominent, what has worked well before; severity and impact of feeling lonely), review CBT model, identify maladaptive thoughts
- Session 2: Identifying and changing maladaptive thoughts
- Session 3: Identifying and changing maladaptive thoughts
- Session 4: Behavioral activation and exposure
- Session 5: Behavioral activation and exposure
- Session 6: Problem solving and relapse prevention

Participants will use a four-step process for identifying and addressing maladaptive thoughts by discussing: (1) their stated beliefs, (2) whether the belief is 100% true, (3) alternative beliefs, and (4) whether anything could change the accuracy of the belief (i.e., how realistic is this belief). For example, if a participant states "No one wants me at my mom's birthday party because my drug use has hurt them," they would be asked to estimate the accuracy of this belief (0-100%) and to dispute it. For example, the original belief may be altered to "They wouldn't have asked me if they didn't want me there," "I love my mom and she would appreciate it," or "It's uncomfortable being at these events because of my drug use, but it's important to be with connected for my recovery." Similarly, the therapist will focus on correcting myths affecting interpersonal engagement to help the participants understand that many negative beliefs about being lonely and feeling like a burden are inaccurate.[62] Behavioral activation is used to increase the participant's activity level to improve mood. Loneliness contributes to avoidance thereby limiting use of adaptive coping strategies and reinforcing loneliness and negative affect. By increasing one's activity level, particularly pleasant non-drug use social activities, the participant's mood may improve by decreasing avoidance, increasing the potential for social contact, and increasing self-efficacy to engage in such activities. In the final session, the therapist will help the participant identify ways to cope with loneliness-related problems by identifying strategies, evaluating the potential solutions, and selecting a plan to implement the strategies. This discussion will occur in the context of preventing a return to behavioral inactivation and allowing maladaptive thinking to drive poor coping, further maladaptive thinking, and lack of activity.

All participants randomized to CBT-L will be administered the same structured intervention; however, content discussed within the session is tailored based on their within-session responses and beliefs. While different participants may frequently endorse similar beliefs, their ideas about that specific belief may differ. Therefore, the intervention is structured, but not scripted. The same therapist will deliver all 6 sessions.

Physical Health Education Training (PHET; control condition): PHET provides information on the importance and benefits of and guidelines for living a healthy lifestyle. PHET is manualized and contains educational materials on topics such as diet, water consumption, exercise, and sleep. The topics will be delivered across six sessions, which will last ~45 minutes. The same therapist will deliver all 6 sessions. The control condition will help account for nonspecific conditions, such as providing attention or contact by the study interventionist, providing support or building rapport, and managing participants' expectations of treatment outcomes. Importantly, PHET is inert with respect to the outcomes of interest.[63-65] We selected an active intervention to help maintain engagement. Importantly, both conditions are just 6 weeks, increasing the likelihood of sustaining engagement relative to CBT interventions that are 8-12 weeks. This active intervention also helps decrease the likelihood of participants feeling marginalized, while also providing relevant educational content to facilitate issue-oriented

focus.[66] Supporting the ability of PHET to engage participants, our prior work with PHET indicates that, on average, participants found PHET to be mostly to extremely "easy to understand," found themselves to be "engaged," and "would recommend it to a friend.[67]"

Training and Supervision

Training for Research Staff: Drs. Ashrafioun and Stecker will train the project coordinator to administer verbal consent and administer and score the assessment measures through instruction and extensive observed role play. Dr. Ashrafioun will model the administration of the consent and assessments while the coordinator observes, then they will observe the coordinator administer the consent script and baseline assessment instruments, providing feedback as needed. If more training is required, we will continue to model the interview and/or observe the interview until the coordinator reaches a satisfactory level of skill and comfort. The training will seek to promote reliable, fluid administration of the forms; maintaining a non-threatening, natural manner; accurately recording all responses; and careful checking to ensure that missing data is minimized. The same process will be used for each follow-up assessment session. The coordinator will be blinded to the participants' treatment conditions for the assessments.

Training for Interventionists and adherence rating: Interventionists with at least a master's degree in a counseling/health-related field and prior CBT training will deliver CBT-L and the education control. Drs. Ashrafioun and Stecker will train the interventionists using the manual. Initial training will consist of lecture and role play "rehearsal" techniques. Ongoing supervision will also be provided throughout the study. No identifying information will be used, noted, or discussed during supervision.

Because each CBT-L session has unique content, we developed session adherence measures that itemize the session-specific content (See **Adherence Checklist Appendix**). Each session will emphasize the completion of worksheets for identifying/changing maladaptive thoughts. Adherence scores will be given for each session and the entire intervention by transforming the total number of points into a percentage of content delivered. Study therapists will track adherence as they complete sessions.

Supervision for Research Team and Interventionists: Weekly meetings will be conducted to focus on monitoring: a) recruitment, b) conducting interviews, c) coding interview data, d) communication between research staff, e) retention; f) completeness of documentation, and g) storing and safeguarding data. To maintain blinding, separate meetings among interventionists and coordinator will occur as needed.

Measures

When feasible, well-validated measures available as common data elements will be used. All data collection will be completed by telehealth.

Loneliness: The 20-item Revised UCLA Loneliness Scale will be our primary outcome measure.[68] We will use the 5-item NIH Toolbox Loneliness Scale[43] as our loneliness screening measure. The NIH Toolbox Loneliness Scale is correlated highly (r = .80) with the Revised UCLA Loneliness Scale.[43,69] T-scores >60 indicate loneliness scores 1 standard deviation above the mean and will be used to assess eligibility.[70]

Opioid-related outcomes. *Opioid Use Disorder:* The OUD module in the SCID-5-RV will be used to identify an OUD at screening and will be re-assessed at the final follow-up.[42] *Opioid use:* We will use the Timeline Follow Back (TLFB)[71] from the 60 days prior to baseline through to the end of participation in the study (i.e., 60-day follow-up) to assess days used opioids and percent days abstinent. The TLFB will be completed at each assessment time point so there are shorter intervals facilitating participant recall of their substance use. The TLFB has long-

standing strong psychometric properties and is highly correlated with urine drug screen results,[71-74] which would be difficult to obtain because there is no in-person contact in the current study. Another advantage of TLFB is that participants may be more honest about their opioid use because there will be no in-person meetings thus increasing relative anonymity and decreasing social desirability/ under-reporting. *Craving: The Penn Craving Scale* (PCS) is a 5-item measure assessing aspects of past-week craving for opioids. Research supports the psychometric properties of the opioid version of the scale.[75] *Consequences of substance use*: The Inventory of Drug Use Consequences (InDUC-2) will be used to assess drug use consequences in the following domains:

impulse control, social responsibility, physical, intrapersonal and interpersonal.[76] Consequences will be assessed for the last 3 months at baseline and the follow-up will be since the previous assessment.

Table 1. Schedule and content of assessments

Primary outcome	
Loneliness-NIH Toolbox Loneliness Scale	S,B,F
Loneliness-UCLA Loneliness Scale	B,I,F
Secondary outcome	
Opioid use-TLFB	B,I,F
Mechanistic primary outcomes	
Quality/quantity of social interactions-DSSI	B,I,F
Negative affect-depression, anxiety PROMIS	B,I,F
Tertiary/exploratory outcomes/mechanisms	
Burdensomeness/belongingness-INQ-12	B,F
Craving - PCS	B,F
OUD-SCID-5-RV opioid module	S,F
Overdose risk behaviors-ORBQ	B,F
Drug use consequences-InDUC-2R	B,F
Key descriptive variables	
Possible SUD, substance use-ASSIST, TLFB*	B,I,F
Physical functioning, sleep, pain-PROMIS Profile-29	B,F
Treatment utilization	B,F
Demographics	B

S-*Screening*; B-*Baseline*, I- *Intervention*; F-*Follow-ups/Post; *only TLFB for mid-intervention assessment*

<u>*Social factors*</u>. *Quality/Quantity of Social Interactions:* The Duke Social Support Index-assesses several domains of perceived social support, including social network size, social interaction, social satisfaction, and instrumental social support. Research supports the psychometric properties of the DSSI scales.[77,78] Although all variables will be considered, analysis are focused on the role of the social interaction and social satisfactory scales as measures of quantity and quality of social interactions, respectively.[79] *Belongingness*: The Interpersonal Needs Questionnaire (INQ-12) assesses thwarted belongingness (i.e., an unmet need to belong) and perceived burdensomeness (i.e., feeling a burden to social support network). This measure will assist in identifying potential cognitive-related mediating pathway between loneliness and opioid use. Research supports the scale's psychometric properties.[80-82] We will also explore the quality and quantity of interactions via social media with friends, family, and strangers as there is a mixed results in this area.[83]

<u>*Negative Affect*</u>. The depression and anxiety subscales from the PROMIS Profile-29 will be used to assess depression and anxiety. Research supports the psychometric properties of these scales.[84]

<u>*Substance Use Disorder Screener*</u>. Lifetime and past three-month possible substance use disorder will be assessed using the NIDA-modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).[85] The ASSIST is an 8-item screening measure originally developed by the World Health Organization to assess substance use and problems.[86] The ASSIST asks about both "street" opioids and prescription opioids. Scores ranging from 0-3 suggest lower risk, 4-26 suggest moderate risk, and 27+ suggest high risk. The ASSIST has

strong support for its reliability and validity.[87] We will capture other substance use during the study period using the TLFB.

Physical health and overall functioning. The PROMIS Profile-29 will be used to assess the following domains: physical function, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference, in addition to anxiety and depression domains noted above. There is strong support for the measure's psychometric properties.[84]

Overdose Risk Behavior. The Overdose Risk Behavior Questionnaire (ORBQ) assesses the frequency of past-month engagement in behaviors that are associated with overdose. Higher scores on the ORBQ are associated with number of prior overdoses.[88]

Treatment utilization. We will assess participant past and current utilization of pharmacological (e.g., buprenorphine, anti-depressants), psychological, and other supportive interventions (e.g., Narcotics anonymous, CBT) related to substance use and mental health at baseline and follow-up.

COVID questions. This questionnaire was developed to assess if a participant had been diagnosed with the COVID-19, how the disease affected them, if they knew anyone who was diagnoses with COVID-19, and the extent to which the pandemic has affected them across a variety of domains in the last year.

Demographics. At screening, we will assess participants' gender, age, educational background, employment, income, race, ethnicity, marital status, and cohabitation status.

Exit Interview. The exit interview will assess overall impressions and impact of treatment, relationship with the therapist, and ways to improve the treatment (See Appendix). The exit interview will inform future feasibility and acceptability and to further refine the intervention protocol as needed. A modified version of the Abbreviated Acceptability Rating Profile will be used to further assess treatment acceptability.[89]

Perceives Invalidation of Emotion. The Perceived Invalidation of Emotion Scale (PIES) is a 10-item measure assessing the extent to which the respondent perceives that an individual implies that their emotions are incorrect or inappropriate. Research supports the psychometric properties of the measure and construct.[90] The PIES will be administered at the baseline and post-treatment assessments.

Attachment The Revised Adult Attachment Scale-Close Relationship version (AAS) assesses 3 dimensions of adult attachment (close, dependent, anxiety) over 18 items on a 5-point Likert scale (1 – Not at all characteristics of me to 5 – Very characteristic of me). The scale is widely used with strong psychometric properties.91 The AAS will be delivered at baseline and post-treatment assessments.[91]

Scope of Work for non-University of Rochester investigators

Tracy Stecker, PhD (co-Investigator), is the Co-Research Director at the VA Center of Excellence for Suicide Prevention and Assistant Professor in the College of Nursing at the Medical University of South Carolina. Dr. Stecker is an experienced researcher in implementing studies on brief cognitive-behavioral interventions to address mental health issues and treatment engagement. Dr. Stecker will provide guidance on the implementation of the intervention, staff training and supervision, and recruitment and retention. Supervision, guidance on intervention implementation, and recruitment and retention activities will occur over the course of the study. Staff training will occur in the beginning of the study and will occur as needed when/if new research staff members are added. She will also assist in manuscript writing, and implementation and dissemination planning from the findings from this study. Dr. Stecker will be involved in

weekly supervision and team meeting calls with PI and other research team members. The PI will oversee all activities completed by Dr. Stecker.

Nicholas Allan, PhD (co-Investigator), is an Assistant Professor of Clinical Psychology at The Ohio State University. Dr. Allan will provide statistical support, data coding, and supervise the data management. Dr. Allan has served as a biostatistician on numerous NIH- and DoD-funded projects. He will initially be responsible for the creation and management of the randomization procedures and interim analyses to ensure the group distributions are correct. He will conduct longitudinal analyses to assess the effect of the intervention and assess meditational processes and provide interim analyses for the DSMO and continuing reviews as needed. Dr. Allan will be involved in weekly team meeting calls with the PI and other research team members. The PI will oversee all activities completed by Dr. Allan.

Ashleigh Baker (Other Study Personnel) is a Bachelor's of Nursing student from the Medical University of South Carolina who also has a master's degree. She is currently serving as an unpaid intern at the University of Rochester through March 2023. Ashleigh will work under the supervision of the PI and coordinators and will assist with screening, data collection, data entry, and delivery of educational content.

Emma Lape (Other Study Personnel) is a clinical psychology student from Syracuse University with a master's degree. Emma will work under the supervision of the PI and the coordinators and will assist with delivery of the study conditions.

10. AUDIO RECORDINGS

There will not be any audio recording.

11. RISKS TO SUBJECTS

Psychological distress. The potential risks are negligible. There are no known risks associated with the procedures. Participants will be informed that they may feel slightly uncomfortable discussing some of their symptoms. Mild discomfort may be likely during the intervention session; however, this is unlikely to have a serious negative impact on the participant's well-being. Participants will be told they can withdraw from the study at any time. Participation or withdrawal from the study will not affect any benefits to which they are otherwise entitled. Special precaution will be taken to safeguard confidentiality. During assessments, if the study staff member is concerned about thoughts and planning of a suicide attempt, the study staff member will ask two follow-up questions: Do you have a desire to kill yourself that you think you might act on and Do you have a plan for killing yourself and intend to carry the plan out? With this information and available suicide assessment measures, the interviewer will evaluate the severity of the participant's suicide risk. If the participant is deemed to be at imminent risk, a safety plan will be initiated. All study staff will receive adequate training in suicidal ideation and risk assessment, and all work will be supervised by Dr. Ashrafioun, who is a licensed clinical psychologist who is also employed at the VA Center of Excellence for Suicide Prevention, a national research, data, and education dissemination center for suicide prevention.

If the interviewer is concerned about imminent risk, we will use a procedure used in ongoing research studies: warm transfers to the National Suicide Prevention Hotline. Emergency procedures will be initiated if participants are determined to be at imminent risk for suicide using the risk assessment described above. Participants determined to be at risk will be asked if they are willing to be transferred to the National Suicide Prevention Hotline. Hotline responders are

well trained in emergency procedures and have working protocols for locating callers and initiating rescues. Calls can be transferred with a four-step process.

It is possible that participants may refuse to be transferred to the Crisis Line or hang up. As a result, participants will be asked to use a landline so that the number can be tracked to an address if emergency services are needed. For participants who only have a cell phone, interviewers will begin each session by asking the participant for the address from which they are calling so that the clinician can send help if it is needed. Because participants may give a false address, clinicians will consult with Crisis Line responders who have a protocol for emergency responses for cell phone callers.

Warm Transfer Process

1. Press the **conference** button.
2. Dial 1-800-273-8255 and a hotline responder will answer.
3. Describe the participants risk and provide name and telephone number.
4. Pressing the **conference** button and participants will be linked with hotline counselors.

Adverse Events (AE). AEs may include, but are not limited to: worsened physical or mental health, or inadvertent disclosure of confidential research information. Serious Adverse Events (SAE) may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. Per IRB regulations, SAEs, any event resulting in a deviation from the study protocol (e.g., emergency hospitalization to address suicidal behaviors) or death will be reported to the PI within 24 hours and to the IRB in 48 hours. This will be completed in order to assess significance and determine an appropriate response. AEs that involve temporary distress will be noted by interviewers and provided to the IRB in an annual report.

Confidentiality of Records. Numerous protections are in place to reduce the likelihood of loss of confidentiality. All research data will be kept in locked filing cabinets in secure areas, absent of identifying information, and coded by research number only. Files containing consent forms and other items with identifying information will also be kept in locked filing cabinets, but these will be separate from cabinets containing data from this study. All electronic data will be stored on a secure, password-protected server.

Should the individual elect not to participate in the study, they will be provided with a website containing available substance use and mental health treatment centers available across the country.

12. POTENTIAL BENEFITS TO SUBJECTS

There may be direct and/or indirect benefits of study participation. Participants are receiving a brief intervention that addresses a transdiagnostic factor that may reduce opioid use. This intervention can be used for both participants who are not engaged in treatment and for participants who are engaged in treatment, it may augment current services. Dissemination of the findings from the study will contribute to the extant literature, provide data to guide a larger trial, and may contribute to reducing loneliness and opioid use, and understanding how reductions in loneliness impact opioid use.

13. COSTS FOR PARTICIPATION

None

14. PAYMENT FOR PARTICIPATION

Participants will receive compensation for their participation in the study. The compensation amount will be based on the schedule that follows:

Baseline Assessment	$40
Completing first 3 sessions within 4 weeks	$20
Mid-intervention assessment	$20
Post-treatment Assessment (w/in a week)	$40
30-day Assessment	$30
60-day Assessment	$30

Therefore, the total compensation for completing all the study components would be $180. Payments will be made following each study procedure listed above. Participants who do not complete the entire study for any reason, will receive compensation for the components that were completed per the above schedule of payments.

15. SUBJECT WITHDRAWALS

- The only anticipated circumstances under which subjects will be withdrawn by the investigator from the research without their consent would be if they were lost to contact and if new information about them suggested that they did not meet eligibility criteria.
- Subjects may withdraw from the research themselves at any time and/or completes some but not all study procedures. We will utilize all data collected.
- If we have not met our target 'n' for study completers, to the extent that funding and staff time allow, we will replace subjects withdrawn from the study.

16. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

With respect to confidential data collection, all project data will be collected by trained research interviewers using IRB approved data collection instruments. In addition, research interviewers and interventionists will receive on-going supervision through the course of the project. All data will be stored in locked file cabinets and password protected databases and will be accessible only by appropriate research personnel. All subject data will be identified by a unique number. Subject identifiers (e.g., name, address, telephone number) will be stored separately from research data and linkable through a unique identification number. All study personnel will receive mandatory education in human subjects' protection. All data will be used for research purposes only, and will not be revealed without the participants' written consent unless to protect individual's immediate safety. All paper data will be kept in locked files in a locked study office. Computerized data will be stored in databases on a secure, password protected server that is regularly backed up. As an added protection, NIH funded studies are covered by a Federal Certificate of Confidentiality.

All research and clinical information obtained is kept confidential unless the subject is an immediate danger to him/herself or to others. Subject well-being will be monitored throughout the study. If the clinical information obtained in the course of research assessments pertains to patient safety (e.g., intent to harm one's self or others) then, to promote safety, confidentiality will not be maintained, and appropriate treating professionals will be informed. During crisis situations, this clinical information may be provided to other clinicians (or family members) in order to facilitate appropriate treatment and minimize the risks of self-harm or harm to others. This information may include the subject's medical history, financial and social resources, and history of suicidal behavior, if known. Confidentiality is the ethical and/or legal right that information, such as research data, will be held

secret and safeguarded from disclosure unless consent is provided permitting disclosure.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

We will share data with other researchers and use widely used measures that will facilitate harmonization with other research. However, the data sharing agreement involves sharing only de-identified data with other investigators and the use of data-sharing agreements that provide for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed. A Data Use Agreement (DUA) will be made with The Ohio State University. The DUA will be for sending the de-identified dataset electronically. Dr. Stecker will not have access to any data.

16. DATA AND SAFETY MONITORING PLAN

Data Safety. To ensure safety of participants in the study proposed and validity and integrity of data collected, the PI (Ashrafioun) will oversee all data and safety monitoring functions and the research team will be advised that he will be the primary contact overseeing these activities. The PI and the research team will meet regularly to monitor study progress and discuss the implementation of monitoring procedures. He will also meet regularly with the research coordinator and to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants. The PI will have an independent Data Safety Monitoring Officer (DSMO) to help monitor safety issues. The DSMO will be at least an Assistant Professor at University of Rochester who is independent of this study and has substantial randomized clinical trial experience for individuals with substance use disorder or mental health condition. As indicated below, the PI will track all negative outcomes and incidents as well as conduct interim data analysis every 12 months after the study has started. The study design will be significantly modified (and even screening stopped) on the suggestion of the DSMO that the study is creating potential harm to our participants.

The PI will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, management, and analysis, as well as regularly assess the risk/benefit ratio associated with participation in the study. All research staff will participate in an intensive training to help them understand the importance of reducing the risk for participants and learning how to recognize and report any AE or SAE. SAEs may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. AEs may include, but are not limited to: physical injuries, worsened physical or mental health, or inadvertent disclosure of confidential research information.

If an SAE occurs, the PI will immediately contact the DSMO and IRB, followed by a written report in 24 hours. He will make a decision whether there is sufficient evidence to suspend data collection, allow for further IRB review, modify the protocol, or make other changes to reduce potential risk to participants. The study will resume based on agreement of the PI, an IRB member, and the DSMO. In the event that an AE that is not an SAE is reported to the PI, the PI will discuss the event with the DSMO. Immediate evaluation will occur to determine if any extra steps can be taken to minimize the likelihood of that type of AE occurring again. If changes can be made, a report/amendment will be written and submitted to the DSMO and IRB.

As part of a standard practice, the PI will supervise the implementation of one audit within 4 months after study recruitment with subsequent audits each year of the materials collected and produced as part of the study to ensure proper confidentiality and compliance with ethical principles, including informed consents, electronic medical record documentation, questionnaire data, and to make sure that the research staff are following established protocols. The PI will provide an annual summary report of all AEs to the IRB and the DSMO as part of the annual review. If no adverse events have occurred, the report will state, "No adverse events affecting human participants have occurred during this project year."

Data Monitoring. To ensure adequate participant recruitment and enrollment, each week, the PI will discuss the current number of participants contacted, screened, and enrolled from each site and compare those numbers to the expected based on our preliminary data. If after the first 4 months, it appears we are not reaching our expected number of participants, the PI will discuss potential barriers/obstacles and solutions with the DSMO. Discussions regarding recruitment and enrollment will continue at each meeting with the DSMO to ensure proper implementation of the study.

Data Safety Monitoring Officer. The purpose of the DSMO is to review protocols and consent documents for this study, monitor safety issues throughout the study, provide an overview of the quality of the accumulating data, and provide guidance on interim analyses and stopping rules. The DSMO will have no direct involvement in the study or conflict of interest with the research team conducting the clinical trial. The DSMO will have expertise in: research and monitoring at-risk research participants; research in longitudinal clinical trials with using cognitive-behavioral intervention; and research expertise with individuals using substances. The DSMO responsibilities will include:

(1) Review, provide approval/disapproval, and provide suggestions to protocols and consent documents.
(2) Monitor, provide suggestions, and report on ethical issues regarding protection of human subjects, and advise on ethical issues regarding AEs. The DSMO will coordinate with the PI to report to the IRB any unanticipated problems involving risk. The DSMO will provide potential solutions or other appropriate actions (e.g., altering inclusion/exclusion criteria, changing consent documents).
(3) Ensure appropriate balance between clinical care, safety, and patient confidentiality.
(4) Monitor data regarding effectiveness. The DSMO will review outcome data for outcomes by treatment condition. If differences in results between conditions appear to be clinically significant, the DSMO will review whether the clinical trial should continue with or without further enrollment of new participants.
(5) Monitor and review any data relevant to quality control.

The PI will convene semi-annually with the DSMO for the duration of the study. The meetings will be held in-person or via video teleconference. The DSMO and PI will decide on the format of the meetings. Additional meetings will be held on the recommendation of the DSMO and meeting logistics will be based on clinical urgency and the availability of the DSMO. The PI will submit reports to the DSMO a week prior to the scheduled meeting. Reports will

include all data up to and including 2 weeks prior to the reporting deadline (except for SAEs, which are to be reported within 24 hours of an event). For each meeting at which the study is to be considered or monitored, the PI will present an overall progress statement containing the assurance that the PI has considered the clinical trial's progress and that there is/is not evidence of safety issues that should be addressed by the DSMO. The reports will also include information related to problems in recruitment, biases in attrition, biases with respect to AEs, or other operational problems that affect the integrity of the study. At the additional request of the DSMO, interim analyses will be conducted to determine whether the emerging findings may lead to a discussion of discontinuing the trial early.

The DSMO will be kept apprised of all SAEs and AEs on an ongoing basis and will decide whether individual patients should be removed from the protocol. Although research staff, under the PI's supervision, are able to take whatever immediate action is necessary to safeguard the welfare of individual patients, the DSMO will be called on whenever possible to make decisions as a result of a SAE. There may be rare instances where some unanticipated situations occur that may affect participant welfare. In these situations, the IRB or the DSMO may be contacted to help resolve the situation.

17. DATA ANALYSIS PLAN

Aim 1: To assess the efficacy of CBT-L's impact on loneliness, negative affect and the quality and quantity of social interactions among individuals with OUDs. Outcomes variables will include loneliness, negative affect, and the quality and quantity of social interactions. We will conduct mixed regression modeling with condition, time, time by condition interactions, and relevant covariates included as predictors.

Aim 2: To assess the cognitive, affective, and behavioral mechanisms of the effect of CBT-L on opioid use trajectories. Outcome variables for this aim will include opioid use and craving. Exploratory mediation analysis will be conducted to examine whether CBT-L reduces opioid use trajectories and whether these reductions occur due to reductions in loneliness and/or negative affect and social interaction quality/quantity.

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