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A Concept Note for a Grant

Ketamine Psychotherapy for Mental Health Disorders of Ukrainian Citizens

Affected by War with the Russian Federation

Opportunity

Under current Ukrainian law, state-funded medical institutions (including military hospitals) are not permitted to offer Ketamine-assisted therapy. Consequently, very few members of our highest-risk population have access to a potentially-transformative intervention.

Members of the Ukrainian Parliament have indicated that a successful research study of 50 PTSD-afflicted Ukrainian war veterans would enable them to pass legislation allowing state-funded medical institutions to offer Ketamine-assisted therapy.

An initial grant of \$68,400 would make a major impact in three key areas:

1. Provide a powerful and necessary treatment for 50 military veterans
2. Create a formal and empirical research report documenting the findings
3. Unlock larger, institutional delivery models to scale the treatment modality

Background

Research proves the catastrophic impact of wars on mental health. According to WHO estimates, as a result of experiencing psycho-traumatic events, at least 10% of people develop serious mental disorders (including post-traumatic stress disorder - PTSD) and another 10% develop behavioral disorders that significantly reduce their quality of life.

Based on available statistics, we should expect the number of people with mental disorders in Ukraine, particularly with PTSD, to be in the millions because of the war. Thus, a study of the effects of Russian military aggression on the mental health of Ukrainians conducted from 2014 to 2019 revealed PTSD in 37% of subjects, depression in 22%, and anxiety disorders in 17%. According to studies, 20-60% of people with these disorders will have them in a complicated, severe form or not responsive at all to existing therapies. Without proper attention, this can lead to a multitude of negative social consequences, from reduced productivity in the workplace to increased morbidity and mortality in the population, particularly due to suicide. We should also expect that without proper attention, the trauma of war will have a negative impact on the formation of the personality of future generations of Ukrainians.

PTSD is a particularly intractable chronic condition, in which many patients have symptoms even 20 years after trauma, and the incidence often increases with time after trauma. The lifetime prevalence of PTSD in veterans is 15-20% or more.

Epidemiological studies show that more than half of U.S. military veterans with PTSD also have major depressive disorder, which can make adequate treatment of both conditions difficult, as well as mood changes, anhedonia, guilt, sleep and concentration difficulties, alcohol and substance abuse.

Despite the disabling nature of PTSD and its relatively high incidence in veterans, therapy options remain limited. There are several empirically validated psychotherapeutic treatments for PTSD, among which the most effective are trauma-focused cognitive behavioral therapy and eye movement desensitization and processing therapy. However, psychotherapeutic treatments have a significant percentage of unresponsive patients. A number of pharmacotherapies have also been proposed, where selective serotonin reuptake inhibitors such as paroxetine and sertraline have shown the greatest success. Unfortunately, pharmacotherapy has an even higher non-response rate than psychotherapy, as well as numerous side effects. Meta-analytic studies show only minor differences between pharmacotherapy and placebo, especially in veterans suffering from PTSD. As a result, a significant proportion of PTSD patients remain treatment resistant. Taken together, these data underscore the urgent need for new effective treatments for this disorder.

One such promising trend is ketamine psychotherapy (to be explained in Methods).

Aim and Objectives:

The aim of this project is to provide new methods of treatment of mental health disorders for those Ukrainian citizens affected by war who cannot get benefit from standard first-line therapy (treatment-resistant).

The objectives include:

- Examining if the integrative approach (ketamine-assisted psychotherapy in combination with additional methods) will be more efficient than standard first-line therapy.
- Assessing the durability of treatment effects over time
- Examining the impact of treatment on patients' overall functioning and quality of life
- Identifying any potential side effects or adverse events associated with treatment.

Main method: Ketamine-assisted psychotherapy

Ketamine (chlorphenyl-methylamine-cyclohexanone) is a licensed medical drug and has been widely used worldwide as a short-acting anesthetic and analgesic for more than 40 years.

Research on ketamine as a treatment for mental disorders began in the 1970s in Argentina and Mexico and has since spread to other countries. Since the beginning of the 21st century, after the resumption of research on psychoactive substances, there has been a significant increase in the number of scientific publications devoted to the use of ketamine for the treatment of depressive disorders and pain syndromes. In microdoses, it has a pronounced psychotropic therapeutic effect that differs from the standard doses used in surgical anesthesia to "turn off" consciousness.

Studies show that ketamine increases the neuroplasticity of the brain, helping to regenerate synaptic connections between brain cells damaged by stress and depression. This can be particularly helpful for veterans who often have post-concussion syndrome as a condition comorbid to PTSD. The drug acts at a completely different level of the neurotransmitter system compared to the traditional antidepressants that now exist. In contrast, even a single injection of ketamine usually has a significant and rapid antidepressant effect on patients with persistent depression resistant to other medications, as well as reducing PTSD symptoms.

In March 2019, the U.S. Food and Drug Administration (FDA) approved the use of ketamine to treat depression, and the European Commission did the same in December 2019. According to Ronald Duman, professor of psychiatry and neurobiology at Yale University, "The rapid therapeutic response of ketamine in treatment-resistant patients is the biggest breakthrough in depression research in a half-century". That is why the number of ketamine therapy centers around the world is rapidly increasing, and today there are already several hundred in the U.S. alone.

Following the use in depression, scientific evidence emerged on the effectiveness of ketamine for increased anxiety, PTSD, obsessive-compulsive disorder, emotional burnout, long-term pain syndromes, alcohol and drug addiction and other pathologies.

Several reviews and meta-analysis published in 2021-2022 and studied 10 to 14 research studies of ketamine to treat PTSD, covering a total of 1107 patients, have found that the drug can significantly alleviate the symptoms of chronic PTSD. Repeated injections of ketamine are safe for patients with chronic PTSD and are generally well tolerated, with brief psychiatric and hemodynamic side effects.

The combination of ketamine with psychotherapy is particularly effective. Depending on the dose, ketamine promotes a shift from conventional, habitual thinking, to more creative thinking, a release of emotional negativity, and an expansion of consciousness with deeper access to the self in terms of self-knowledge. These effects enhance the patient's ability to engage in meaningful psychotherapy during and after the administration of the drug. Ketamine is effective for "resetting" consciousness, introspection and meditative presence, as well as for recovery from depression and the lingering effects of trauma.

A course of treatment usually consists of 4 to 8 intravenous (IV) infusions of ketamine administered 1 to 2 times per week. The positive effect of ketamine therapy is not limited to the short period in which the person is under the influence of the drug. The effects of the medication usually last 3-5 weeks after the course, sometimes up to 12 weeks at low dosages of ketamine and longer at higher dosages.

Outcome measures will include assessments of symptoms of PTSD, depression, and anxiety, as well as measures of overall functioning and quality of life. Assessments will be administered at baseline, post-treatment, 3-month and one-year after the completion of treatment.

Target group

This project will involve patients with diagnosed mental health disorders (PTSD, depression, anxiety) related to war trauma: military veterans, family members of deceased military personnel and civilians affected by military actions.

Patients will be recruited through referrals from mental health providers and outreach to community and veteran organizations.

The needs we see for this project

People affected by war are also usually affected financially and in need of support. Since at the moment we are a small health center, we are limited to several persons per month in our ability to provide a free service as a volunteer help. Should we receive an external financing, we could provide this service for much more people and on continuous base.

Logframe and budget

We can start with a pilot project to treat 50 people, and expect them to be treated in 4 – 5 weeks, if the group will be formed in full in advance. After validation of effectiveness, we can expand our service for long run.

Current price of one ketamine infusion in our center is \$100, which is at minimum twice less than in the West (in average \$200 in Europe and up to \$500 in USA). This allows us to provide our citizens with the advanced modern treatment at the cost that corresponds to current economic conditions.

The program of a *three-week* outpatient course of therapy for moderate PTSD and/or depression and anxiety includes:

- 6 sessions of ketamine-assisted psychotherapy twice a week - \$100 infusion + \$40 psychotherapy = $\$140 \times 6 = \800
 - 5 sessions of integrative psychotherapy – $\$40 \times 5 = \200
 - 2 examination sessions (introductory meeting on intake and closing meeting on discharge) - $\$40 \times 2 = 80$.
- Total is \$1,080 USD per person per course.

The program of a *five-week* outpatient course of therapy for severe PTSD and/or depression and anxiety include:

- 10 sessions of ketamine-assisted psychotherapy twice a week - \$100 infusion +\$40 psychotherapy = $\$140 \times 10 = \1400
 - 9 sessions of integrative psychotherapy – $\$40 \times 9 = \360
 - 2 examination sessions (introductory meeting on intake and closing meeting on discharge) - $\$40 \times 2 = 80$.
- Total is \$1,840 USD per person per course.

We presume that for the trial 50-persons course, 30 patients will have a middle disease severity, where the cost will be $\$1,080 \times 30 = \$32,400$, and 20 patients - high disease severity, where the cost will be $\$1,800 \times 20 = \$36,000$, in total \$68,400.

In case of disproportionate group distribution the total funds amount will be used accordingly.

A detailed calculation will be provided upon request.

We also use additional modern methods of treatment like stellate ganglion blockage, transcranial electrical brain stimulation (TCDS), transcutaneous auricular vagus nerve stimulation, body-oriented therapy, etc, that can significantly enhance the treatment output. This can be added to the basic program above at additional cost.

The current capacity of the center is 8-10 ketamine sessions per day.

This means that in a one year timeframe we will be able to treat approximately 50 patients per month and need accordingly \$68,400 per month, or \$820,000 per year. Should this project work out, we can expand it by hiring more specialists, renting additional facility and provide more help to people who need it.

Staff and locations

This project will be conducted in Kyiv, Ukraine, by Expio LLC Medical Center (service mark Expio Center for Psychotherapy, Psychosomatics and Psychedelic Medicine), the leading Ukrainian organization in the development of the advanced methods of mental health. At the moment, we are the first and the only one medical facility in Ukraine that provides a legal ketamine psychotherapy.

Our credo is innovations. For the first time in Ukraine we implemented the program of psycho-oncological treatment "Anticancer" (2017), the program of integrative treatment of depression "Antidepressant" (2018), and the method of ketamine-assisted therapy (2018).

We adhere to the principles of holistic, integrative medicine, which views the human being as a whole system, where body, mind and spirituality are equal partners.

The center situated on the 5th floor of Kyiv`s state children hospital #9 on 130 s.m. and has 8 rooms. The medical staff includes psychiatrist, psychotherapist-MD, two clinical psychologists and anesthesiologist.

Significance:

This project has the potential to fill an important gap in the treatment of mental health disorders in individuals affected by war in Ukraine. Ketamine-assisted psychotherapy, particularly in combination with additional methods, could provide a much-needed treatment option for individuals who may not respond to traditional therapies, or who may require rapid symptom relief.

Sincerely,

Vladislav Matrenitsky, MD, PhD,

Director