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Randomized controlled trials for alcohol use disorder during the COVID-19 pandemic

A B S T R A C T

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) altered the logistics of ongoing randomized controlled trials (RCTs). The need to reduce in-person research and clinical activities, however, presented an additional level of complexity in order to continue conducting RCTs that focused on the development of medications for Alcohol Use Disorder (AUD). The visits required a systematic objective evaluation from the physician and mental health professional and clinical staff, as many of the safety and efficacy assessments are self-reported. The following commentary addresses the successes and limitations our RCTs encountered during the coronavirus (COVID-19) pandemic.

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Introduction

Global spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a worldwide coronavirus pandemic (COVID-19) and has altered nearly every aspect of our contemporary lifestyle, including the logistics of clinical research. As the virus spread and confirmed cases rose, academic institutions, public health facilities, and government facilities deemed it unsafe for both patients and clinical staff to continue in-person research activities. In the past, clinical research has been affected by natural catastrophes (hurricanes, earthquakes, and flooding) (Daugherty & White, 2010; Lunt & Heenan, 2019; National Academies of Sciences, Engineering, and Medicine, 2017). However, there is limited research within the scientific literature for discussing the best practices on how to quickly transition randomized controlled trials (RCTs) to remote settings to limit physical interaction. For safety reasons, many RCTs could not immediately halt their studies (McDermott & Newman, 2020), therefore, investigators developed creative methods to transition from in-person visits to remote visits that allow for “infection control” while preserving integrity of data collection. Limitations pertaining to physical interaction, however, are of major concern in RCTs designed to develop medications to treat alcohol use disorder (AUD), as many safety and efficacy assessments are self-reported and require the systematic objective evaluation from the physician, mental health professional staff, and clinical staff (e.g., Structured clinical interview for DSM, SCID) (First, 2014).

Prior to the COVID-19 pandemic, we were actively recruiting subjects and had enrolled patients in two pharmacological RCTs that evaluate the stress-induced alcohol relapse in patients with AUD (NCT02243709; NCT04135846). On March 20, 2020, our laboratory, among others at Brown University, was required to pause all

in-person research activities. We immediately developed new remote procedures, ratified by the study physician and approved by the Institutional Review Board (IRB) in order to continue conducting our research safely. The following viewpoint addresses the successes and limitations our laboratory encountered over the past few months of remote data collection within pharmacological RCTs for AUD. We specifically evaluate the following RCT components: 1) recruitment and retention, 2) safe administration of the study medications and behavioral assessments, and 3) the efficacy of the study medication on alcohol-related behaviors: consumption, craving, and withdrawal.

Recruitment and retention

Research with human subjects relies heavily on patient retention and new enrollment, which became a major concern when developing plans to transition our RCTs to remote visits. Unfortunately, we could not enroll and obtain consent from new patients during the mandatory lockdown, as all of our RCTs require a complete physical exam, electrocardiogram, and blood draw. While many other RCTs were actively enrolling new patients, the majority of these trials were focused on investigating therapeutic agents to combat the virus (North, Dougan, & Sacks, 2020).

It should be noted that the patients discussed below were previously enrolled and provided informed consent prior to transitioning to remote procedures. We did not experience any difficulties with retaining previously enrolled patients in the remote visits. Complete patient retention may be due, in part, to the mandatory lockdown in the state of Rhode Island, as we have recently discovered (within an ongoing secondary remote study) that as quarantine restrictions were lifted, retaining patients became more difficult. In addition, we speculate that retention may have been

due to pre-quarantine in-person engagements between patients and research staff.

Safe administration of study medication and behavioral assessments

For drugs that require dose titration, frequent in-person visits are scheduled to monitor potential adverse events (AEs) and ensure the safety and tolerability of the increased dose. When quarantine was enacted, we had seven patients, in various stages of medications administration, enrolled in two RCTs (an 11-week-long trial and a 12-week-long trial). During the pandemic, we assessed potential AEs and determined the medication dose during the remote visit (conducted via a telephone/video call). The decision to titrate up, taper down, or keep patients at the current dose was determined by evaluating AEs through a systemic organ-based questionnaire and by monitoring hemodynamic parameters through a portable at-home blood pressure machine provided to each patient. Study medication or matching placebo was then prescribed by the study physician and shipped from the compounding pharmacy directly to patients' homes. No additional expenses accrued when medication was shipped directly to patients' homes. To help patients recall the specific dose needed for each day, we utilized weekly pill counters. In addition, the compounding pharmacy provided colored pills for the different doses (rather than a non-descriptive white pill). We did not experience any complications when the pharmacy dispensed medication to patients, or with patients taking the incorrect dose of the study medications. Furthermore, through prescription of a "personalized dose," we provided patients the exact number of pills that were needed, limiting accidental ingestion of the incorrect dose and waste of study resources.

Remote data collection is not a new procedure within the field of behavioral and social science. Administration of a typical remote assessment involves sending an online survey link via email (Garcia-Romeu et al., 2019; Grant, Lust, & Chamberlain, 2019) to each patient to fill in of their own accord, a method frequently utilized during the COVID-19 pandemic (Ahmed et al., 2020). While the typical survey option may be the more efficient method of data collection within the field of behavioral and social sciences, implementation of online surveys within RCTs has several limitations. First, online surveys tend to elicit a response bias that favors the younger population (Oppenheimer, Pannucci, Kasten, & Haase, 2011). Most of our AUD patients were more than 40 years old, which is consistent with the average age among treatment-seeking individuals enrolled in other AUD studies (Haass-Koffler et al., 2020). In addition to recruiting older individuals, we found that several of our patients did not have reliable access to a computer or the ability to utilize the internet. This dilemma was further complicated by the mandatory shutdown of libraries and other community facilities amidst the pandemic.

Furthermore, administration of a web-based survey would limit the breadth of data collected. As part of our clinical protocol to assess medication safety, we administered assessments to monitor for anxiety and depression, including suicide risk. We could not use web-based surveys during remote visits, as data was reviewed by the research staff retrospectively when it was too late for clinical intervention. We developed a remote protocol to administer assessments in real-time where, in the event that an individual expressed signs of distress or suicidality risk, we would alert the clinical staff. Development of a "remote safety plan" was critical for IRB approval and enabled monitoring for anxiety, depression, suicide risk, or potential AEs in the absence of having the patient on site. This "remote safety plan" was important for the safety of our patients, maintenance of the integrity of the research, and compliance with FDA regulations.

Efficacy of alcohol-related behavior: consumption, craving, and withdrawal

We faced several challenges in systematically assessing alcohol-related outcomes within our population during the remote visits. We relied on patients to verbally self-report whether they were consuming alcohol or any substances, as we could not obtain a Breath Alcohol Content (BrAC) recording or urine toxicology screen.

Craving was also only assessed retrospectively by administering questionnaires during the telephone/video call, and we were unable to test the effect of the study medication on acute alcohol craving. While we could not test the effect of acutely induced stress in our laboratory, the emergence of the COVID-19 pandemic provided an environment in which to evaluate and monitor these novel pharmacotherapies under natural stressful conditions (Bavel et al., 2020). A recent report from the Centers for Disease Control and Prevention (CDC) found an increase in substance use due to the pandemic (Czeisler et al., 2020). Indeed, a recent population survey found that alcohol consumption increased by 14% (Pollard, Tucker, & Green, 2020). Therefore, we expected that many of our AUD study patients would experience a significant increase in stress-induced risky behaviors and alcohol consumption as consequences of the pandemic, as stress and social isolation can be exacerbated in individuals with addictive disorders (Hosseini, Yassini Ardekani, Bakhshani, & Bakhshani, 2014).

Finally, to assess the effect of the study medications on withdrawal symptoms, we utilized the Clinical Institute Withdrawal Assessment for Alcohol—Revised (CIWA-Ar), a 10-item scale that asks about symptoms commonly displayed by those experiencing alcohol withdrawal (i.e., profound perspiration, tremors, auditory or visual disturbances, etc.) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989). During a remote visit, we were unable to visibly note these changes and relied heavily on patients to accurately report their physical behavior. The research staff were able to visually assess physical behavior through the use of a video call with two of the patients. However, many of our patients were not equipped with this technology and conducted visits strictly via a telephone call.

Conclusions

While we were able to transition many of the in-person procedures to remote visits, it is important to note data that were not captured in the revised COVID-19 protocol. Specifically, we were unable to ensure that patients were sober as we are missing objective alcohol and drug use assessments (i.e., a BrAC recording and a urine toxicology screen) and the physical presentation of alcohol withdrawal symptoms. We are missing acute alcohol craving and consumption, as we could not conduct the laboratory cue reactivity and alcohol administration procedures remotely. Additionally, we could not collect blood and saliva to determine clinical biomarkers of drug response.

Despite these limitations, the majority of the procedures could be achieved remotely and we felt that continuing data collection has preserved the primary (safety and tolerability of the study medication) and secondary (efficacy of the study medication) aims of the RCTs. At conclusion of the trials, as per the original protocol, we will use the intention-to-treat analysis to evaluate the effect of the study medications. This clinical analytical approach has been adopted in many medical RCTs because it can be utilized as an effective way to extract equitable conclusions regardless of patient adherence or additional confounding variables (McCoy, 2017).

Moving forward, we plan to remain proactive and continue utilizing these methods in the event that data collection must be transitioned remotely in order to ensure the safety of patients and limit

missing data. The novel virus required investigators to employ creative methods for continuing RCTs in a remote setting. While the pandemic has drastically altered our research methodologies, the long-term impact of the virus is by no means concluded. Given that individuals with AUD have the greatest risk of acute alcohol-related consequences, it is critical that we continue to test and develop medications that can truly reduce stress-induced alcohol craving, consumption, and withdrawal. Furthermore, the cytotoxic effect of alcohol has been shown to reduce lung function and immune response, highlighting the possibility of AUD as a comorbidity that can adversely affect the COVID-19 severity (Bailey, Samuelson, & Wyatt, 2020). Our laboratory has recently received Brown University approval to return to in-person visits; we are actively recruiting patients with IRB-approved protocols in place that can transition from in-person visits to remote visits and vice versa. We hope that this experience has provided us with the necessary tools to continue research in unprecedented times. Remote data collection provides immense flexibility and opportunity for research with human subjects that must continue to proceed in an unconventional fashion.

Author contributions

CLH-K is the Principal Investigator of the two RCTs (NCT02243709; NCT04135846), designed the clinical protocol and the laboratory procedures, and provided funding used to conduct both studies. ZEB and CLF conducted the studies, including collection of the in-person and remote research data. RMS is the study physician. ZEB, CLF, and TV-K prepared the protocols for IRB approval. ZEB wrote the first draft of the manuscript. ZEB, SMP, CLF, TV-K, RSM, and CLH-K contributed to the writing of the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors have declared that no conflict of interest exists. There are no relationships between financial supporters or other organizations and these authors that could have influenced the study and results.

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References

- Ahmed, M. Z., Ahmed, O., Aibao, Z., Hanbin, S., Siyu, L., & Ahmad, A. (2020). Epidemic of COVID-19 in China and associated psychological problems. *Asian Journal of Psychiatry*, 51, 102092. <https://doi.org/10.1016/j.ajp.2020.102092>
- Bailey, K. L., Samuelson, D. R., & Wyatt, T. A. (2020). Alcohol use disorder: A pre-existing condition for COVID-19? *Alcohol*, 90, 11–17. <https://doi.org/10.1016/j.alcohol.2020.10.003>
- Bavel, J. J. V., Baicker, K., Boggio, P. S., Capraro, V., Cichocka, A., Cikara, M., et al. (2020). Using social and behavioural science to support COVID-19 pandemic response. *Nature Human Behaviour*, 4(5), 460–471. <https://doi.org/10.1038/s41562-020-0884-z>
- Czeisler, M.É., Lane, R. I., Petrosky, E., Wiley, J. F., Christensen, A., Njai, R., et al. (2020). Mental health, substance use, and suicidal ideation during the COVID-19 pandemic – United States, June 24–30, 2020. *Morbidity and Mortality Weekly Report*, 69(32), 1049–1057. <https://doi.org/10.15585/mmwr.mm6932a1>

- Daugherty, E. L., & White, D. B. (2010). Conducting clinical research during disasters. *The Virtual Mentor*, 12(9), 701–705. <https://doi.org/10.1001/virtualmentor.2010.12.9.ccas1-1009>
- First, M. B. (2014). Structured clinical interview for the DSM (SCID). *The Encyclopedia of Clinical Psychology*, 1–6.
- García-Romeu, A., Davis, A. K., Erowid, F., Erowid, E., Griffiths, R. R., & Johnson, M. W. (2019). Cessation and reduction in alcohol consumption and misuse after psychedelics use. *Journal of Psychopharmacology*, 33(9), 1088–1101. <https://doi.org/10.1177/0269881119845793>
- Grant, J. E., Lust, K., & Chamberlain, S. R. (2019). Problematic smartphone use associated with greater alcohol consumption, mental health issues, poorer academic performance, and impulsivity. *Journal of Behavioral Addictions*, 8(2), 335–342. <https://doi.org/10.1556/2006.8.2019.32>
- Haass-Koffler, C. L., Piacentino, D., Li, X., Long, V. M., Lee, M. R., Swift, R. M., et al. (2020). Differences in sociodemographic and alcohol-related clinical characteristics between treatment seekers and nontreatment seekers and their role in predicting outcomes in the COMBINE study of alcohol use disorder. *Alcoholism: Clinical and Experimental Research*, 44(10), 2097–2108. <https://doi.org/10.1111/acer.14428>
- Hosseini, M., Yassini Ardekani, S. M., Bakhshani, S., & Bakhshani, S. (2014). Emotional and social loneliness in individuals with and without substance dependence disorder. *International Journal of High Risk Behaviors and Addiction*, 3(3), Article e22688. <https://doi.org/10.5812/ijhrba.22688>
- Lunt, H., & Heenan, H. (2019). Mitigating the impact of disasters and emergencies on clinical trials site conduct: A site perspective following major and minor unforeseen events. *Contemporary Clinical Trials Communications*, 16, 100487. <https://doi.org/10.1016/j.conctc.2019.100487>
- McCoy, C. E. (2017). Understanding the intention-to-treat principle in randomized controlled trials. *Western Journal of Emergency Medicine*, 18(6), 1075–1078. <https://doi.org/10.5811/westjem.2017.8.35985>
- McDermott, M. M., & Newman, A. B. (2020). Preserving clinical trial integrity during the coronavirus pandemic. *Journal of the American Medical Association*, 322(21), 2135–2136. <https://doi.org/10.1001/jama.2020.4689>
- National Academies of Sciences, Engineering, and Medicine. (2017). *Strengthening the disaster resilience of the academic biomedical research community: Protecting the nation's investment*. Washington, DC: The National Academies Press.
- North, C. M., Dougan, M. L., & Sacks, C. A. (2020). Improving clinical trial enrollment – in the covid-19 era and beyond. *New England Journal of Medicine*, 383(15), 1406–1408. <https://doi.org/10.1056/NEJMp2019989>
- Oppenheimer, A. J., Pannucci, C. J., Kasten, S. J., & Haase, S. C. (2011). Survey says? A primer on web-based survey design and distribution. *Plastic and Reconstructive Surgery*, 128(1), 299–304. <https://doi.org/10.1097/PRS.0b013e3182174413>
- Pollard, M. S., Tucker, J. S., & Green, H. D., Jr. (2020). Changes in adult alcohol use and consequences during the COVID-19 pandemic in the US. *JAMA Network Open*, 3(9), Article e2022942. <https://doi.org/10.1001/jamanetworkopen.2020.22942>
- Sullivan, J. T., Sykora, K., Schneiderman, J., Naranjo, C. A., & Sellers, E. M. (1989). Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*, 84(11), 1353–1357. <https://doi.org/10.1111/j.1360-0443.1989.tb00737.x>

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