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Combination therapy with transcranial magnetic stimulation and ketamine for treatment-resistant depression: A long-term retrospective review of clinical use

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ABSTRACT

Background: Both transcranial magnetic stimulation (TMS) and infused ketamine are recognized treatments for patients suffering from major depressive disorder (MDD). A novel therapy named combination TMS with ketamine (CTK) is introduced. This retrospective review examined the safety and clinical benefits of CTK in patients suffering from treatment-resistant depression (TRD) during the routine practice of psychiatry in a private clinic.
Methods: TRD patients (N = 28) received a coincident application of high-output TMS (30 minutes) with biomarker-determined ketamine infusions (20 minutes). Frequency of treatment was dependent on patient responsiveness (10–30 sessions). Clinical global impression (CGI) data was collected pre- and post-treatment and then two years later.
Results: The mean reduction in CGI severity for the patient group following CTK was 4.46 ± 0.54 at a 99% confidence interval and was deemed statistically significant using a paired t-test ($\alpha = 0.01$, $t = 22.81$ $p < 0.0001$). This reduction was sustained for two years following treatment completion and this remission was deemed statistically significant by a second paired t-test ($\alpha = 0.01$, $t = 27.36$, $p < 0.0001$).
Limitations: Retrospective review of a limited number of patients undergoing CTK in a clinical practice.
Conclusions: This clinical review indicated that CTK is an effective, long-term therapy (after two years) and can be used for TRD patients. The coincident administration of ketamine allowed for higher TMS intensities than otherwise would be tolerated by patients. Further studies for optimization of CTK are warranted.

1. Introduction

Treatment-resistant depression refers to a major depressive disorder (MDD) with a lack of clinically meaningful improvement to an appropriate course (adequate dose over 6–8 weeks) of at least two antidepressants from different pharmacological classes, prescribed for adequate duration, with adequate affirmation of treatment adherence (Little, 2009; EMA Guidelines, 2013). It is estimated that between 15% and 33% of patients will not respond to multiple interventions and therefore be classed as suffering from treatment-resistant depression (Little, 2009). The sequenced treatment alternatives to relieve depression (STAR*D) trial explored the effectiveness of alternative treatments for treatment-resistant depression patients and predicted that only a third of the 20 million Americans suffering from MDD would achieve remission (Warden et al., 2007). Continued depressive symptoms have been linked to social issues, a greater risk of suicide and mortality and ultimately results in increased health-care costs (Lépine and Briley, 2011; Kellar et al., 2016).

The cause of such depressive disorders remains unclear. However, it is commonly agreed that it relates to a system disorder affecting pathways between cortical, subcortical and limbic sites, along with the neurotransmitter and molecular mediators (Mayberg et al., 2005). Patients with unipolar depression have been shown to have prefrontal abnormalities, predominantly on the left and decreased neuronal activities in the dorsolateral prefrontal cortex (PFC) regions, as well as in the rostral anterior cingulate cortex (ACC) areas, closely connected to the dorsolateral PFC (Baeken and De Raedt, 2011).

Research has shown a strong negative correlation between the ACC

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and the dorsolateral PFC (Fox et al., 2012), whereby rTMS clinical outcome can be predicted by the degree of anticorrelation between functional MRI signals in the dorsolateral PFC and the subgenual ACC, which can potentially be used to facilitate personalized treatment (Cash et al., 2019). Llinás et al. (1999) presented the potential cause of various MDD disorders as a thalamocortical dysrhythmia, which is generally identified by abnormal oscillatory activity in the major neural circuit that links the thalamus and cortex. The symptoms that arise are dependent on the location of the rhythm disruption and these disruptions impair the normal communication between different regions of the brain.

Neuromodulation encompasses a number of techniques that alter the neural activity through a targeted delivery of a stimulus, such as electrophysiologic stimuli that are intended to alter network function. These techniques have been shown to be safe, non-invasive and efficient therapeutic methods for psychiatric illnesses, such as MDD.

Prefrontal repetitive transcranial magnetic stimulation (rTMS) repeated daily over 4–6 weeks (20–30 sessions) is approved by the US Food and Drug Administration (FDA) for the treatment of treatment-resistant depression (Perera et al., 2016). TMS is considered a well-tolerated, non-invasive therapy with relatively mild side-effects. TMS uses a specifically designed coil placed in contact with the head that eventually induces an electrical current in the cortex that alters local and remote electrophysiological activity. rTMS uses different frequencies of stimulation pulses to induce excitatory or inhibitory responses.

For therapeutic applications, the motor threshold (MT) has been used to guide the calculation of the patient-specific therapeutic TMS dosage. MT is a measure of the TMS intensity required to produce a peripheral motor response with TMS intensities being set at a given percentage of this value. MT is one way to assess cortical reactivity and it can be used to guide safe TMS dosing. Typically, MT is highly variable across individuals, but remarkably constant for a given individual (Mills and Nithi, 1997). A study by Johnson et al. (2012) indicated that stimulation at 120% of MT (unadjusted for scalp-cortex distances) was safe for a broad range of patients. TMS typically results in few side effects, though some patients can experience sensory phenomena, local discomfort or pain and headaches and these side effects are more prevalent at higher current intensities (Slotema et al., 2010).

Although the mechanisms of action are yet to be clearly defined, neuroimaging data from patients treated with rTMS have shown neural changes in the frontal and limbic regions associated with MDD (Teneback et al., 1999). More specifically, experimental evidence supports a link between the ACC and MDD. Kreuzer et al. (2015) targeted ACC stimulation with rTMS and patients showed significant improvement in their depression compared with butterfly rTMS or a sham stimulation. Moreover, it has also been posited by Paus et al. (2001) that the antidepressant response of rTMS over the dorsolateral PFC is dependent on the modulation of the ACC and therefore of its baseline activity. Overall it has been shown that pulsed magnetic fields can promote molecular changes in an abnormal brain circuit and correct topographical errors to improve synaptic and behavioral function, without inducing changes in the normal healthy parts of the brain (Rodger et al., 2012).

There are more than 10 studies (Class I-II) that support the efficacy of rTMS for unipolar depression (Lefaucheur et al., 2014). However, Berlim et al. (2014) completed a meta-analysis of 29 randomly controlled trials, in which 1371 patients suffered from major depression and showed that 29.3% of individuals responded to rTMS compared to 10.4% to a sham treatment.

The meta-analysis also showed that remission only occurred in 18.6% of patients responding to rTMS, compared to 5% of patients responding to the sham-treatment. This suggests the need for innovative advances to achieve greater efficacy in the treatment of treatment-resistant depression patients.

The N-Methyl-D-Aspartate (NMDA) receptor antagonist and dissociative anesthetic, ketamine, has been shown to act as a rapid antidepressant for depressive patients (Berman et al., 2000) and is now being used, on a limited basis, to rapidly reduce potentially lethal symptoms of depression, and apparently to lessen anhedonia (Lally et al., 2014). A systematic meta-analysis by McGirr et al. (2014) showed ketamine to be an effective short-term treatment of unipolar & bipolar depression, but highlighted the requirement of further studies to optimize dosing and treatment schedules. Ketamine offers rapid antidepressant relief within 4 hours post-infusion (Zarate et al., 2006). Although studies of NMDA receptor antagonists have shown the treatment to be rapid, the relief is brief in nature, relapse typically occurring within one week and most studies do not test for remission beyond seven days following treatment (McGirr et al., 2014; Newport et al., 2015). A double-blind study by Singh et al. (2016) demonstrated that a twice-weekly, fixed-dose treatment regime (0.5 mg/kg) for 4–6 weeks could induce and maintain robust antidepressant effect in the treatment-resistant depression population for a period of 15 days.

The typical fixed-dose ketamine dosage applied in studies (0.5 mg/kg per 40 minutes) relates to a peak plasma ketamine concentration of 70–200 ng/mL, which does not produce general anesthetic effects (surgical anesthesia (2000–3000 ng/mL) and are below the concentrations associated with awakening from ketamine anesthesia (500–1000 ng/mL) (Sanacora et al., 2017). A dose of 2 mg/kg by slow intravenous injection (IV) produces surgical anesthesia within 1–2 minutes, which may be expected to last for 5–10 minutes. Dissociative anesthesia is a form of anesthesia characterized by catalepsy, analgesia, and amnesia, during which the patient does not appear to be anesthetized and can swallow and open their eyes, but does not experience stimulation of the senses. One study demonstrated that the cataleptic anesthetic state induced by ketamine was accompanied by an alternating pattern of hypersynchronous delta wave bursts and low voltage/fast wave activity in the neocortex and thalamus (Miyasaka and Domino, 1968).

The predominant mechanism of action is by non-competitive antagonism of the NMDA receptor, but ketamine will also stimulate the cardiovascular system and interact with opioid receptors, monoamine, cholinergic, purinergic and adrenoreceptor systems, as well as having local anesthetic effects (Persson, 2010). The response of the patient is dependent on the dosage and can induce cataleptic, amnestic, analgesic and anesthetic actions.

The mechanism of action at a molecular level is still unclear, however one study proposes that ketamine decreased the connectivity in the amygdala and subgenual cingulate in MDD subjects and this connectivity was proportional to changes in glucose metabolism (Nugent et al., 2016). Many synapses (~50%) rely upon the amino acid glutamate (via its interaction with the NMDA receptors) as their primary neurotransmitter, and preclinical models of depression have implicated aberrant glutamatergic neurotransmission (Zarate and Niciu, 2015).

Despite recent advances with NMDA receptor antagonists, neuromodulation and other treatments of depression, a significant number of patients remain refractory and are unable to gain adequate sustained relief. This paper presents the novel therapy of combination TMS with IV ketamine infusions (CTK), where it is hypothesized that TMS temporarily interferes with the pathologic synchronization of anterior cingulate gyrus function, whilst ketamine affects neurotransmission.

Initial qualitative feedback from patients following the introduction of CTK to patients at the clinic indicated significant psychosocial recovery (Best, 2014, 2017). This retrospective paper explores the use of CTK in a clinical setting and examines the long-term treatment efficacy in terms of reducing depressive symptoms for patients with treatment-resistant depression.

2. Method

The present study is retrospective research designed to evaluate the results of an intervention provided solely for clinical, rather than investigational, purposes. Our aim was to explore the efficacy of CTK in a private clinic setting, by concurrently administering TMS with ketamine infusions to patients suffering from treatment-resistant depression. CTK was offered to established patients who had shown an inadequate

response to previous treatments at the clinic (including rTMS, ECT, vagus nerve stimulation (VNS), transcranial electrical stimulation (tES) as well as some treatments that took place off-site (including hyperbaric oxygen treatments, medications, ketamine infusions and alternative treatments, such as homeopathy).

Patients discussed CTK with family members, the family Pastor and the treating psychotherapists. Some patients discussed the therapy with other healthcare providers, reviewed medical literature or observed others who received CTK, to ascertain whether they would consent to the therapy. Most patients were already aware of, or had previously received, separate electromagnetic brain stimulation and/or ketamine infusions.

The sample group included 28 patients (aged 41.0 ± 15.6, 13 female) presenting primarily with either unipolar (n = 18) or bipolar (n = 10) depression with a variety of secondary diagnoses (including Obsessive Compulsive Disorder, anxiety, substance abuse or neuropathic pain). The demographic variables and clinical characteristics of the patient group are provided in Table 1.

The treatment was administered by a neuropsychiatrist (the author) with 14 years of experience of administering rTMS, along with an anesthesiologist or certified registered nurse anesthetist to administer ketamine. The TMS equipment used was Neotonus®, which is identical to the equipment sold by Neuronetics®. The ketamine used was Ketalar®, which is a Registered Trademark of PAR Sterile Products LLC.

All patients were evaluated throughout using the Clinical Global Impression scale (CGI), which was developed during clinical trials sponsored by the National Institute of Mental Health (NIMH) and provides a clinician-determined measure of psychopathology that takes into account the patient's history, psychosocial circumstances, behavior, symptoms and the impact of the symptoms on the patient's ability to function (Busner and Targum, 2007). CGI is a 3-item scale that measures illness severity (CGI-S), global improvement (CGI-I) and efficacy (CGI-E).

There is currently no standardized transdiagnostic measure for busy clinicians to apply and all evaluation methods offer both insights and limitations (Dunlop et al., 2017). The CGI severity scale (CGI-S) is amongst the most widely used of extant brief assessment tools in psychiatry for the evaluation of the efficacy of treatments for depressive disorders and therefore allows for a relatively objective measure of remission (Zaider et al., 2003; Murrough et al., 2013). However, the CGI scale does suffer from poorly defined scoring anchors and is subjective, since it expresses the doctor's general impression and measures unclear relationships amongst discriminants (Dunlop et al., 2017). However, the CGI scale does provide a relatively objective measure of the remission of symptoms.

Table 1
Demographic variables and clinical characteristics of the patient group (N = 28) that underwent the novel therapy of combination TMS with ketamine (CTK).

Demographic Variables (N = 28)	
N (%) female	13 (46%)
Age (years, mean ± s.d.)	41.0 ± 15.6
Age range (years)	21–70
Disease History	
Primary Diagnosis	
Unipolar Depression, N (%)	18 (64%)
Bipolar Depression, N, (%)	10 (36%)
Secondary Diagnosis	
Comorbid anxiety disorder, N (%)	13 (46%)
Comorbid Neuropathic Pain, N (%)	9 (32%)
Comorbid Substance Misuse/Abuse	16 (57%)
Treatment History	
History of prior treatment with ECT, N (%)	6 (21%)
History of prior treatment with TMS, N (%)	6 (21%)
History of prior treatment with VNS, N (%)	1 (4%)
History of prior treatment with antidepressants, N (%)	28 (100%)
History of inpatient hospitalization for depression, N (%)	13 (46%)
ATHF score (mean ± s.d.)	3.5 ± 0.8
ATHF range	3–5
CTK Treatment	
Baseline CGI score (mean ± s.d.)	6.1 ± 0.8
Number of CTK treatments received (mean ± s.d.)	20.8 ± 12.0

CGI-S is rated on a seven-point scale, with the severity of illness ranked from 1 (normal) through to 7 (most severely ill patients). The CGI-I gives an overall comparison of the patient's baseline condition with their current state and scores range from 1 (very much improved) through to 7 (very much worse). CGI-E provides an overall comparison of the patient's baseline condition to a ratio of current therapeutic benefit and severity of side effects.

This multi-subject clinical case study reports the results of a routine practice of medicine in a private clinic. All patients provided written informed consent for clinical treatment after receiving a complete description of CTK. The proposal for retrospective chart review was approved by an Institutional Review Board.

Of the 28 patients, 20 received either pre-treatment with rTMS (3–14 days, 3 rTMS sessions daily) or a priming rTMS treatment immediately prior to the main concurrent therapy sessions. This rTMS pre-treatment was used to familiarize patients with the treatment and alleviate any related uneasiness with prolonged continuous TMS. The biomarker for whether pre-treatment was required by patients was phobia as a behavioral trait. Eight patients did not require any pre-treatment or priming prior to CTK.

All patients then received CTK over the course of a 30-minute session, which delivered TMS (30 minutes) in combination with the NMDA receptor inhibitor, ketamine (20 minutes). The TMS head-coil was placed on the patient's head and focused mid-sagittally on the medial prefrontal area that overlays the ACC, i.e., Fz position on the international electroencephalography (EEG) 10–20 system (roughly corresponding to the boundary between Brodmann Areas 8 and 9). The output power to the head coil was set according to established safety guidelines. The TMS (1 Hz) was applied continuously for 30 minutes at a power output setting equivalent to 130% of MT.

Five minutes after the commencement of TMS, the ketamine infusions began. The IV ketamine infusion was delivered in a standard commercial formulation over a period of 20 minutes. A biomarker-dependent dosing strategy was applied, whereby ketamine was gradually titrated in small increments until the patient entered a mildly cataleptic state. Catalepsy refers to the nervous condition characterized by muscular rigidity and fixity of posture regardless of external stimuli, as well as markedly decreased sensitivity to pain. Titrations began at 20 mg, with an average dosage range of 0.4–2.3 mg/kg (full range from 0.2 - 4.7 mg/kg). Once the patient began to stiffen or posture, the ketamine infusions could be discontinued. Following the completion of the ketamine infusion, the TMS would continue for a further 5 minutes, after which the CTK procedure was complete.

It was deemed that the TMS stimulation location was sufficiently far from the motor cortex that values exceeding 130% of MT could be used, thus applying the most powerful coil output that a person could manage without significant pain. The incremental titration of ketamine until catalepsy was a crucial component of the CTK therapy. Its analgesic effect dissolved any painful effect and made it possible to apply TMS of unusually high intensity.

The frequency of CTK sessions was dependent on the treatment-responsiveness of the patient. Patients typically began with three CTK sessions per week, before tapering. Some patients were more responsive to the CTK therapy and required 10–20 sessions, whereas some patients required upwards of 30 sessions. An indication of the variability of previous depressive treatment responsiveness of these patients is provided by the antidepressant treatment history form scores (ATHF) provided in Table 1. The ATHF scores for the patients in this study ranged between three and five, whereby a score of three is the threshold for considering a previous trial adequate and the patient resistant to that treatment (Sackeim, 2001).

To monitor the long-term efficacy of CTK for treatment-resistant depression patients, the severity of symptoms were monitored using CGI evaluation at different times; pre-treatment (T_1), post-treatment (T_2)

and two years following the completion of treatment (T_3). The comparison of CGI-S and CGI-I data over time provides a relatively objective measure of remission of depression symptoms.

This study had two objectives; The first objective was to establish whether CTK resulted in a reduction in CGI-S values for patients (A comparison of CGI-S data at T_1 and T_2). The second objective was to establish whether CTK resulted in a sustained reduction in CGI-S values for patients after two years following the completion of treatment (A comparison of CGI-S data at T_1 and T_3).

The statistical significance of any changes in patient CGI-S values over time were evaluated using a paired t-test at a significance level, α, of 0.01. The first null hypothesis, H_0, states that the pairwise difference in patient CGI-S values between T_1 and T_2 is equal (H_0: $\mu_{d(T1,T2)} = 0$). The second null hypothesis stated the pairwise difference in patient CGI-S values between T_1 and T_3 is equal (H_0: $\mu_{d(T1,T3)} = 0$). These hypotheses were tested using paired t-tests ($\alpha = 0.01$) and confidence intervals (CI) were evaluated at 99%.

3. Results

All patients (N = 28) started and completed the entire CTK program and 2 year follow-up, with no drop-outs. All patients were monitored on a quarterly basis following CTK therapy completion. CGI values for all patients (N = 28) were determined at three time points, T_1, T_2 and T_3.

All patients at T_1 had a CGI-S of between 5 and 7 ($\mu_1 = 6.1$, $\sigma_1 = 0.8$), which translates to markedly, severely or most-severely ill patients. Figure 1 presents the mean CGI-S values, μ_1 μ_2 and μ_3 and standard deviations, σ_1, σ_2 and σ_3, for the patient group (n = 28) as calculated at T_1, T_2 and T_3, respectively.

There was a mean reduction in the CGI-S group value from 6.1 to 1.7 ($\sigma_1 = 0.8$, $\sigma_2 = 0.7$) at T_1 and T_2, respectively. This reduction in CGI-S value following treatment was sustained for two years, since the mean CGI group value at T_2 and T_3 was 1.7 and 1.4 ($\sigma_2 = 0.7$ and $\sigma_3 = 0.5$), respectively. The mean CGI-I value for the group at T_2 and T_3 were 1.3 ($\sigma = 0.6$) and 1.0 ($\sigma = 0.2$), respectively, showing that the patients were 'very much improved' following treatment and two years afterwards. The mean CGI-E value for the group at T_2 and T_3 were 1.4 ($\sigma = 1.6$) and 1 ($\sigma = 0$).

To ascertain the statistical significance of the reduction in CGI-S value per patient following CTK, a two-tailed, paired t-test was performed. The number of patients (n) was 28, the degrees of freedom (n-1) was 27, the significance level, α, was 0.01 with an associated critical t-value of 2.771.

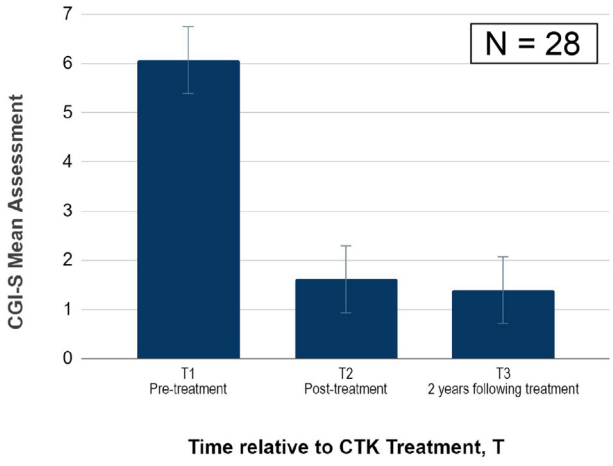

Fig. 1. Mean CGI-S score of sample group at times representing pre-treatment (T1), post-treatment (T2) and two years following treatment completion (T3). Bars represent respective standard deviations. Statistical significance of CTK efficacy was tested using paired t-tests. Statistically significant reduction in CGI-S following treatment (T1→T2: $\alpha = 0.01$, $t = 22.81$ $p < 0.0001$), which was sustained for 2 years following treatment (T2→T3: $\alpha = 0.01$, $t = 27.36$, $p < 0.0001$).

The first null hypothesis, H_0, was that the pairwise difference in patient CGI-S values between T_1 and T_2 is equal (H_0: $\mu_{d(T1,T2)} = 0$). The p-value represents the probability that the results from the sample were due to chance. The t-value for the sample data was calculated as 22.81 giving rise to $p < 0.0001$, which is lower than the significance level $\alpha = 0.01$. In this case, $p < \alpha$ and therefore the reduction in CGI-S value following treatment was deemed statistically significant. The efficacy of this treatment was confirmed with a standard mean reduction ($\mu_{D(T1,T2)}$) in CGI-S value of 4.46 $\pm$ 0.54 at a 99% confidence interval (CI). This result affirms the significant decrease in CGI-S value achievable with CTK for treatment-resistant depression patients.

To ascertain the statistical significance of the sustained reduction in CGI-S value per patient after two years post-treatment, a second paired t-test was performed. The second null hypothesis stated that the pairwise difference in patient CGI-S values between T_1 and T_3 is equal (H_0: $\mu_{d(T1,T3)} = 0$). The t-value of the sample data was calculated as 27.4 giving rise to $p < 0.0001$, thus the reduction in CGI-S value from T_1 and T_3 was statistically significant. The long-term efficacy of this treatment was confirmed with a standard mean difference in CGI-S values ($\mu_{D(T1,T3)}$) of 4.68 $\pm$ 0.47 at a 99% CI. This result affirms the long-term remission (up to two years following treatment) achieved with CTK for treatment-resistant depression patients.

3.1. Patient vignettes

In addition to the quantitative data, there was also significant qualitative data from patient feedback, regarding their symptoms and improvements in their daily life following CTK.

Patient A compared CTK with other treatments: "*I had* 38 ECT *treatments over a period of time and, while effective, they were taking a toll on me. rTMS was effective, but it took many treatments before the results persisted. I tried CTK and found it more effective than just rTMS. I need fewer treatments and can go longer between them*". Patient B commented on the long-term benefits of the treatment: "*Maximum prolonged benefit* (with rTMS alone) *occurred when I would be treated everyday or every other day for a number of weeks or months…*(but with CTK) *the positive effect of the treatments would last longer. Two or three treatments a week for a month could provide an elevated mood for up to six months.*"

Patient C described, "*Compared to the gradual onset of rTMS, the effects of CTK are rapid: the alleviation of my symptoms of depression are felt with the initiation of treatment and continue during the days after treatment, leaving me with pre-depression cognitive abilities. CTK treatments are not as taxing on the body and the process is much more enjoyable.*" Patient C also described the CTK process: "*During the CTK infusion there is an almost immediate absence of the mental pain from depression and anxious thoughts. I feel in a state of calm that is similar to, but more pronounced than, meditation. Over the course of the infusion this feeling gradually gives way to a mental fog. This fog is not unpleasant, but it does feel like my powers of cogitation are dimmed. The second phase entails the lifting of the fog. Over the next two days post-treatment, the fog and fatigue continue to disappear, leaving me at peak levels of mental endurance and completely free of depression symptoms. My mind feels clean and refreshed; absent is the mental and physical fatigue that comes with rTMS alone. It's as if the benefits of a full week or more of rTMS are packed into a single day of CTK.*"

4. Discussion

This group study, to our knowledge, is the first to examine the long-term clinical benefits of combining two established depression treatments, TMS and ketamine infusions, for patients suffering from treatment-resistant depression. This clinical study has demonstrated that depressive symptoms, as determined with the CGI severity scale, could be markedly reduced following CTK. The paired t-test confirmed that this reduction was statistically significant and that CTK is an effective therapy for otherwise refractory patients.

Most importantly, the second paired t-test has also demonstrated that this reduction in depressive symptoms could be sustained in this cohort of patients for a period of two years following treatment.

CGI-E provides an overall comparison of the patient's baseline condition to a ratio of current therapeutic benefit and severity of side effects. According to CGI guidelines the CGI-E values at T_2 (1.4) and T_3 (1), related to marked therapeutic effect with no side effects. These low CGI-E values obscure the presence of any side-effects, due to the dramatic therapeutic effect experienced by patients. Complaints and side effects experienced during CTK therapy included occasions of transient nausea, transient vertigo, transient local discomfort, and the inconvenience of fasting. Most of the patients had transient psychedelic experiences and they came to see these as benign and sometimes helpful. The psychedelic experiences were dose-dependent and tended to be visual, such as visual distortions. At increasing doses the internal imagery became more captivating - such as seeing their dreams more vividly. At the highest doses, patients describe not only tolerating the psychedelic experience, but using them to move past psychological roadblocks or transcend patterns that had become automatic. Dakwar et al. (2014) showed that ketamine infusions can induce dose-related transient psychedelic experiences, including dissociative phenomena, as well as alterations in consciousness similar to those engendered by serotonergic hallucinogens, which can be considered beneficial by patients. Despite some side effects experienced, they did not interfere significantly with the patient's functioning. Overall, CTK was well-tolerated by the patients and it should be noted that no treatment-limiting adverse outcomes occurred during or after treatment.

Patient vignettes also provided insight into the tolerability, efficacy and long-term benefits of CTK. Patients described the perceived efficacy and need for fewer treatment sessions in order to gain longer term results. Importantly, many patients in this study had experienced other treatment options, but had remained refractory until CTK treatment (as indicated in Table 1).

CTK delivers TMS treatment at a relatively low frequency (1Hz) compared to the higher frequencies (10–20 Hz) typically applied for clinical treatments of depression (Perera et al., 2016). Low frequency TMS typically relates to an inhibitory effect and therefore decreased cortical excitability (Caparelli et al., 2012).

Despite dozens of studies across nearly two decades of research, there is no definitive guidance on ketamine dosage, session frequency and duration and administration route of ketamine (Andrade, 2017). This study applied an average ketamine dosage range of 0.4–2.3 mg/kg and used the biomarker-based predictive dosing strategy of ketamine, whereby the biomarker was patient catalepsy. It would be important to further assess the suitability of catalepsy as a biomarker for adequate ketamine dosing and to ascertain whether TMS influences the time, at which the cataleptic state is reached by a patient.

The analgesic effect of ketamine appeared to increase the tolerability of TMS, which allowed the output power to the head coil to be raised to unusually high intensity. The painful side effects that can occur during TMS at high intensities were abated when the patient experienced conscious sedation/moderate anesthesia during the simultaneous ketamine infusion. This is particularly relevant since side effects contribute to drop out rates in clinical studies (Rossi et al., 2009).

With the addition of ketamine infusions, this study used fewer and shorter TMS sessions than standard treatment protocols that utilize rTMS alone. The extended remission of symptoms for all partaking patients following CTK treatment, demonstrates the significant role that both TMS and ketamine play in the therapy. Individually, both treatments have been shown to offer some patients relief from treatment-resistant depression symptoms, but without offering extended remission. The mechanism of action of CTK is currently unknown. It is proposed that TMS causes the ketamine to have a greater effect than usual, which in turn allows for a higher TMS intensity, thus heightening the network effects. It is hypothesized that TMS temporarily interferes with the pathologic synchronization of anterior cingulate gyrus function, whilst ketamine affects neurotransmission leading to a synergistic effect and more tolerable treatment. A previous study has shown that the ACC area of the brain is a putative biomarker of treatment response to ketamine during a cognitively demanding task and TMS has been shown to modulate the ACC connectivity (Salvadore et al., 2010).

Notably this study was a retrospective analysis of treatment results obtained with a novel therapy, CTK, during the routine practice of medicine in a private clinic. The statistically significant improvements observed now warrant further controlled, prospective studies into CTK; Future work will further evaluate results from the point of view of efficacy, safety, predictors of response, effect size etc. The efficacy of CTK could also be directly compared with the efficacy of high-intensity rTMS or high-dose ketamine infusions alone.

Based on previous studies, the electrode position over the ACC may have been critical to achieving the positive modulation of the area. Future studies might utilize functional brain imaging, functional near infrared spectroscopy and EEG on a serial basis as a direct measure of the abnormality and subsequent normalization of the thalamocortical circuit. Such an aim would be highly compatible with the Research Domain Criteria initiative (rDOC) launched by the NIMH. The rDOC seeks to identify neurobiological dimensions that underlie mental disorders so that individuals at risk for developing a particular disorder can be identified and effectively treated prior to its emergence.

4.1. Limitations

This is a retrospective review of a limited number of patients undergoing the combination therapy of TMS with ketamine in a clinical practice. While the results clearly indicate a favorable outcome both by clinical evaluation and from the CGI values pre- and post-treatment, further work is indicated, as mentioned above. Indeed a comparison with the efficacy of rTMS or high-dose ketamine infusions alone would further validate the advantages of the combination therapy, especially of its long-term efficacy. Finally, the CTK treatment was only offered to the most extremely ill patients who attended the clinic and had not achieved satisfactory relief in spite of good treatment at both this clinic and others.

5. Conclusions

This study examined the clinical benefits of combining two established depression treatments, TMS and ketamine infusion, for patients suffering from treatment-resistant depression. The impressive and statistically significant reduction in CGI-S values for 28 participating patients following CTK (4.46 ± 0.54) indicates a synergistic effect. Furthermore, results confirmed the long-term remission (two years following treatment) achieved with CTK for patients with depressive syndromes.

It is important to note that CTK has offered long-term efficacy for treatment-resistant depression patients where other treatments had failed. It combines the rapid onset of relief, commonly experienced with ketamine infusions, with the longer term benefits observed with TMS treatments. Higher intensities of TMS were achievable through the conscious sedation/moderate anesthesia resulting from the ketamine infusion, which in turn resulted in high treatment efficacy and reduced drop-out from TMS. The requirement of fewer treatment sessions further improves patient adherence to the CTK protocol leading to the effective treatment-resistant depression treatment with lasting remission. The significant, long-term favorable results shown in this study justify further evaluation for the purpose of optimizing CTK, as well as detailing its mechanisms of action.

Declarations

Author contribution statement

Steven D. Best: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Dan Pavel: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Natalie Haustrup: Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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