



## RAPID RELIEF OF TREATMENT RESISTANT DEPRESSION BY FACILITATED KETAMINE INFUSION: A PRELIMINARY REPORT

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### Abstract

By combining transcranial magnetic stimulation (TMS) with intravenous ketamine therapy, we sought to increase the therapeutic value of TMS and, at the same time, to improve the efficacy of intravenous ketamine therapy among depressed patients previously classified as non-responders. In this preliminary report, we provide evidence for a new and much more reliable method of treating patients with treatment resistant depression. Twenty-eight patients with various degrees of treatment unresponsive depression were treated with a combination of TMS and ketamine infusion. Of these patients, twenty received pretreatment for 3 days to 2 weeks involving intensive (thrice daily) rTMS treatment administered 6 or 7 days/week or priming TMS treatment immediately prior to the combination TMS-ketamine infusion combination therapy. Eight patients received neither pretreatment nor priming. All of the 28 patients who did fully participate in the first month of treatment experienced relief of psychiatric symptoms, and showed significant psychosocial recovery. In contrast to previous studies examining ketamine or rTMS individually, the positive outcomes presented here suggest a synergistic effect of the combination therapy of TMS and ketamine infusion.

Key words: *Treatment-resistant depression; Transcranial magnetic stimulation (TMS); Transcranial Electrical Stimulation (tES); NMDA-R antagonist; Ketamine infusion; Neuromodulation; Synergistic effect; Remission*

### 1. INTRODUCTION

#### 1.1. Scope of the Problem

Neuropsychiatric disorders strike millions of people worldwide. Many patients do not respond to traditional treatments for these disorders. This is particularly true of major depression, which is associated with substantial economic burden. For instance, results of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study predict that only a third of the 20 million Americans diagnosed with a major mood disorder will achieve full remission, with a significant patient population remaining refractory to pharmacologic interventions even after well targeted attempts at treatment with trials of a variety of

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antidepressant medications (National Institute of Mental Health; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Similarly, a third of the United States population suffers from depression-related chronic, non-remitting emotional pain. By some estimates 40% of the population experiences chronic pain when somatic and emotional sequelae are combined (Institute of Medicine of the National Academies of Science, Report Brief, June 2011).

## **1.2. Options for treatment resistant depression**

The application of novel brain stimulation techniques to treat depression, other neuropsychiatric disorders, and “somatic pain” is a new and rapidly growing field. Among these techniques, transcranial low voltage electrical stimulation (tES) and transcranial magnetic stimulation (TMS) are emerging as promising approaches because of their relative ease of use, safety, and neurobiological effects (Gersner, Kravetz, Feil, Pell, & Zangen, 2011; Muller, Toschi, Kresse, Post, & Keck, 2000; Walter, 2011). TMS appears to be more potent than transcranial low voltage electrical stimulation (Holtzheimer & Mayberg, 2012; Loo et al., 2012; Walter, 2011). Unfortunately, TMS is limited by the need for a substantial period of rigorously scheduled treatments (daily for 4-6 weeks), which can create a significant human burden in terms of delayed onset of relief, time, and money. These limitations often result in poor patient compliance (O’Reardon et al., 2007). Even when we accelerate the process by treating more times per day, the outcome of rTMS treatments is less than satisfying (Anderson et al., 2006; Holtzheimer et al., 2010). Although some of the inconvenience is mitigated by this acceleration, the response and remission rates achieved are about the same (Anderson et al., 2006; Holtzheimer et al., 2010).

The use of conventionally applied rTMS has been variously reported to produce a significant response in 41% of patients (IDS-SR outcome) and remission in 24%-29 % of patients (IDS-SR outcome) (Allan, Herrmann, & Ebmeier, 2011; Carpenter et al., 2012). The same application of rTMS was reportedly somewhat less effective in treating severe depression (Cusin & Dougherty, 2012). Treatment resistance is an important factor in predicting the likelihood of response to rTMS—the more resistant a patients’ illness has been to well applied medication protocols, the less likely that rTMS will be helpful (Lisanby et al., 2008). Because of this finding, conventional rTMS has been positioned as a treatment for people who have not responded to one adequate trial of medication. In the form in which it is typically available in the USA, rTMS is not currently seen as a treatment for people with multiple treatment failures. Nevertheless, rTMS has been found to have beneficial effects on overall brain function in experimental studies both in individuals who are ill as well as in those who are “well” (Chang et al., 2010; Gersner et al., 2011; Lou, Luber, Stanford, & Lisanby, 2010; Muller et al., 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Rossi et al., 2001; Snyder et al., 2003; Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010).

A variant of TMS called “deep TMS” was recently approved by the U.S. Food and Drug Administration because it was apparently capable of causing a significant response in 36.7% of patients in treatment-resistant depression, compared with a response rate of 20.5% in the control group, and causing remission in about 30.4% of patients with treatment-resistant depression compared with a remission rate of 14.5% in the control group (source was a press release posting by the manufacturer in April 2012 (Globe Newswire, 2012), see also Bersani et al. (2013). Thus, antidepressant medications and commonly used neuromodulation protocols appear to be about as effective as the so-called placebo response of approximately 40% (Fava, Evins, & Dorer, 2003; Rutherford & Roose, 2013; Rutherford, Rose, Sneed, & Roose, 2013).

In addition to techniques such as external neuromodulation, many pharmaceutical agents are currently available to treat neurological disorders in outpatient settings. However, these pharmaceutical agents are limited in their effectiveness and also by their significant side effects. For example, many of these medications are known to cause light-headedness, depression, insomnia, weight change, sexual dysfunction, cognitive dysfunction, weakness, fatigue, tinnitus, hallucinations, and other side effects that severely limit their use in the clinic.

Recently, interest has grown concerning the use of novel glutamatergic drugs (Lapidus, Soleimani, & Murrrough, 2013; Pankevich, Davis, & Altevogt, 2011) including the NMDA receptor antagonists to treat neuropsychiatric disorders (Preskorn, 2012). NMDA inhibitors are a class of psychopharmacologic agents that work to antagonize or partially inhibit the action of the *N*-methyl-D-aspartate receptor (NMDA-R). The state of anesthesia they can induce is referred to as dissociative anesthesia.

One particular NMDA inhibitor, ketamine, has been shown to be effective in treating depression in patients with bipolar disorder who have not responded to antidepressant medications (Preskorn, 2012). In patients with major depressive disorder and bipolar depression, ketamine can produce a rapid antidepressant effect, acting within 2 hours as opposed to the several weeks often needed to achieve a response with typical antidepressants. When used alone, ketamine appears to provide 4-7 days of relief from suicidality; however, ketamine does not appear to provide lasting relief from suicidality or depression (Murrrough et al., 2013; Preskorn, 2012). Similarly, ketamine is effective for pain relief when administered in highly complicated infusion programs to patients with severe pain syndromes like CRPS/RSD (Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy); however, it unfortunately has no particular utility for effecting psychosocial rehabilitation (Sigtermans et al., 2009).

Hence, the primary goal of the present study is to identify a therapy that will provide a greater likelihood of lasting successful results than has been achieved with ketamine or TMS alone, while hopefully reducing the undesirable adverse effects of the conventional pharmacopoeia (Cazzoli et al., 2012; Gersner et al., 2011; Wang et al., 2011).

### **1.3. Scientific Rationale**

In the N-back test, patients are presented with a consecutive series of stimuli and asked to respond when a given stimulus was presented N steps previously, where N is a number of steps, usually 1-3. The N-back test places a heavy cognitive load on the working memory system, which is involved in depression (Salvadore et al., 2010). Salvadore and colleagues showed that patients who exhibited the least activation of the perigenual anterior cingulate cortex (pgACC) during the N-back task also showed the most improvement in depression symptoms after ketamine administration. In addition, functional connectivity between the pgACC and the left amygdala was negatively associated with depression symptom reduction, suggesting that synchronization of this circuit may play a role in maintaining depression (Salvadore et al., 2010). We hypothesized that TMS temporarily interferes with the pathologic synchronization of anterior cingulate gyrus function and that this interference could make combined ketamine/TMS treatment a very useful therapy in the everyday toolbox at the clinic (Allen, Pasley, Duong, & Freeman, 2007; Briggs & Usrey, 2008; Esser, Hill, & Tononi, 2005; Fuggetta & Noh, 2013; Johnson, Hamidi, & Postle, 2010; Massimini, Ferrarelli, Sarasso, & Tononi, 2012; Sherman, 2007; Thut et al., 2011).

## **2. METHODS**

All patients (15 male, 13 female) gave informed consent (see Table 1). The combination therapy was discussed with family members, a few times with the family Pastor, and any psychotherapists treating the patients. Relevant data were gleaned retrospectively from patient medical records, and IRB approval was obtained from an independent review board. The combination therapy was provided concurrently by the author, a neuropsychiatrist with 14 years of experience administering TMS, and an anesthesiologist or certified registered nurse anesthetist. This combination therapy was offered to established patients who had shown an inadequate response to previous treatments at the clinic (including rTMS, vagus nerve stimulation [VNS], transcranial Electrical Stimulation [tES]), and off-site treatment in other

clinics ([ECT], hyperbaric oxygen treatments, medications including more traditional ketamine infusions, and alternative treatments such as homeopathy). Some of the patients had been fully treatment-resistant to their previous treatments, while some had only been able to maintain stability from active illness and fragile remission at the expense of regular clinic visits. Most patients were already aware of electromagnetic brain stimulation, and some had also experienced ketamine treatment in other clinical settings. The patients were informed of the new combination therapy and how it would make their everyday schedule lighter by adding ketamine infusions to the cocktail of treatments they were already receiving. Some patients discussed the idea with other healthcare providers and some reviewed medical literature, while others observed the treatment of other patients from a distance in order to develop an understanding of whether they wanted to be involved in the new combination therapy.

Patients were treated with TMS in combination with the NMDA Receptor inhibitor ketamine. The dosage for infused ketamine ranged from about 20 mg at the beginning, to about 300 mg, delivered in a standard commercial formulation within the time-course of the TMS treatment—dosage was individually tailored for each patient in relation to response (see Table 2). The duration of the combination treatment ranged from approximately 20 minutes to about 120 minutes at an appropriate dosage level. Ketamine was infused within the course of a TMS treatment lasting approximately 60 minutes. The electromagnetic stimulation of the combination therapy was applied shortly before the ketamine was administered and was then continued during the infusion and for 5 minutes after the infusion was completed. In these patients with treatment-resistant depression, the TMS head-coil was directed toward the medial prefrontal area that overlays the anterior cingulate region. The frequency of the dose was generally 1 Hz and stimulation was continuous during the combination treatment.

*Table 1. Patient demographics*

Patient ID	Age	Gender	Primary Dx	Secondary Dx
D23	44	Female	Unipolar Depression	PTSD, Fibromyalgia
D26	23	Male	Bipolar Depression	Substance Abuse
D3	23	Female	Unipolar Depression	ADD
D6	27	Female	Bipolar Depression	None
E11	30	Male	Bipolar Depression	Tic Disorder
F20	60	Male	Unipolar Depression	ADD
F8	71	Female	Unipolar Depression	Anxiety
J2	31	Female	Bipolar Depression	None
M10	26	Female	Unipolar Depression	Complex Regional Pain Syndrome
O12	35	Female	Unipolar Depression	Epilepsy
O19	35	Male	Unipolar Depression	Substance Abuse
O25	35	Male	Unipolar Depression	Panic Disorder
O33	45	Male	Bipolar Depression	Substance Abuse
P13	70	Male	Bipolar Depression	Chronic Pain
P14	65	Male	Unipolar Depression	ADD, Alcohol Abuse
P30	65	Female	Unipolar Depression	Fibromyalgia, Back Pain
P7	35	Female	Unipolar Depression	Multiple Head Injuries
Q34	42	Male	Unipolar Depression	ADHD, Head Injuries, Back Pain, Substance Abuse
S9	45	Male	Bipolar Depression	None
T17	30	Female	Unipolar Depression	PTSD, Substance Abuse
T32	21	Male	Unipolar Depression	OCD, Substance Abuse
U1	30	Female	Unipolar Depression	Generalized Anxiety Disorder
U36	50	Male	Unipolar Depression	Panic Disorder
V15	40	Male	Bipolar Depression	
V29	30	Male	Bipolar Depression	Past Substance Abuse
Y24	66	Male	Unipolar Depression	
Y27	25	Female	Bipolar Depression	ADD
Y4	50	Female	Unipolar Depression	ADD

Table 2. Treatment and outcome data.

Patient ID	Total Treatments	Ketamine Dosage Range (mg)	Mean Ketamine Dosage (mg)	Outcome	Overall Response
D23	27	20-160	98.0	Off pain medication, calm, more active, experienced severe nausea	Excellent
D26	9	25-120	67.8	Returned to college, got married	Excellent
D3	13	30-100	65.4	Entered graduate school, ended abusive relationship	Excellent
D6	32	33-185	77.2	Entered graduate school, moved out of family house	Excellent
E11	23	25-330	230.4	Requires fewer medications, calm, in school	Good
F20	18	25-150	110.6	Depression remitted, attention improved	Excellent
F8	16	25-180	97.5	Back to work and active family life	Good
J2	15	25-190	94.3	Returned to home life and active parenting	Good
M10	40	25-215	180.1	Entered trade school	Excellent
O12	19	28-110	89.1	Went back to work, then relapsed	Good
O19	31	45-250	118.4	Maintained sobriety, more active in family business	Excellent
O25	42	60-250	143.9	Entered graduate school, maintained sobriety, active in church life	Excellent
O33	6	50-125	87.5	More calm	Very Good
P13	13	25-300	181.2	Not using opioid narcotics, calm, walking well	Very Good
P14	36	45-80	55.3	Sober, repaired family and business life	Very Good
P30	12	35-70	55.8	Not using opioid narcotics, depression remitted	Excellent
P7	12	25-50	39.3	Not using opioid narcotics, back to church life	Excellent
Q34	16	25-250	131.9	Back to work	Excellent
S9	15	65-130	111.7	Back to work, repaired marital difficulties	Excellent
T17	9	25-160	106.7	Learned to read, entered college, sober	Excellent
T32	10	25-200	125.0	Back to college, sober	Excellent
U1	17	25-60	52.9	Back to college and work, sober	Excellent
U36	10	25-70	49.5	Repaired marital and family difficulties	Excellent
V15	24	25-70	53.8	Back to church and active family life	Excellent
V29	13	25-80	57.7	Entered graduate school, running family business, sober	Excellent
Y24	17	25-325	185.9	Back to work and active in family life	Excellent
Y27	32	30-150	94.0	Entered college, working part-time, sober	Very Good
Y4	55	35-325	154.5	Ended difficult marriage, more active	Very Good

### 3. RESULTS

Twenty-eight patients with depressive syndromes and various degrees of unresponsiveness to standard therapies were selected for the combination treatment. Our description of outcome is not derived from statistical analysis of standardized measurement tools. Our clinical style is one of continuously engaging the patient and their family or friends, as well as very frequent collaboration with other providers. So when we describe an outcome as partial or nearly-full remission, we are indicating that the patient has achieved both significant relief from discrete symptoms, and commenting on our perception of the objective signs noticed during the lengthy clinic contacts, and also from the vantage of psychosocial outcome. Significant positive outcomes were associated with the combination therapy of TMS plus ketamine when the combination was delivered on a weekly or bi-weekly basis. Most patients were able to slowly taper the treatment frequency and then stop treatment after having met their individual objectives for well-being; some returned to the combination treatment after a number of weeks or even months in the manner of ongoing widely spaced maintenance treatments (Table 1). Seven patients left treatment for reasons not related to the efficacy or tolerability of the combination treatment (one diagnosed with a fatal illness, two moved from area, one disliked the anesthetic procedure, and one each dropped out for finances, schedule issues, or desire to stay on opioids). Of the 28 patients who fully participated in the first month of this treatment, each responded in clinically significant ways, and had measurable psychosocial recovery that met the definition for partial remission or nearly full-remission (Table 2).

Our clinical work is guided by the idea that both symptom relief *and* stable psychosocial recovery should be considered as equally valid components in measuring outcome. We did not apply study measures such as rating scales because we were not conducting a study. Although the patients were fully aware that this was an un-tried approach, it was not created as a research project and it was not managed in that way at any time.

Obvious improvements in symptoms and psychosocial function were observed after about five treatments, which typically occurred over 3-5 weeks. However, positive outcomes were also achieved when treatments were administered at longer or shorter intervals---intervals were sometimes sporadic due to everyday schedule conflicts. Patients with depression showed the fastest response to treatment while several additional treatment sessions were usually needed before there were strong indications of recovery in patients with co-morbid chronic pain, especially when the pain was accompanied by severe depression and/or addiction. The positive response observed with this combination treatment, which tended to be robust, was obtained with negligible adverse effects; positive outcomes included: a return to work, rehabilitating a failing business, returning to college, getting married, reconciling a failing relationship, dependable recovery from substance abuse, and dramatic reductions in destructive doses of prescribed opioid narcotics. Each of the 28 patients who achieved positive results after receiving the combination therapy had previously failed all other treatments for their conditions.

### 4. DISCUSSION

Based on the findings from this open-label treatment, the combination therapy described here appeared to produce better outcomes while using lower doses of ketamine in combination with TMS. Because less ketamine was necessary, the treatment resulted in fewer side effects, and no adverse outcomes occurred. In addition, the need for less frequent TMS resulted in better patient adherence, which itself contributes to more positive outcomes. In fact, patients who initially experienced relief from the combination treatment tended to be motivated to receive additional treatments that provided lasting benefit.

#### 4.1. Limitations

This open-label treatment was offered to only the very most ill patients in my clinic during the months in question. These patients were chronically impaired and had not achieved satisfactory relief in spite of good treatment by other clinics and also while under my care. The patients tend to be unusual in that they have been referred in order to obtain neurophysiologic measures of brain health and illness. So, our patients may tend to have a greater level of hopefulness.

#### 4.2. Future Research Directions

In addition to using standardized methods to assess patient symptomatology, future research should evaluate EEG on a serial basis as a direct measure of normalization of thalamocortical circuit reactivity. 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 and cut across mental disorders so that individuals at risk for developing a particular disorder can be identified and treated prior to its emergence. Additionally a well defined control group with at least a single blinded study design would be beneficial. In the best of worlds, we would examine specific genetic, metabolic, neurophysiologic, and personality measures as we worked to discern the reasons for why such a blunt procedure works uniformly for so many different types of suffering (Liu, Franaszczuk, Crone, Jouny, & Lenz, 2011) and how we can use this opportunity to interrupt a disease process and re-direct nervous function to a robust well-state. The factors to consider for evaluating, intervening, and treating are stunningly complex.

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