Title: Proposal for Retrospective Review of Ketamine Assisted Psychotherapy Program on Mental Health at Field Trip Health Centres in North America

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Introduction

Psychedelics are again at the forefront of psychiatric research as the search intensifies for more effective interventions to address emotional disturbances beyond conventional treatment (Carhart-Harris et al., 2017). Several psychedelics have been identified as having breakthrough potential when administered in combination with psychotherapy, including ketamine-assisted psychotherapy (KAP) (Ezquerra-Romano et al., 2018; Greenway et al., 2020; Luoma et al., 2020; Reiff et al., 2020). Overall the clinical trials evidence for psychedelic-assisted therapies is early (Wheeler et al., 2020) and multiple randomised controlled trials (RCTs) are underway around the world (see clinicaltrials.gov).

Although RCTs can best answer questions of safety and efficacy, there remains an urgent need to clarify the real-world effectiveness of psychedelic-assisted therapies. Field Trip Health administers KAP for adult clients coping with mental health. KAP consists of 4-6 guided ketamine sessions with psychotherapy-only visits after dose 1 and 2 and then after every 2 subsequent doses.

This proposal is for a retrospective intervention-only effectiveness trial based on review of Field Trip Health patient outcomes across its North American centres. Its objectives are: 1. to characterise baseline patient characteristics; 2. to identify treatment variation; 3. to determine the trajectory of mental health outcomes; and 4. to estimate effect sizes associated with treatment. We hypothesized sustained reductions in depression, anxiety, and post traumatic stress over time.

Method

Sample and Procedure

Patients treated at Field Trip Health are initially assessed by a psychiatrist or a psychiatric nurse practitioner to determine appropriateness for treatment. Eligibility criteria are as follows.

- Inclusion Criteria:
    - Written informed consent
    - Over the age of 18
    - Should be psychologically and medically cleared by a psychiatrist, family physician, or treatment team
    - Diagnosed with Major Depressive Disorder (MDD), Bipolar Depression, Generalized Anxiety Disorder, Obsessive Compulsive Disorder (OCD), and Eating

Disorder by a licensed healthcare practitioner (including Field Trip Consultants)
    - A significant history of trauma and/or formal diagnosis of PTSD as per the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM 5)
    - Individuals who have received Electroconvulsive Therapy (ECT) or other neuromodulatory treatments like Transcranial Magnetic Stimulation (TMS)
    - Individuals reporting suicidal ideation may be included, as suicidal ideation is a symptom of a Major Depressive Episode (MDE)

- Exclusion Criteria:
    - Individuals who are unable to consent to the treatment
    - Pregnant women and nursing mothers
        - Note that Post Partum Depression (PPD) can be considered on a case-by-case basis in consultation with the National Medical Director.
    - There is a relative (not absolute) contraindication for individuals with a Body Mass Index (BMI) of above 35. These clients must be given thorough consideration by the medical team.
    - Any individual who has met DSM 5 criteria for a Substance Use Disorder in the past 3 months.
        - Note that patients with alcohol, opioid, benzodiazepine, cocaine, and amphetamine use disorders need to go through detox (for alcohol/benzodiazepines) and be sober for 4 weeks.
        - Note that mild active alcohol, cocaine, and cannabis use can be considered on a case-by-case basis at the comfort level of the treatment team if the client has demonstrated abstaining or significant reduction of use prior to starting treatment.
    - Daily use of moderate to high doses of benzodiazepines
    - Individuals who are experiencing psychotic symptoms as part of an MDE (mood congruent/ mood incongruent)
    - Psychosis: Schizophrenia, Schizoaffective disorder, Bipolar 1 with psychotic features during mania
    - Active Mania: Bipolar 1 (chronic non-disruptive hypomania is an exception at the discretion of the consultant)
    - Borderline Personality Disorder
    - Uncontrolled medical disorders
    - Physical conditions with negative interaction with ketamine (e.g., metabolic blood disorder)
    - Individuals with symptomatic acute brain injury within 90 days of serious injury
    - Individuals diagnosed with moderate to severe sleep apnea
    - Individuals who are unable to identify a person or service to assure their safe transport to home post treatment

As a part of the intake process of the program, patients provide written informed consent and complete questionnaires via a Health Insurance Portability and Accountability Act (HIPAA) and Personal Health Information Protection Act (PHIPA) compliant Electronic Medical Records (EMR) system.

Questions include information on demographics, past medical history as well as standardized mental health questionnaires. Patients are also encouraged to complete these scales at several additional points during the treatment program and then at 1, 3, and 6 months after program completion. Data will be reviewed from patients who were treated with KAP across 11 Field Trip Health locations across North America from March 2020 to June 2022.

These locations include:
1) Toronto, ON, Canada
2) Vancouver, BC, Canada
3) Fredericton, NB, Canada
4) New York City, NY, USA
5) Atlanta, GA, USA
6) Chicago, IL, USA
7) Houston, TX, USA
8) Seattle, WA, USA
9) Santa Monica, CA, USA
10) San Diego, CA, USA
11) Washington, DC, USA

Data Handling
The full clinical dataset is managed by a data administrator who will collate the assessments and de-identify the data so that no personal identifying information remains. This de-identified dataset will then be analysed by research team members. Full clinical data is held on encrypted servers with password protection and accessible only to internal clinical staff. Only research team members will be allowed access to the de-identified research dataset which will also be kept on password protected servers and computers.

Should a data breach or leak should occur, our data mitigation plan is to contact Veritas Internal Review Board (IRB) to inform them of the breach, assess the extent of the breach, and determine what steps can be taken to address the situation. We will also plan to inform affected clients of the event and the actions being taken.

Measures of Interest
a) Demographic variables, including age and gender.
b) Medical variables, including main diagnosis and length of illness.
c) Treatment-related variables, including number and timing of ketamine sessions, number and timing of psychotherapeutic sessions, and site.
d) Primary clinical outcomes were:

i. Change in depression at 3 months relative to baseline assessed by 9-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001);
ii. Change in anxiety at 3 months relative to baseline assessed by 7-item Generalized Anxiety Disorder measure (GAD-7) (Spitzer et al., 2006);
iii. Change in post traumatic stress at 3 months relative to baseline by 6-item Post Traumatic Stress Disorder (PTSD) Checklist (PCL-6) (Lang & Stein., 2005).

e) Secondary clinical outcomes were:
i. Change in depression at 1 month relative to baseline assessed by PHQ-9;
ii. Change in anxiety at 1 month relative to baseline assessed by GAD-7;
iii. Change in post traumatic stress at 1 month relative to baseline assessed by PCL-6;
iv. Change in depression at 6 months relative to baseline assessed by PHQ-9;
v. Change in anxiety at 6 months relative to baseline assessed by GAD-7;
vi. Change in post traumatic stress at 6 months relative to baseline assessed by PCL-6.

Statistical Analysis

Descriptive statistics will characterize the sample. This will include an analysis of variations in treatment delivery and the extent of missing values across measurement occasions. Analysis of treatment effects is by intention to treat. The main analysis will be mixed linear models to plot the normative patient trajectories or growth curves for each outcome, producing estimates of mean changes at each endpoint (i.e. 1, 3, and 6 months) relative to baseline (Bell et al., 2013). Cohen's d will be our standardised measure of effect size. By convention, values of d = 0.2, 0.5, and 0.8 correspond to small, medium, and large effects.

Secondary analyses will include evaluating case reductions (identified by validated cut-off values relevant to each measure) and proportions of patients reporting minimal clinically important differences (MCIDs) at each endpoint relative to baseline. Additional analyses may include a sensitivity analysis involving multiple imputation of missing values to examine the stability of estimates. Demographic, medical, and treatment-related variables may be tested as predictive factors.

Impact

Field Trip Health's large-scale dataset may provide real-world benchmarks concerning the sustained benefits of ketamine-assisted psychotherapy. Given the scale of interest by policymakers, clinicians, researchers, and patients, these findings may be suitable for publication in a high impact journal, offering scientific validation of Field Trip Health's therapeutic product.

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