

## **Long-term review of clinical use of combination therapy with TMS & ketamine in depressive illness**

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**Background:** Repetitive Transcranial Magnetic Stimulation (rTMS) is used to treat major depressive disorder and bipolar depression. However, patients require more than 25 sessions for only small decrements in suffering. The NMDAR antagonist, ketamine, is used on a limited basis to rapidly reduce potentially lethal symptoms of depression. However, clinical improvements are temporary in nature. The combination of TMS & ketamine offers a synergistic effect and has proven to be invaluable in treating otherwise treatment-refractory illness.

**Method:** Clinical case series. Participants: 128 TRD patients attending a private clinic. Intervention: Some patients received pre-treatment of rTMS (3-14 days, 3 rTMS sessions daily). Coincident application of TMS (25 - 40 minutes) applied with ketamine infusions (15-30 minutes, 0.5-5.0 mg/kg). Combination therapy continued on average for one treatment every 12 days (27 treatments). Outcome: CGI data and SPECT imaging of brain collected pre- and post-treatment. CGI provides a relatively objective measure of remission. SPECT imaging depicts changes in regional brain perfusion.

**Results:** Reduction in CGI-S from 5.7 to 1.7 ( $\sigma = 1.9$ ) following treatment. SPECT imaging indicated significant improvement in perfusion within brain 14 months following treatment. Combination therapy shown to create semi-permanent forms of remission (based on original study of 28 patients that began 7 years ago). Mechanisms of action are yet to be determined.

**Conclusion:** Combination therapy offers long-term efficacy for TRD patients, where other treatments failed. Combination therapy results in lower doses of ketamine and fewer sessions of TMS, thereby reducing side effects and improving patient adherence to treatment plan.

# Long-term Review of Clinical Use of Combination Therapy with TMS & Ketamine in Depressive Illness

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## Abstract

- Transcranial Magnetic Stimulation (rTMS) and the NMDAR antagonist, ketamine, are used individually to treat depressive illnesses.
- However, patients require numerous treatments for only small decrements in suffering and any improvements are temporary in nature.
- Combination therapy of TMS & ketamine offers a synergistic and long-term effect and has shown to be invaluable in treating otherwise treatment-refractory illness.

## The Problem:

### Treatment-Resistant Neuropsychiatric Conditions

#### The Cause:

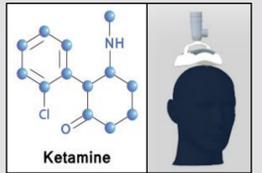
- Putatively related to a thalamocortical dysrhythmia
- Involving abnormal function of the Anterior Cingulate Cortex (ACC)
- And abnormal function of remaining limbic system

## The Hypothesis:

### Combination Therapy of TMS & Ketamine

Administration of TMS to medial prefrontal area (focused at Fz on EEG 10-20 system) is apparently affecting limbic system, while a patient receives therapeutic doses of ketamine.

- Enhanced response to treatment
- Synergistic effect that improves normal function
- Suffering ↓ and Quality of Life ↑



## The Study:

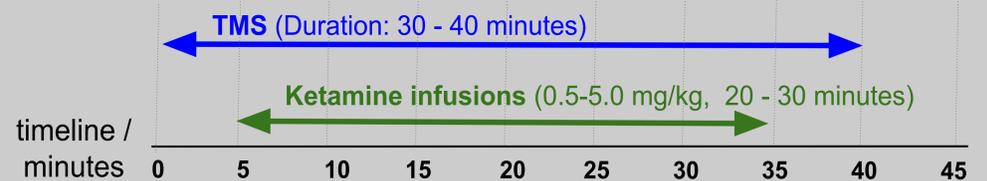
**N:** 128 TRD patients  
Of which, long-term data also presented from 28 original patients from start of study 7 years ago

**Data:** CGI data in each case  
Before & After SPECT imaging of brain in some cases

**Pre-Treatment:**  
Depending on severity of illness, patients may undergo pre-treatment of TMS:  

- 3-14 days
- 3 sessions daily

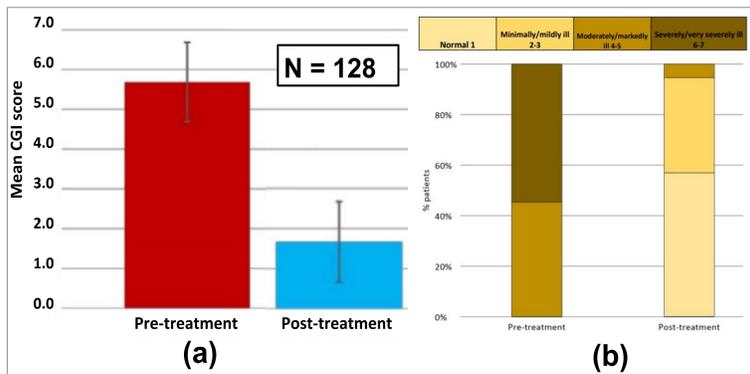
## The Combination Therapy:



**Dosing:** Gradually titrated upward until patient enters mildly cataleptic state  
**Frequency:** Dependent on severity of illness. Begin with 3 sessions / week before tapering. Mild cases: 10-20 sessions Severe cases: ~30 sessions

## Clinical Global Impression (CGI)

CGI is a relatively objective measure of remission  
Note: this is not a "blinded" assessment



Statistically significant reduction in CGI-S from **5.7 to 1.7** ( $\sigma=1.9$ ) following treatment

Figure 1: (a) Mean CGI score and (b) Frequency distribution of CGI score pre- and post-treatment (3 months after leaving program). Bars represent standard deviation.

## Example of SPECT Imaging of Brain

- Single Photon Emission Computed Tomography
- Depicts regional cerebral perfusion

### Pre-Treatment

### 5 months after 30 TMS/Ketamine treatments

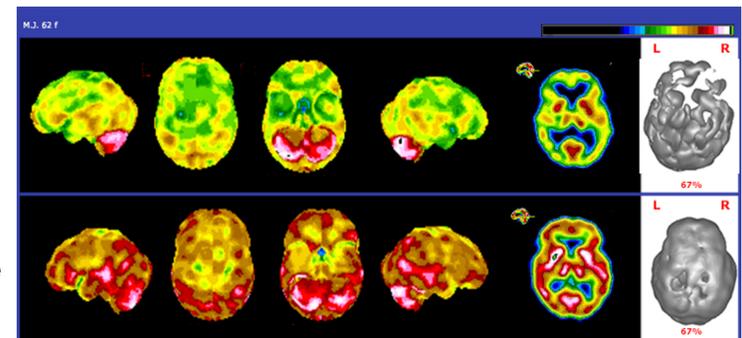


Figure 2: Five months after treatment with combination TMS / ketamine infusion (30 sessions) a marked improvement in perfusion is noted across the board in cortical and subcortical structures. This corresponded to a dramatic clinical improvement sustained at 2½ year follow-up.

## Long-Term Efficacy

Sustained CGI reduction 2 years after combination therapy indicates long-term remission. Data from original 28 patients.

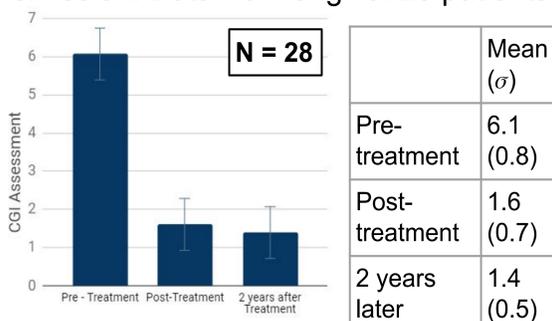


Figure 3: Mean CGI score pre- and post-treatment and 2 years after completion of treatment. Bars represent standard deviation.

## Impact of Our Work:

- Successful long-term outcomes, where other treatments fail
- When TMS applied with ketamine:
  - Lower doses of ketamine & fewer TMS sessions required vs. monotherapy
  - Fewer side-effects
  - Leads to better adherence by patients to the treatment plan

## Future Work in Our Clinic:

- Functional Near Infrared Spectroscopy (fNIRS) and EEG to measure physiological responses to combination therapy in-situ during administration

## Summary:

- Statistically significant reduction in CGI from 5.7 to 1.7 ( $\sigma=1.9$ ) following treatment for N=128 patients.
- In cases where SPECT imaging was possible, the majority showed significant improvement of regional brain perfusion.
- Combination therapy shown to create long-term forms of remission; CGI remained at same reduced level for 2 years post treatment (based on original N=28 patients)

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