Safety and feasibility clinical trial of nucleus accumbens deep brain stimulation for treatment-refractory opioid use disorder

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OBJECTIVE There were more than 107,000 drug overdose deaths in the US in 2021, the most ever recorded. Despite advances in behavioral and pharmacological treatments, over 50% of those receiving treatment for opioid use disorder (OUD) experience drug use recurrence (relapse). Given the prevalence of OUD and other substance use disorders (SUDs), the high rate of drug use recurrence, and the number of drug overdose deaths, novel treatment strategies are desperately needed. The objective of this study was to evaluate the safety and feasibility of deep brain stimulation (DBS) targeting the nucleus accumbens (NAc)/ventral capsule (VC) and potential impact on outcomes in individuals with treatment-refractory OUD.

METHODS A prospective, open-label, single-arm study was conducted among participants with longstanding treatment-refractory OUD (along with other co-occurring SUDs) who underwent DBS in the NAc/VC. The primary study endpoint was safety; secondary/exploratory outcomes included opioid and other substance use, substance craving, and emotional symptoms throughout follow-up and 18FDG-PET neuroimaging.

RESULTS Four male participants were enrolled and all tolerated DBS surgery well with no serious adverse events (AEs) and no device- or stimulation-related AEs. Two participants sustained complete substance abstinence for > 1150 and > 520 days, respectively, with significant post-DBS reductions in substance craving, anxiety, and depression. One participant experienced post-DBS drug use recurrences with reduced frequency and severity. The DBS system was explanted in one participant due to noncompliance with treatment requirements and the study protocol. 18FDG-PET neuroimaging revealed increased glucose metabolism in the frontal regions for the participants with sustained abstinence only.

CONCLUSIONS DBS of the NAc/VC was safe, feasible, and can potentially reduce substance use, craving, and emotional symptoms in those with treatment-refractory OUD. A randomized, sham-controlled trial in a larger cohort of patients is being initiated.

Clinical trial registration no.: NCT03950492 (ClinicalTrials.gov)

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KEYWORDS opioid use disorder; addiction; deep brain stimulation; neuromodulation; overdose; treatment refractory; nucleus accumbens; functional neurosurgery

ABBREVIATIONS AC = anterior commissure; AE = adverse event; BSA = Brief Scale for Anxiety; CPRS = Comprehensive Psychopathological Rating Scale; DBS = deep brain stimulation; DSMB = Data and Safety Monitoring Board; MADRS = Montgomery Asberg Depression Rating Scale; MOUD = medication for OUD; NAc = nucleus accumbens; NIDA = National Institute on Drug Abuse; OUD = opioid use disorder; SAE = serious adverse event; SUD = substance use disorder; VC = ventral capsule.

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SUBSTANCE use disorder (SUD) continues to be one of the most significant medical challenges in the US. Approximately 40.3 million people had an SUD diagnosis in 2020. Since 1999, drug overdoses have been the leading cause of unintentional injury-related death in the US. There were more than 107,000 drug overdose deaths in 2021 (80,000 opioid-related), the most recorded in history. It is estimated that there will be 1.2 million future overdose deaths in the US and Canada by 2029. Despite advances in behavioral and pharmacological treatments, including medication for opioid use disorder (MOUD) such as buprenorphine, more than 50% of those receiving treatment for opioid use disorder (OUD) experience drug use recurrence (previously referred to as drug relapse) of opioids and/or other substances. Given the prevalence of OUD and other SUDs (with many individuals having limited access to available medication treatments), the high drug use recurrence rates, and the alarming number of drug overdose deaths, novel treatment strategies are desperately needed.

Studies addressing the neurobiological basis of SUD suggest the nucleus accumbens (NAc) is integral to the reward neurocircuitry with connectivity to brain regions involved in the behavioral aspects of addiction (e.g., craving, emotional regulation, disinhibition, and insight). Therefore, neumodulation of the NAc has emerged as a potential treatment option. Deep brain stimulation (DBS) is a commonly used neumodulation therapy for movement disorders and other conditions. Case reports and a case series investigating DBS for SUD suggest that DBS may reduce substance use and craving (see Fatthahi et al. and Mahoney et al.). Based on these findings, we initiated the first US clinical trial to rigorously assess the safety and feasibility of DBS among individuals with treatment-refractory OUD who were at higher risk of death based on their substance use and overdose history.

Methods

Study Overview and Procedures

The study design was a prospective, open-label, single-arm trial among participants with severe treatment-refractory OUD and a history of multiple drug overdoses. This clinical trial was funded by the National Institute on Drug Abuse (NIDA), award no. UG3 DA047714, and registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT03950492. The protocol was approved as an investigational device exemption study by the US FDA and the West Virginia University IRB and was overseen by a Data and Safety Monitoring Board (DSMB). Recruitment for this study was conducted between August 2019 and September 2021. The protocol we followed adhered to the US Code of Federal Regulations and the principles of the World Medical Association Declaration of Helsinki. All participants met the following general eligibility criteria: severe, treatment-refractory OUD evidenced by past participation in multiple levels of treatment (including MOUD within outpatient, inpatient, and residential settings) without substance abstinence. Prescreening and eligibility characteristics are included in the consort diagram (Supplementary Fig. 1). Full inclusion and exclusion criteria are described in Supplementary Appendix A.

The study protocol involved the following phases: screening, baseline, DBS implantation and titration (all conducted as an inpatient over 4–6 weeks), and the outpatient follow-up phases. Following the baseline phase, participants underwent standard stereotactic implantation of bilateral quadripolar DBS leads (Medtronic DBS lead model 3387, Medtronic Inc.) targeting the NAc/ventral capsule (VC) under local anesthesia/monitored anesthesia care. The bilateral NAc/VC targeting and safe avascular DBS lead trajectory plan was achieved on a StealthStation (Medtronic Inc.) surgical planning station using 3-T brain MRI. The NAc/VC was targeted such that the ventral-most DBS lead contact lay within the NAc and the dorsal-most contact within the VC. The anterior commissure (AC) was set as the reference point, and the coordinates for the NAc were as follows: 6- to 9-mm lateral and 1- to 3-mm anterior to the AC, and 4- to 6-mm inferior to the midcommissural plane. Standard microelectrode recording was performed during surgery. The postoperative CT scan was merged with preoperative MRI to verify the location of the DBS lead. Bilateral DBS leads were connected to a pulse generator (Activa PC or Percept PC, Medtronic Inc.) and implanted in the chest wall below the clavicle (Fig. 1). The activated DBS electrode contacts, mode (monopolar/bipolar), and parameters of polarity, pulse width, frequency, and intensity were optimized during the inpatient titration phase (Table 1) and guided by the participants’ reported anxiety, mood, and substance cravings. Subsequently, participants were discharged to outpatient follow-up. The primary outcome endpoint was outpatient week 12 as well as long-term follow-up.

Outcome Measures and Assessments

Urine Toxicology

Qualitative urine toxicology was performed twice weekly through outpatient week 12, then once weekly through week 52, and thereafter performed routinely per the clinical standard of the outpatient addiction treatment programs. Quantitative urine toxicology (gas chromatography–mass spectrometry) was performed during screening intake and the outpatient week-12 follow-up visit. Toxicology results were obtained for opioids/opioid analogs, cocaine, amphetamine, benzodiazepines, barbiturates, and delta-9-tetrahydrocannabinol.

Substance Craving

Cravings for opioids, benzodiazepines, stimulants, cannabis, and other substances were assessed using a visual analog scale in which 0 = no craving and 100 = maximum craving. During inpatient phases, craving assessments were conducted approximately 3–5 times per week. During the outpatient phase, assessments were conducted approximately once weekly through outpatient week 12, and then approximately once monthly through outpatient week 52.

Emotional and Psychiatric Functioning

Anxiety and depression were assessed via the Compre-
hensive Psychopathological Rating Scale (CPRS), which includes the Brief Scale for Anxiety (BSA) and the Montgomery Asberg Depression Rating Scale (MADRS). During the inpatient phases, the CPRS was administered approximately three times per week, and during the outpatient phase, approximately twice weekly through outpatient week 12 and then approximately once monthly through outpatient week 52.

**PET**

$^{18}$FDG PET/CT was performed using a Siemens Biograph 20 mCT scanner after DBS implantation prior to the titration phase (i.e., before DBS was activated), and subsequently at the outpatient week-12 endpoint. Details regarding PET procedures and analyses are described in Supplementary Appendix B.

**Statistical Analysis**

The primary study outcome was safety at the outpatient week-12 endpoint. Safety and substance use data (including nonopioid substances) were assessed throughout the long-term follow-up. For secondary/exploratory outcomes of substance craving ratings, anxiety, and depression, one-way ANOVA was utilized to determine differences in assessments between pre- and post-DBS outpatient time points. To date, the timing of secondary/exploratory outcome endpoints is as follows: participant 1, 3, and 4, outpatient week 52; participant 2, outpatient week 11, prior to explantation. The $p$ value is descriptive only and has no inferential interpretation (and therefore without correction for multiple comparisons) due to the small sample size. Of note, this open-label safety and feasibility trial was conducted to determine whether this line of research should advance to a second phase involving a randomized, sham-controlled clinical trial in a larger cohort of participants. As such, there was no power analysis performed when determining sample size for the current study as efficacy was not a primary outcome. Craving/behavioral data were analyzed using SPSS (version 26.0, IBM Corp.).

**Results**

**Participant Characteristics**

Four male participants (age range 22–44 years) were enrolled who had experienced multiple drug overdoses (range 5–11) and multiple unsuccessful SUD treatment attempts with drug use recurrence within 1–2 weeks following past treatments. All participants had a longstanding history of OUD (range 5–15 years), were prescribed MOUD both prior to and during study enrollment, and reported frequent use of other substances (benzodiazepines, methamphetamine, cocaine, alcohol, and/or cannabis).

**TABLE 1. DBS settings and parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participant No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrode contacts (bilat)</td>
<td></td>
<td>1−, 2+</td>
<td>2−, C+</td>
<td>1−, C+</td>
<td>1−, 3+</td>
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<td>Frequency (Hz)</td>
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<td>140</td>
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<tr>
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<td>4.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Outcome endpoint (outpatient study week)†</td>
<td></td>
<td>52</td>
<td>11</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Final DBS adjustment (outpatient study week)‡</td>
<td></td>
<td>8</td>
<td>10</td>
<td>0‡</td>
<td>14</td>
</tr>
</tbody>
</table>

* For participant 2, settings reflect most recent parameters prior to explantation. † Craving and behavioral assessment (BSA, MADRS) endpoints include data from post-DBS outpatient week 1 through the outpatient week indicated in this row. ‡ Final adjustment made during inpatient titration phase, no adjustments made during outpatient phase.
Detailed demographic and drug use characteristics are described in Table 2.

**Primary Outcomes**

**Safety and Tolerability**

All participants underwent DBS surgery without complication and were discharged to the outpatient phase after titration and optimization of the DBS settings. DBS was safe and well-tolerated with no serious adverse events (SAEs) nor any surgical or DBS-related complications in any participant to date. Participant 2 was persistently non-compliant with the study protocol, and the participant and study team (in consultation with the DSMB) agreed to discontinue his enrollment and explant the device at outpatient week 11. There were no safety concerns related to the device, surgical procedure, or stimulation for participant 2 through explantation.

### Substance Use

Participants 1 and 3 were completely abstinent from opioids and all other substances (other than prescribed buprenorphine), confirmed via frequent qualitative and quantitative urine toxicology performed at the outpatient week-12 endpoint assessment. To date, through long-term follow-up, both participants have sustained abstinence from all substances per urine toxicology tests for > 1150 and > 520 days, respectively. Participant 2 had two episodes of drug use recurrence prior to DBS explantation and study discontinuation. Participant 4 experienced four episodes of drug use recurrence through the primary outpatient week-12 endpoint. The quantitative urine toxicology test performed during the outpatient week-12 endpoint detected fentanyl and cocaine metabolites and prescribed buprenorphine. Drug use recurrences also occurred during weeks 14 and 17 (fentanyl and/or stimulants), 33, 37,
and 38 (cannabis), 40 (methamphetamine), and 46–52 (methamphetamine and/or heroin/fentanyl), coinciding with elevated psychosocial stress (unemployment and homelessness). Despite this, recurrent use, frequency, and severity (drug overdoses) were improved relative to pre-surgical baseline, which had included multiple weekly episodes of heroin/fentanyl and methamphetamine use and hospitalizations due to overdose. Subsequent to DBS placement, participant 4 has not experienced drug overdose hospitalizations.

Secondary Outcomes

Substance Craving

Compared to pre-DBS baseline craving ratings, participant 1 demonstrated significant post-DBS craving reductions for benzodiazepines ($F_{1,39} = 32.52, p < 0.001$) throughout the 52-week endpoint (Fig. 2A). Participant 2 showed significant post-DBS craving reductions for opioids ($F_{1,14} = 5.41, p = 0.036$), benzodiazepines ($F_{1,14} = 16.91, p = 0.001$), and cannabis ($F_{1,14} = 8.77, p = 0.010$) through the 11-week endpoint (Fig. 2B). Participant 3 evidenced significant post-DBS craving reductions for heroin ($F_{1,28} = 30.03, p < 0.001$), benzodiazepines ($F_{1,28} = 54.07, p < 0.001$), and cannabis ($F_{1,28} = 62.30, p < 0.001$) throughout the 52-week endpoint (Fig. 2C). Participant 4 did not experience significant post-DBS craving reductions for heroin ($F_{1,35} = 0.97, p = 0.332$) or opioids ($F_{1,35} = 0.96, p = 0.333$) throughout the 52-week endpoint (Fig. 2D).

Emotional/Psychiatric Functioning

Compared to pre-DBS baseline self-reported anxiety (BSA) and depression (MADRS), participant 1 showed significant post-DBS reductions in anxiety ($F_{1,43} = 152.69, p < 0.001$) and depression ($F_{1,43} = 70.11, p < 0.001$) throughout the 52-week endpoint (Fig. 3A). Participant 2 evidenced significant post-DBS reductions in anxiety ($F_{1,18} = 8.88, p = 0.008$), but not depression ($F_{1,18} = 0.04, p = 0.842$) through the 11-week endpoint (Fig. 3B).
3 experienced significant post-DBS reductions in anxiety ($F_{1,35} = 77.44, p < 0.001$) and depression ($F_{1,32} = 108.36, p < 0.001$) through the 52-week endpoint (Fig. 3C). Participant 4 evidenced significant post-DBS reductions in anxiety ($F_{1,29} = 10.64, p = 0.003$) and depression ($F_{1,29} = 21.93, p < 0.001$) through the 52-week endpoint (Fig. 3D).

PET Neuroimaging

$^{18}$FDG-PET examining changes in glucose metabolism from baseline to outpatient week 12 revealed increased glucose metabolism for participants 1 and 3, with the greatest changes occurring in the dorsolateral prefrontal regions (Fig. 4A and 4B). Participant 4 did not demonstrate notable changes in glucose uptake over time (Fig. 4C). Post-DBS activation $^{18}$FDG-PET was not completed with participant 2 because the DBS device was explanted and the participant discontinued protocol enrollment during outpatient week 11.

Discussion

The presented results suggest that DBS of the NAc/VC is safe, feasible, and potentially reduces substance use, craving, and drug use recurrence (relapse) in individuals with treatment-refractory OUD, multiple overdoses, and co-occurring SUDs who were not successful in achieving abstinence following all previous treatment attempts. There were no SAEs nor any surgical or DBS-related complications in any participant. Two participants (participants 1 and 3) have remained entirely substance abstinent since study enrollment without a single episode of drug use recurrence for > 1150 and > 520 days, respectively, to date. Substance abstinence was accompanied by progressive and significant reductions in substance craving, anxiety, and depression. Both participants showed increased glucose uptake bilaterally in the frontal regions known to be key loci for executive functions such as attention, inhibition, and working memory. Importantly, both individuals have remained fully engaged and compliant with their behavioral treatment, reported improved social functioning and family relationships, and secured employment as peer recovery support specialists helping others in recovery.

Participant 2, who underwent DBS explantation and

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FIG. 3. Bar graphs of anxiety and depression ratings for each participant. Red bars represent the mean anxiety/depression ratings pre-DBS and green bars represent mean anxiety/depression ratings across the post-DBS outpatient follow-up phase. Error bars represent the standard deviation. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001. Figure is available in color online only.
was discontinued from the study protocol due to persistent noncompliance with study procedures despite multiple efforts to re-engage him, experienced two drug use recurrences despite having significant reductions in craving and anxiety during the outpatient phase. While the reduction in craving and anxiety with DBS was promising, his noncompliance and early discontinuation preclude further conclusions. Participant 4 had drug use recurrences after DBS, but the frequency was profoundly reduced compared with drug use prior to study enrollment. None of these recurrences resulted in overdoses or periods of unresponsiveness, nor did any require naloxone administration. This contrasts with the 12-month period preceding DBS implantation in which naloxone was required on at least one occasion and multiple episodes of unresponsiveness following substance use were reported. While participant 4 had significant post-DBS improvements in anxiety and depression, similar to the two participants who remained drug abstinent, he did not have significant reductions in drug cravings. Also, this participant’s FDG-PET revealed a profile that differed from abstinent participants, showing minimal change in glucose uptake between his baseline and 12-week scans.

The impact of psychosocial factors and post-DBS outcomes also warrants consideration. Both participants who remained successfully abstinent had the support of family, remained in treatment, and successfully secured employment and housing. Participant 4 secured employment and housing and showed psychosocial improvements coinciding with approximately 120 days of abstinence. However, losing employment and housing resulted in homelessness and exposure to individuals actively using substances, which in combination with substantial distress, contributed to the drug use recurrences. This participant’s ongoing psychosocial stress may have contributed to the drug use recurrences given the established relationship between these factors and SUD outcomes.29,30 This finding highlights that DBS treatment alone may not be sufficient in leading to sustained abstinence if other basic needs are not concurrently met.

The NAc is a crucial region in the brain’s reward circuitry involved in addiction.7–10 We selected the NAc as the target for DBS in the treatment of refractory OUD due to its important role in addiction and the more than 20-year track record of safety and improvements in anxiety and obsessive behavior with DBS implants in this location.21–24 DBS can potentially modulate and regulate dopamine in the NAc and reward circuitry, normalize the activity of the NAc, and improve prefrontal cortex decision-making and behavioral self-regulation. In this context, all participants experienced significant reductions in anxiety with DBS. Additionally, there were significant post-DBS craving reductions for the two participants with complete abstinence which was not the case in participant 4 who experienced recurrences of substance use. Chronic, prolonged DBS treatment may be important to facilitate active engagement in behavioral therapy that is crucial to successful outcomes.

While there have been published case reports and a small case series investigating DBS for addiction, we believe that this first US FDA-regulated clinical trial is unique, novel, and expands on the previous literature for several reasons. Previous reports included variable and less-frequent follow-up assessments. For example, the published case series by Chen et al.12 involved in-person follow-up assessment at 1, 3, 6, 12, and 24 months, and the DBS treatment was discontinued at approximately 24 months. In contrast, the participants in our trial were followed in-person twice weekly for 12 weeks, then once weekly through 52 weeks, and subsequently enrolled in our long-term follow-up phase. In addition, unlike the current study, prior reports did not evaluate DBS as an ad-

FIG. 4. 18FDG-PET examining changes in glucose metabolism from baseline to outpatient week 12 revealed increased glucose metabolism for participants 1 (A) and 3 (B) with the greatest changes occurring in the dorsolateral prefrontal regions. Participant 4 (C) did not demonstrate notable changes in glucose uptake over time. Figure is available in color online only.
junctive treatment to already established and validated standard-of-care interventions (MOUD and behavioral treatments). We believe this is critical as we conceptualize DBS as a method of augmenting established treatments for those who have not had success sustaining abstinence, rather than viewing DBS as an intervention that can be independently used to treat addiction.

Limitations of the Study

While the findings presented in the current report are promising, they must be interpreted in the context of the following limitations. This was an open-label, safety, and feasibility trial with a small sample size. To further assess the utility of DBS for SUD, a NIDA-sponsored randomized, sham-controlled trial in a larger cohort of participants is being initiated with an intention of 1:1 randomization of active versus sham DBS (crossover delayed start) and an anticipated power > 80%. This larger sample will also allow for a more rigorous statistical analysis of PET data. A sham-controlled trial will also address potential confounding of placebo effects secondary to a surgical procedure, DBS adjustment, and follow-up requirements. Future directions include refinement of the DBS target using tractography and connectomics and functional brain imaging evaluating the impact of DBS on prefrontal cortex activity and dopamine changes in the NAc.

Conclusions

The results from this initial NIDA-sponsored US clinical trial suggest the safety and feasibility of NAc/VC DBS with a potential for reducing substance use, craving, and emotional symptoms in treatment-refractory OUD. The SUD crisis in the US is worsening with no end in sight and increasing overdose deaths. The utility of neuromodulation approaches such as DBS for SUD needs to be investigated in a rigorous and controlled fashion.

Acknowledgments

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Disclosures
Drs. Rezai, Finomore, and Mahoney have filed two patents for “Neuromodulatory methods for improving addiction using multi-dimensional feedback” (pending) and “Methods and systems of improving and monitoring addiction using cue reactivity” (pending).

Author Contributions

Supplemental Information
Online-Only Content
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