

# A Double-Blind, Randomized, Placebo-Controlled, Dose Frequency Study of Intravenous Ketamine in Patients with Treatment-Resistant Depression

## BACKGROUND:

- Major depressive disorder is a highly prevalent illness with major limitations when it comes to treatment
- Up to 35% of patients fail to respond to drug therapy
- All existing antidepressants have a delayed onset of action
- Recent studies with single dose ketamine demonstrated a rapid onset of antidepressant effect (2-24 hours) but it also has a short duration of antidepressant effect (3-17 days)

## OBJECTIVE:

- Primary objective: To evaluate two dosing regimens, two or three times a week, of intravenous (IV) ketamine 0.5 mg/kg compared with placebo in sustaining initial antidepressant efficacy in patients with treatment resistant depression.
- Secondary objectives: To assess the onset of antidepressant response and the safety of repeated doses of ketamine in this population.

## METHODS

- Phase II, randomized, double-blind, placebo-controlled parallel design study • Study duration
- 165 patients were screened for eligibility and 68 were randomized into one of the four study groups
- Inclusion Criteria
  - 18 – 64 years of age who met DSM-IV criteria for recurrent major depressive disorder without psychotic features, confirmed by the Mini International Neuropsychiatric Interview
  - Qualifying valid depressive episodes assessed with the SAFER criteria
  - Inadequate response to at least two antidepressants (with at least one treatment failure in the current episode) assessed by medication history and Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
  - Score  $\geq 34$  on the 30-item Inventory of Depressive Symptomology
- Exclusion Criteria
  - Primary DSM-IV diagnosis of OCD, PTSD, an eating disorder, or a prior history or current diagnosis of a psychotic disorder, bipolar disorder, mental retardation, borderline personality disorder, mood disorder with postpartum onset, or somatoform disorders.
  - History of previous non-response of depressive symptoms to ketamine
  - Clinically significant suicidal or homicidal ideation
  - Substance abuse or dependence within the past year
- Statistical tests used were appropriate
- Assuming a treatment difference of  $\geq 8$  points in the mean change from baseline to endpoint MADRS score between the ketamine and placebo groups, 14 patients were required in each group to detect a treatment difference with a power of 90% at an overall one-sided p-value of 0.15
- Intent-to-treat data handling method was used to analyze the data

## RESULTS

- 25 patients completed the double-blind phase of the study (1 in twice weekly placebo, 12 in twice weekly ketamine, 1 in thrice weekly placebo, and 11 in thrice weekly ketamine groups)
- Primary outcome measures
  - The change in baseline to day 15 in score on the Montgomery-Asberg Depression Rating Scale (MADRS) in the double blind phase was analyzed using a mixed effect model with repeated measures, with baseline MADRS score as a covariate, center and time-by-treatment interaction as fixed effects, and patient as a random effect
    - Twice weekly: -18.4 (SD =12) vs placebo -5.7 (SD = 10.2) ( $p < 0.001$ )
    - Three times weekly: -17.7 (SD = 7.3) vs placebo -3.1 (SD = 5.7) ( $p < 0.001$ )

- Secondary outcome measures
  - Early onset of clinical response (number of patients with an improvement  $\geq 50\%$  from baseline MADRS score during week 1 that was maintained through day 15) was analyzed using the Mantel-Haenzel test
    - Least-squares mean change from baseline was -16.0 (SE = 3.7) in the twice weekly group and -16.4 (SE = 2.4) in the three times weekly group
  - Total number of responders at each time point up to day 15 was analyzed using descriptive statistics
    - Twice weekly: 11/16 vs 2/13 placebo (p = 0.005)
    - Three times weekly: 7/13 vs 1/16 placebo (p = 0.004)
  - Change in MADRS score from baseline to day 29 was analyzed using mixed-effect model
    - Twice weekly: -21.2 (SD = 12.9) vs placebo -4.0 (SD = 6.6)
    - Three times weekly: -21.1 (SD = 11.2) vs placebo -3.6 (SD = 6.6)
  - Clinical Global Impressions severity score (CGI-S) change at endpoint was analyzed using a rank-based analyses of covariance model
    - Twice weekly median: -2 (-4 – 1) vs placebo 0 (-4 – 0) (p = 0.02)
    - Three times weekly median: -2 (-4 – 0) vs placebo 0 (-1 – 1) (p <0.001)
  - CGI improvement score (CGI-I) was analyzed using a rank-based analyses of variance model
    - Twice weekly median: 2 (1 – 5) vs placebo 4 (1 – 5) (p = 0.01)
    - Three times weekly median: 2 (1 – 5) vs placebo 4 (2 – 5) (p <0.001)
  - Change in Patient Global Impression severity score (PGI-S) was analyzed using a rank-based analyses of covariance model
    - Twice weekly median: -4 (-8 – 0) vs placebo 0 (-3 – 2) (p <0.001)
    - Three times weekly median: -3 (-8 – 1) vs placebo -1 (-3 – 1) (p <0.001)
  - Patient Global Impression of Change score (PGI-C) was analyzed using a rank-based analyses of variance model
    - Twice weekly median: 2 (1 – 4) vs placebo 4 (2 – 6) (p = 0.001)
    - Three times weekly median: 3 (1 – 4) vs placebo 4 (3 – 6) (p <0.001)
- **Authors' conclusion(s):** “Ketamine, administered intravenously at 0.5 mg/kg either two or three times weekly, appeared to be comparably effective at both achieving rapid onset and maintaining antidepressant efficacy in patients with treatment resistant depression across the 15 day period of assessment for the primary efficacy endpoint. Twice weekly treatment regimen administered for 4 – 6 weeks can induce and maintain a robust antidepressant effect in the treatment-resistant depression population. Studies of sustained effects over longer periods are needed.”

## STRENGTHS

- Good study rationale and background
- Used random assignment
- Used an appropriate dose of ketamine
- They used independent raters to verify that patients met inclusion criteria
- Discussed limitations

## LIMITATIONS

- Significant conflicts of interest that led to bias in the study design, methods, discussion, and conclusion
- The blinding could have been improved by giving the same number of doses to each group and just giving a placebo dose to the twice weekly placebo group
- Blinding success was not evaluated
- Unclear where from and how patients were enrolled and they didn't elaborate on the sites used
- Sample size was pretty small and led to significant variations in patient demographics
- Excluded patients with many disorders associated with depression
- The patients' current antidepressant regimen was continued despite lack of efficacy and they did not

elaborate on the treatment regimen drugs, doses, amount of antidepressant medications tried, etc.

- They did not discuss training of the independent raters
- The duration of the study and follow-up period was not long enough to evaluate long-term maintained antidepressant effects
- Significant amount of drop out in the placebo group
- The intent-to-treat data handling method was used when, because of significant drop out rates in one group, exclusion of subjects may have been a more valuable method
- One-tailed tests with a p-value of 0.15 were used
- Mostly white, female patients
- No confidence intervals were reported
- Adverse effects were not statistically analyzed
- Biased and positive, as opposed to a neutral more scientific, tone
- The use of behavioral therapy and its standardization was not evaluated

## CONCLUSIONS

- This study, while not clinically significant, provides some rationale for a larger, more well-designed study
- The role of ketamine in clinical practice should remain investigational until further phase II research provides evidence of safety and efficacy in larger study samples
- The potential risks currently still outweigh the potential benefits with this drug due to adverse effects, administration method, and abuse potential which further puts clinical significance into question
- The key take away from this study is that further studies in this area are required and that twice daily dosing may be an appropriate regimen to use when comparing to other antidepressants
- Studies of refractory depression with larger sample sizes, long treatment duration, and long-term follow up are needed to get an accurate picture of clinical effectiveness
- Further research is needed using ketamine alone, comparing ketamine to an active control, with larger sample sizes, and in acute depressive episodes