

Can the MADRS Measure Rapid Changes in Depressive Symptoms in Response to Esketamine Treatment?

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Introduction

Treatment-resistant depression (TRD) is defined by a failure to adequately respond to two or more courses of antidepressant treatment at adequate dosage and duration. TRD represents a serious and ongoing health problem globally. There is significant interest in determining how to measure the efficacy of rapid-acting antidepressant compounds in treatment-resistant depressed adult populations (e.g., Murrough et al, 2013), as well as in clinically depressed patients who are actively suicidal. Studies evaluating compounds such as ketamine, esketamine and other NMDA-receptor antagonists compounds typically use rating scales that were developed to assess mood state over weeks rather than hours, such as the Montgomery-Åsberg Depression Rating Scale (Montgomery, 1979).

There also appears to be a nonlinear response pattern present in esketamine treatment that presents a different profile than other antidepressant compounds. For example, in the STAR*D study and other large population studies, treatment effects appear generally linear and gradual (with, in some cases, 30% -50% of patients not responding at all) (Rush, et al, 2006). Unlike these studies, the response curve for esketamine is more pronounced and subject to increases in score before ultimately decreasing.

We analyzed the behavior of the MADRS scale total score and individual item level at critical time points in a trial of esketamine, ESKETIVTRD2001. This was a double-blind, double-randomization, placebo-controlled study of the efficacy of intravenous esketamine in adults with treatment-resistant depression. The visit schedule included screening, double-blind treatment, and post treatment (follow-up) phases. MADRS assessments took place at every visit and at pre-dose, 2 and 4 hours post-infusion, and at visits 3 and 6 where study drug or placebo was administered.

Objectives

To assess the efficacy of the MADRS to measure rapid therapeutic onset and to describe the response characteristics of esketamine, as reflected in the MADRS total and items scores.

Methods

A retrospective analysis compared mean MADRS total scores pre- and post-dose across each of three treatment groups. Analysis was conducted using SPSS 21.0 for Windows. Assessment of rate of change, as well as response was conducted. Individual MADRS items were then assessed for sensitivity to change.

Conclusion

Esketamine has a different response profile than other classes of antidepressants. It is apparent that the rapid onset of effect as well as response characteristics are significantly different than what may be expected in clinical trials with more traditional antidepressants (e.g., SSRIs, SNRIs, MAOIs or atypicals). The MADRS can effectively capture rapid change, but mood items appear to be more sensitive to change than both the reduced sleep and suicide items. Further research should be conducted to determine the impact of this compound on suicidality, as well as the differential effect on MADRS items.

Results

Treatment Response: Mean MADRS Total Score Change

Comparing the short-term changes in mean MADRS total scores pre- and post-dose by Visit 3 treatment group (placebo, 0.2mg/kg esketamine, 0.4mg/kg esketamine), all three groups showed an immediate reduction in mean score in the 2 and 4 hours following infusion, followed by some degree of total score increase over the following 3 days.

- The high dose (0.4mg/kg) esketamine group had the largest change in mean MADRS total score, with >50% score reduction followed by a small total score increase by visits 5 and 6.
- The low dose (0.2mg/kg) esketamine group had an initial reduction of ~50% by 4h post-infusion, which increased slightly by visit 6. Despite the small increase in scores, the 0.2mg/kg and 0.4mg/kg esketamine groups had mean MADRS total scores at visit 6 that represented ~40% reduction from the pre-dose mean scores.
- The placebo group showed a small initial reduction of ~15% after the 4h post infusion at visit 3, and this remained stable through visit 6.

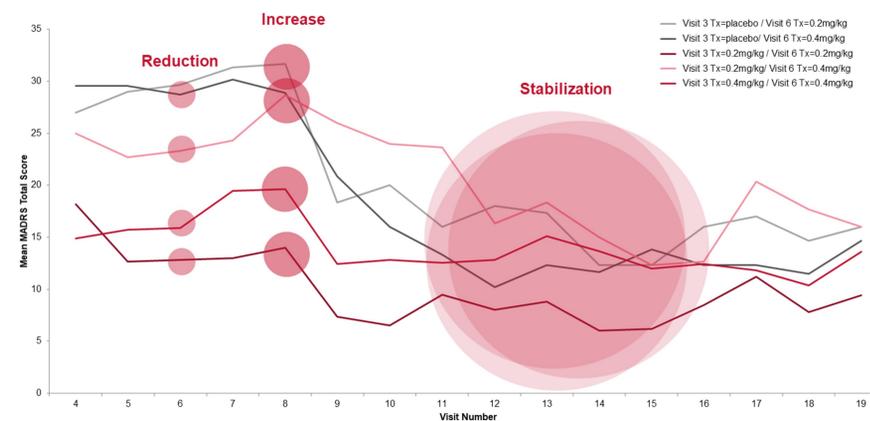


Fig. 1. Mean MADRS score by treatment group across visits.

Treatment Response: MADRS Items

As with the total scores, for most of the individual MADRS items, the mean scores in each group showed an initial drop, followed by at least a partial increase. For several items (Reported Sadness, Apparent Sadness, Suicidal Thoughts), the 0.4mg/kg esketamine group had a greater initial reduction in score, followed by a total score increase, compared to the 0.2mg/kg esketamine group, which showed a smaller initial reduction in score that remained somewhat stable or had a smaller increase.

- The largest overall improvements in scores from Visit 3 pre-dose to Visit 6 post-dose were in Reduced Appetite and Pessimistic Thoughts, with both the 0.2mg/kg and 0.4mg/kg groups showing >50% reductions. For Reduced Appetite (not assessed at 2- and 4h post-infusion) and Pessimistic Thoughts, the placebo group had negligible changes in scores through Visit 6.
- For Reported and Apparent Sadness, Inner Tension, Concentration Difficulties, Lassitude, and Inability to Feel, overall mean score reductions of 30-45% by Visit 6 were seen for both the 0.2mg/kg and 0.4mg/kg groups, compared to small to negligible (<20%) reductions in scores for the placebo group.
- The items that seem to have had the least treatment response from Visit 3 pre-dose to Visit 6 post-dose were Reduced Sleep and Suicidal Thoughts. Reduced Sleep had the smallest overall score changes, with ~25% reduction in the 0.2mg/kg group, ~20% in the 0.4mg/kg group, and no change in the placebo group. (Reduced Sleep was not administered 2- and 4h post-infusion.) Although both esketamine groups had >50% overall reductions in score for Suicidal Thoughts, the placebo group showed ~50% reduction in this item as well.

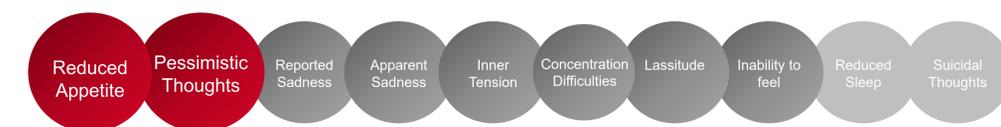


Fig. 2. Largest overall improvements in scores from Visit 3 pre-dose to Visit 6 post-dose were in Reduced Appetite and Pessimistic Thoughts.

References

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