Efficacy of Oral Ketamine Combined with Psychotherapy for Treatment Resistant Depression

Tatiana Zdyb and Michael Hart

ABSTRACT

Background: Treatment resistant depression (TRD) is defined as a major depressive episode that does not improve in response to at least two trials, each of a different class, of antidepressant medication. Pharmacotherapy of TRD with low dose ketamines has been shown as relatively successful in recent studies. Effects of such pharmacotherapy can be augmented by combining ketamine with psychotherapeutic interventions such as Zdyb's Therapeutic Reset of Internal Processes (TRIP) protocol.

Method: 10 adult TRD patients (4 men, 6 women) were treated with low dose ketamines and were also receiving psychotherapeutic intervention as per TRIP protocol. All patients were administered the Patient Health Questionnaire, module 9 (PHQ9) which is a measure of a major depressive episode. The PHQ9 was administered twice: on baseline (i.e., prior to treatment) and after the treatment.

Results: On average, our patients fell in the moderate range of severity with respect to symptoms of TRD at baseline (pre-TRIP) as by their mean PHQ9 score of 17.9, (SD = 5.1). Their mean PHQ9 score decreased post TRIP treatment to 9.5 (SD = 6.6): the difference is significant in a t-test, $t(10) = 4.3172$, $p = 0002$ (two-tailed). The magnitude of the decrease amounts to 46.9% of the average baseline score.

Discussion and Conclusions: Our patients experienced significant reductions in symptoms of TRD in this pilot study. Research studies are now needed with control groups of TRD patients on a waiting list or also of those receiving only the ketamine pharmacotherapy.

Keywords: ketamine, psychotherapy, treatment resistant depression, TRIP protocol.

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T. Zdyb*

MindSetting Clinic, London, Ontario, Canada. (e-mail: tatiana@dyb.ca)

M. Hart*

Optimind Pharma, London, Ontario, Canada.
(e-mail: reception@readytogoclinic.com)

*Corresponding Authors

I. INTRODUCTION

Cross-cultural studies by Weismann's team estimated the lifetime prevalence of a major depressive episode from 1.5% to 19.0% [1]. While seventy to eighty percent of people respond to pharmacotherapy, psychotherapy, or a combination of the two, the remainder continue to suffer declines in social and occupational functioning, as well as physical, emotional, and cognitive health. Many also experience suicidal thoughts. Despite advances in understanding the multiple factors that influence the etiology and maintenance of this illness, there remains a need for additional treatment options. Between 29% and 46% of depressed patients fail to respond fully with antidepressant treatment of adequate dose and duration [2]. Individuals afflicted with severe treatment resistant depression (TRD) have likely undergone pharmacotherapy, electroconvulsive therapy (ECT), psychotherapy, neurofeedback, transcranial magnetic stimulation, and/or combinations thereof resulting in little to no impact on the depressive episode. There is an urgent need for novel treatments in response to this global mental health crisis.

Within the last decade there has been a renewed interest

in researching psychiatric applications of compounds such as ketamine. Preliminary data on its therapeutic use are promising [3].

Ketamine has been used as an anesthetic for decades in children, adults, and the elderly. Ketamine has also been found to be a safe and beneficial treatment for chronic pain and certain psychiatric conditions [4]. The mechanism by which ketamine has its anti-depressant impact has yet to be determined. One theory focuses on the antagonism of NMDA receptors within the glutamate neurotransmitter matrix. Animal models suggest that ketamine-induced synaptic potentiation and proliferation plays a key role in eliciting antidepressant effects [5]. According to Wallach [6], ketamine impacts other neurotransmitter systems as well, affecting the cholinergic, monoaminergic, kappa opioid, and GABAergic functioning.

Another hypothesis involves the suppression of parts of the brain collectively known as the Default Mode Network (DMN), or anatomically as the medial frontoparietal network (M-FPN). Reducing activity in the DMN moderates the rumination, which is implicated in the maintenance, if not etiology of depression. Interrupting the rumination allows an individual to access and attend to psychologically

important material that may otherwise remain unidentified and unprocessed and thus, to continue to contribute to depressive symptomatology.

From a biopsychosocial perspective, anchoring has been posited as being a way of understanding the mechanism by which ketamine has its psychotherapy lubricating results. Anchoring was described by Greenway's team [7] in phenomenological terms as the "essential elements gained from the experience." It is described as a direct experience of seeing oneself and one's circumstances in a different way, via less intellectualized, embodied knowing.

At present, ketamine is available in Canada by prescription from a physician, as an intervention for a major depressive disorder, especially for TRD with acute suicidal ideation, and is most commonly administered intravenously without a psychotherapeutic component. This is in keeping with a medical paradigm (see [8]) in which the patients assume a passive role with respect to their treatment, aside from attending the infusion appointments.

The review by Rosenblat *et al.* [9] examined the efficacy of the use of ketamine without psychotherapy and determined that oral ketamine has antidepressant efficacy. The combination of case studies, and randomized controlled trials (RCT) examined in Rosenblat's systematic review had varied dose (0.5 to 7.0 mg/kg) and frequencies (ranging from 3 times daily to once monthly), however, clinically significant changes in the severity of depressive symptoms ($p < 0.05$) were observed in all studies, see Rosenblat [9].

Since the mid-1970s, ketamine has been used in conjunction with psychotherapy in some studies. Khorramzaadeh and Lofty [10] administered ketamine to 100 psychiatric patients who were also undergoing psychotherapy and reported that 90% experienced clinically significant reductions in symptoms of depression, obsessive-compulsive disorder, and anxiety. Salvador Roquet also pioneered ketamine assisted psychotherapy and Krupitsky used ketamine in 1985 for the treatment of alcoholism. Seventy percent of Krupitsky's patients were able to maintain abstinence from alcohol one year after their therapy [11]. Krupitsky and Grinenko [12] also determined ketamine to be beneficial in treating posttraumatic stress disorder and depression. Jennifer Dore *et al.* [13] reviewed studies into the efficacy of ketamine assisted psychotherapy within a multi-site context. Outcome measures from 235 patients collected from 2013 to 2018 suggest that ketamine assisted psychotherapy is an effective means for decreasing symptoms of depression. According to Hasler [14] "Ketamine leads to fast changes in synaptic function and plasticity that go well beyond effects of classical antidepressants. As a result, ketamine may turn out to have the capacity to considerably enhance the effects of psychotherapy." [14]. There is evidence that psychotherapy prolongs the antidepressant effects of ketamine: "Such enhancing effects may become an important clinical indication for ketamine since its purely pharmacological effect is transient." [14].

Ketamine enhanced psychotherapy has also been applied to the treatment of end of life anxiety. Kolp's team [15] gave patients diagnosed with terminal cancer 150 mg of ketamine intramuscularly. The findings determined that

ketamine enhanced psychotherapy is effective in decreasing death anxiety [15].

The research on ketamine enhanced psychotherapy confirms that it is a viable intervention for psychiatric illnesses, including but not limited to, treatment resistant depression (TRD).

The Therapeutic Reset of Internal Processes (TRIP) protocol is a 5-step treatment developed by Zdyb (published in 2020) that can be used to enhance therapeutic impacts of ketamine. The TRIP protocol involves the patients actively participating in a psychotherapy session while under the influence of 75 mg of orally administered ketamine. The psychotherapeutic sessions occur within 24 to 48 hours after administration of ketamine.

The purpose of this study is to evaluate the efficacy of the TRIP protocol for enhancing ketamine therapy of TRD.

II. METHOD

This study calculated de-identified statistical data on ten adult patients (4 men, 6 women), mean age = 36.2 years, SD=9.77. All 10 patients met the criteria for treatment resistant depression (TRD) defined here as a major depressive episode that does not improve in response to at least two trials, each of a different class, of antidepressant medication [17]. All 10 patients completed the Patient Health Questionnaire, module 9 (PHQ9) [18] which measures the severity of a major depressive episode. The PHQ9 was at first administered prior to treatment to establish the baseline score and then, post-treatment.

The ketamine used in this study was a mixture of R and S ketamine supplied by The Ultimate Care Compounding Pharmacy, by Ms. Monica Miatello, registered pharmacist.

Patients self-administered their prescribed dose of oral ketamine (75 mg) on an empty stomach, after fasting for 6 hours, in the clinic, in the presence of Dr. Zdyb, 20 minutes prior to the start of their psychotherapy session. Each patient obtained two sessions of TRIP psychotherapy [16], each session lasting two hours. The two sessions were spaced by 4 weeks apart.

In the first 20 minutes prior to the start of the psychedelic enhanced psychotherapy session, the patient was alone in the room waiting for the ketamine to take effect while laying on a chaise, with their eyes closed or an eye mask on, listening to Mendel Kaelen's playlist for depression for 20 minutes. The playlist was originally created for studies of depression psychotherapy at the Imperial College London. Then, psychotherapy sessions began with the therapist asking what the patient was noticing and how they were feeling, and this was followed by the rest of the itinerary co-created with the patient during the planning session. The TRIP psychotherapeutic procedure is described in a separate article by Tatiana Zdyb (publication forthcoming).

III. RESULTS

Prior to treatment, i.e., on baseline, the average PHQ9 score of the 10 patients was 17.9 (SD=5.1), i.e., within the moderate range of severity with respect to symptoms of treatment resistant depression (TRD). After the two sessions

of psychotherapy, the PHQ9 scores of our patients decreased to 9.5 (SD = 6.6). The difference is significant in a t-test, $t(10) = 4.3172$, $p = 0.0002$ (2-tailed).

The mean difference in pretreatment and posttreatment scores amounted to 8.4 points on the PHQ9, i.e., 46.9% of the pre-treatment average PHQ9 score.

IV. DISCUSSION AND CONCLUSIONS

The preliminary data suggest that the TRIP protocol [16] mitigates risk and is effective in relatively rapid therapy of depressive symptoms, without major undesirable side-effects. The results of our pilot study are consistent with existing literature demonstrating the efficacy of oral ketamine combined with psychotherapies.

Future studies are needed with control groups of TRD patients on a waiting list and also with control groups of those receiving only the ketamine pharmacotherapy.

From psychological perspective, research is needed to determine, via pre-treatment scores on standard multivariate personality tests, possible statistical predictors of which TRD patients are most likely to benefit from TRIP enhanced ketamine therapy.

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Tatiana Zdyb, Ph.D., M.A., C. Psych, is a clinical psychologist, founder of the Zdyb Centre for Health Promotion and MindSetting. Dr Zdyb completed her Ph.D. in Health and Rehabilitation Sciences at the University of Western Ontario and has been practicing psychotherapy for 17 years. She created the TRIP protocol for psychedelic-enhanced psychotherapy and is actively engaged in testing its efficacy with various adult clinical populations. Additionally, Dr. Zdyb is a part-time faculty member in the psychology department at King's University College.

Michael Hart, MD, is the medical director and founder at Readytogo Clinic in London, Ontario. Dr. Hart graduated from Saba University School of Medicine in 2010 and completed his family medicine residency at Western Schulich School of Medicine in 2012. Dr. Hart is a recognized speaker on the topic of cannabis and co-authored the Amazon best-selling book "Friendly Fire: Why Vets Are Lighting Up and Ditching Pills to Treat PTSD." His outspoken stance on cannabis landed him an appearance on the Joe Rogan Experience podcast in 2019. His interests are in treating pain and mental health, and he has been published for his work for both cannabis and Ketamine.