Clinical Predictors of Antisuicidal Response to Ketamine: Characterizing the Suicidal Ideation Response

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Introduction

- There are no pharmacological treatments for active suicidal ideation (SI).
- Recent studies suggest ketamine, a glutamate modulator, elicits rapid changes in SI.[1]
- As this efficacy literature develops in the era of precision medicine, two important questions must be addressed:
  - What is the acute course of SI following ketamine?
    - How is an outcome defined?
    - Should researchers use a 50% symptom reduction as a "response"?
  - Are there any demographic or clinical predictors of SI response to ketamine?

The aim of this analysis was to model change in SI after ketamine administration in order to identify classes of responders and non-responders. These classes were then used evaluate potential clinical and demographic predictors of antisuicidal response to ketamine.

Methods

- Data from four independent studies of ketamine in treatment-resistant MDD and bipolar I or II depression without psychotic features.
- Patients received a single subanesthetic (0.5 mg/kg) dose of ketamine over 40 minutes. Bipolar patients were maintained on lithium or valproate.
- Measures: Composite SI score, developed from previous exploratory factor analysis of MADRS, HDRS, BDI and SHAPS.[2] Possible scores on this composite range 0 to 1, reflecting the average proportion of available points per item.
  - SI score comprised of two BDI items (hopelessness and SI), one MADRS item (SI).
  - Depressed mood score comprised of 4 MADRS items, 3 HDRS items and 1 BDI item.
  - Sociodemographic and clinical variables were evaluated as predictors of class membership across trials.
- Statistical Analysis: Growth mixture modeling is a person-centered latent variable method to parse heterogeneity in a sample. Latent class growth curve analysis was used to model change in SI after ketamine administration. Predictor analyses were performed in a subset of the sample (N=107), using multinomial logistic regressions. All growth mixture model analyses were completed in MPlus version 7.4 20; other analyses were performed in IBM SPSS Statistics 24.

Acknowledgements

Results

Table 1: Participant Demographics

	Growth Mixture Model Sample (N=128)		Predictor Analysis Sample (N=107)	
	M	**SD**	**M**	**SD**
Age	43.83	12.12	43.07	12.18
BMI	29.55	6.79	29.04	6.35
Length of Illness (Y)	25.01	12.49	24.78	12.67
Clinical Ratings				
MADRS Total	33.47	4.68	33.47	4.68
SI (EFA Score)	0.35	0.18	0.36	0.18
	N	**%**	**N**	**%**
Sex (Male)	58	45.30	50	46.70
Race (White)	105	82.70	93	87.70
Diagnosis (MDD)	86	67.20	65	60.70
History of Psychiatric Hospitalization	80	62.5	70	65.40

Note: SI (EFA score) is a composite suicidal ideation rating on a 0 to 1 scale, where 1 is the most severe rating possible.

Figure 1: Raw Data and Summary Boxplot of SI Response to Ketamine
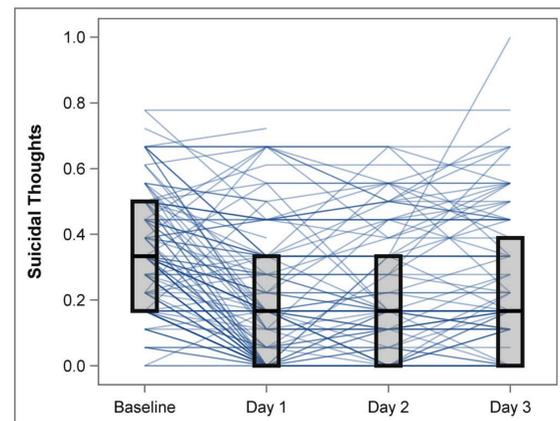
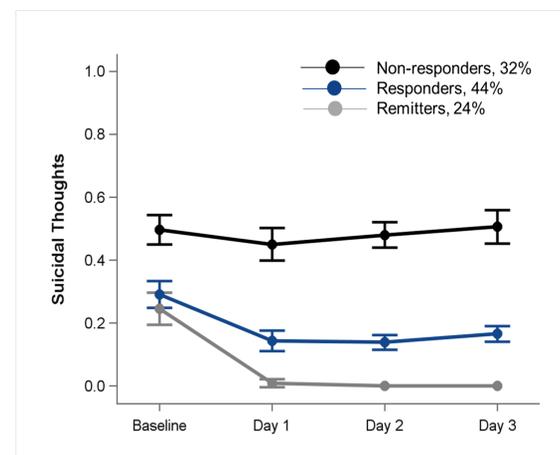### Figure 2: Best-Fitting Three-Class Model Describing Patterns of SI Response to Ketamine

- The heterogeneity of SI response to ketamine is depicted in Figure 1. The average baseline SI subscale score was 0.35 (SD = 0.18), on a scale of 0–1.
- Figure 2 presents the overall 3 class solution of SI response to ketamine. The relative fit indices suggested that the three-class solution was best fit to the data.
  - Class 1 (Non-Responders) reported highest baseline SI and no change in SI at Days 1, 2, or 3.
  - Class 2 (Responders), the largest class, demonstrated an improvement in SI.
  - Class 3 (Remitters) improved significantly during the course of the study, such that all members had scores of zero by Day 2. Class 2 and Class 3 did not differ in baseline SI.

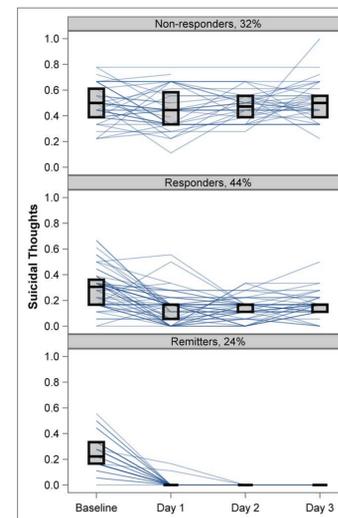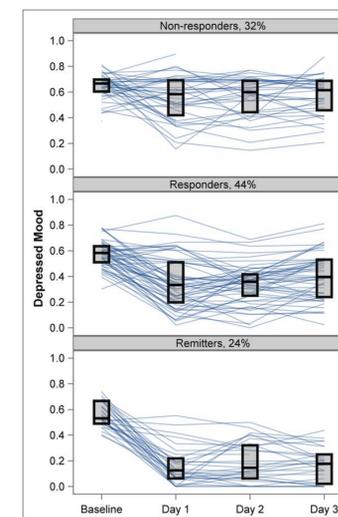### Figure 3: Trajectory of SI across SI classes

Figure 4: Trajectory of Depressed Mood across SI Classes

Results (Con't)

- Figures 3 and 4 depict the trajectories of SI and depressed mood by SI Response Class.
- Predictor Analysis: Older age was associated with lower odds of being in the moderate responder group compared to the remitter group (OR=.095, 95% CI: 0.91 – 0.99), as was a longer length of one's current depressive episode (OR=0.99, 95% CI: .98 – 1.0).
- Sexual abuse history was associated with lesser odds of being a non-responder compared to a remitter (OR=0.24, 95% CI: 0.07 – 0.86). History of self-injury was associated with greater odds of being a non-responder compared a remitter (OR=12.00, 95% CI: 1.44 – 100.36). SI on hospital admission was associated with greater odds of being a non-responder versus a remitter (OR=4.46, 95% CI: 1.12 – 17.76) or a moderate responder (OR=5.22, 95% CI: 1.66 – 16.40]).
- Figure 3 depicts the relationship between SI response class and responder group defined by a 50% reduction in SI composite score at Days 1 and 3 post-ketamine.

Figure 5: 50% Response by SI Class
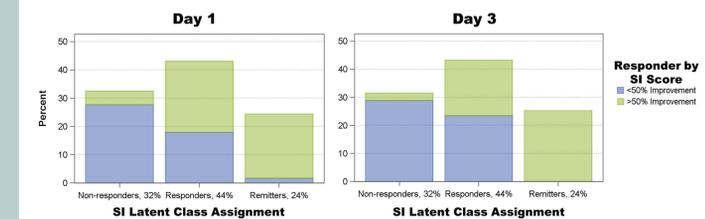
Discussion

- The present analysis defined three classes of SI after ketamine administration, demonstrating the utility of data-driven approaches to characterize the heterogeneity of response to a rapid-acting intervention.
- This approach allowed for a more fine-grained analysis of symptoms than would be permitted by traditional approaches, including evaluating mean response to treatment or dichotomizing response by a 50% reduction in symptoms.
- When examining clinical predictors of class membership, the individuals least likely to experience improvement in SI with ketamine were those with the most severe SI and a history of chronic suicide risk.
- Clinical predictors of SI responder membership diverged from the previous literature on antidepressant response.[3]

References

1. Wilkinson, Ballard, Bloch et al., 2017. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. AJP.
2. Ballard, Yarrington, Farmer et al., 2018. Parsing the heterogeneity of depression: An exploratory factor analysis across commonly used depression rating scales. JAD.
3. Niciu, Luckenbaugh, Ionescu et al., 2014. Clinical predictors of ketamine response in treatment-resistant major depression. Journal of Clin Psychiatry.