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Group Format Psilocybin-Assisted Therapy: Commentary on the HOPE trial (HOPE: a pilot study of psilocybin-enhanced group psychotherapy in patients with cancer)

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Depression and depressive symptoms are an all too common bedfellow for many cancer patients, adding to an already daunting array of symptoms requiring palliation[1-4]. Without successful treatment, depression significantly increases mortality rates[5,6], sabotages quality of life[7], reduces cancer treatment compliance[8], and multiplies the rates of completed suicide rates four-fold[9,10]. Not surprisingly, caregivers for depressed cancer patients experience a degree of depression and hopelessness strongly correlated with these same clinical features in patients[11].

Standard antidepressants including selective serotonin reuptake inhibitors (SSRIs) have several key therapeutic disadvantages. A significant fraction of patients does not fully respond to these treatments. Achieving a full treatment effect may take up to 6-8 weeks. Finally, the multifaceted polypharmacy of cancer therapy often results in drug-drug interactions with these daily medications, increasing the risks for toxicity or dangerous side effects. There is an urgent need for new, rapid-acting antidepressant treatments that have fewer side effect risks.

Psilocybin may provide new hope. Considered a 'classic psychedelic': it resides in a class of compounds of 5HT-2A agonists like lysergic-acid diethylamide (LSD), dimethyltryptamine (DMT), and mescaline. These compounds reliably induce alterations in brain functional connectivity with associated profound changes in conscious experience thought to be related to downstream therapeutic effects[12-14]. Following decades of a politically generated moratorium on clinical trials, a recent resurgence of clinical and research has revived development of new practices for safe administration[15].

Psilocybin-assisted therapy (PAT) has emerged in recent years as a safe, feasible, and highly effective treatment option for refractory depression[16-20]. Affected cancer patients have duly been the target of several randomized controlled trials on PAT to date[21-24]. These studies have demonstrated rapid and significant symptom relief following a single high-dose psilocybin administration in an individual format. Results are also durable, lasting 6 months[21-23] and even >5 years for up to 80% of participants[25]. Furthermore, these studies demonstrated that the psilocybin experience was well-tolerated by patients without any serious adverse events. It is worth comparing this magnitude of effect to the remission rates expected with standard antidepressant treatment: 36.8% remission rate with first trialed antidepressant[26].

The current accepted model of PAT employed in clinical trials employs an individual model across preparatory sessions (2 hours each), 1-3 individual psilocybin sessions (8 hours each), and subsequent integration sessions (2 hours each) generally with two therapists present for each encounter. This model is resource intensive and presents challenges for scalability and accessibility. A protocol involving a single psilocybin session with this format requires 40+ clinician hours per participant. Group formats dramatically expand the scale on which these treatments can be offered. Furthermore, there are reasons to hypothesize synergistic effects between the psilocybin experience and group process which might be uniquely helpful for symptoms of depression. Our research group has completed a 12-person pilot study on the safety and feasibility of group-format PAT (HOPE: a pilot study of psilocybin-enhanced group psychotherapy in patients with cancer)[27,28]. This study is the first modern study to employ a full group format for this intervention.

Nonetheless there is a long history of classic psychedelics used in group settings for spiritual purposes by indigenous groups. There have been a number of group format serotonergic psychedelic studies conducted prior to rescheduling of these compounds by the DEA[29] however design of these early modern trials was heterogeneous, lacking in rigor, with resultant difficulties in interpretation. Prior to the HOPE trial there have been two recent trials employing variations on group format. This includes a study of PAT for 30 patients with major depressive disorder associated with a cancer diagnosis run at The Aquilino Cancer Center[24] as well as a pilot study of PAT for male AIDS survivors with demoralization[30]. Both of these studies reduced the standard 2:1 therapist to participant ratio, however neither employed a group-format psilocybin dosing session.

We investigated the safety and feasibility of group format PAT with the HOPE trial, a single-arm, open-label pilot study of group psilocybin-assisted psychotherapy in 12 participants with symptoms of depression and anxiety associated with a cancer diagnosis. This study was designed to assess the safety and feasibility of a full group model intervention that employs a group psilocybin administration session (25mg) as well as group preparation and integration sessions, with cohorts of four participants at a time. This study demonstrated the safety and feasibility of this model of psilocybin-assisted therapy with all participants completing the intervention and no serious adverse events. There was a total of twelve AEs across six participants which were self-limited. While this study was not designed to test efficacy we demonstrated a clinically substantial reduction in HAM-D scores from baseline to the 2-week primary endpoint (*21.5 to 10.09, F1,9.00=33.81, p<0.001, d=1.71)* and 26-week endpoint *(21.5 to 14.83, F1,6.49=15.58, p=0.006, d=1.28)*. We also demonstrated significant improvement in measures of quality of life and well-being (FACIT-Sp)[27]. We also observed significant correlation between scores on the Mystical Experience Questionnaire (MEQ-30)- a 30-item questionnaire designed to assess experiential aspects of the psilocybin experience- and HAM-D scores at the 2-week primary outcome timepoint.

In addition to primary outcome measures this study gathered qualitative data from study participants regarding response to the group-based protocol. 10/12 participants completed this qualitative survey, administered at 2 weeks post completion of the full study intervention[28]. We found that participants felt that the group format was well-tolerated and perceived to be a critical component of their therapeutic process.

This study has several limitations in addition to its small size. The lack of a control group problematizes assessment of efficacy of psilocybin and suggests amplification of likely expectancy effects. Five out of twelve participants had prior experience with classic psychedelics: a higher rate than predicted by estimated population prevalence and suggestive of possible selection bias. Our participant sample was predominantly Caucasian with limited diversity. This continues rather than improves upon a concerning trend in the field to date. Use of a non-manualized supportive-expressive group psychotherapeutic intervention also presents challenges for replicability.

Despite these limitations, the HOPE trial represents a requisite first step on the path of redesigning PAT into a scalable treatment capable of relieving depressive symptoms in cancer patients. With less intensive resource utilization and a group format, HOPE does promote 'hope' for relief from a debilitating and far-reaching bedfellow of depression in the cancer world.

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