The Association Between Body Mass Index and Remission Rates in Patients With Treatment-Resistant Depression Who Received Intravenous Ketamine

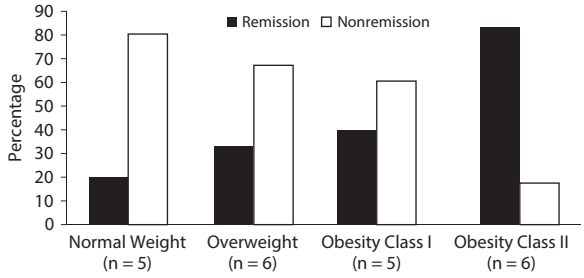
To the Editor: Few studies have evaluated optimal dosing of intravenous (IV) ketamine for treatment-resistant depression (TRD).[1,2] Landmark studies[3–5] infused ketamine at 0.5 mg/kg actual body weight. However, a consensus statement by Sanacora et al[1] suggested dosing based on calculated ideal body weight, especially in patients with body mass index (BMI) ≥ 30 given concerns about greater hemodynamic instability. Preliminary studies[6] identified an association between BMI and ketamine response with 0.5 mg/kg infused over 40 minutes. The association was postulated to be due to clinically effective dose, as patients with the highest dose had more improvement.[6] We completed 2 open-label trials[7,8] of racemic ketamine infused intravenously, 0.5 mg/kg actual body weight, over 100 minutes in TRD patients. We conducted a secondary analysis from these studies to assess association between BMI and ketamine response at a slower infusion rate.

Methods. We combined subject-level data from 2 open-label, adjunct IV ketamine trials[7,8] that enrolled adults with treatment-resistant *DSM-IV* unipolar or bipolar major depressive disorder (defined as failure to respond to 2 adequate trials of antidepressive treatments, including pharmacotherapy with antidepressants, mood stabilizers, or atypical antipsychotic drugs with bipolar antidepressive effects;, electroconvulsive therapy; or transcranial magnetic stimulation). Multiple infusions were given weekly until remission was achieved or maximum number of infusions administered (twice weekly up to 4 infusions[8] or thrice weekly up to 6 infusions[7]). Remission was defined as Montgomery-Asberg Depression Rating Scale (MADRS) score ≤ 9 after the 4 infusions.[9] The quantitative outcome percentage change in MADRS score was also analyzed (see Supplementary Appendix 1 for details). We analyzed BMI as a continuous measure and categorized BMI per World Health Organization guidelines (normal, overweight, obesity classes I and II).

Continuous variables are reported as mean ± SD and categorical variables as counts and percentages. The Wilcoxon rank sum test was used to compare continuous variables. Chi-square and Fisher exact tests were used to compare categorical variables. Logistic regression was used to evaluate the association between BMI and remission. Because the sample size was small, the Cochran-Armitage trend test was utilized to test for association between BMI obesity categories (stepwise increases from normal BMI through class II obesity) and remission. JMP Pro 13.0.0 statistical software (SAS Institute, Cary, North Carolina) and R version 3.4.2[10] were used for the analysis.

Results. The study sample consisted of 22 subjects with depression who were middle-aged (mean ± SD age = 46.4 ± 11.5 years), had a mean ± SD BMI of 30.7 ± 6.6, and were predominantly female (77%) (Supplementary Tables S1 and 2). Mean (SE) change in MADRS score was −16.18 ± 2.84 ($P < .0001$), a significant reduction (improvement) from baseline (mean ± SD = 31.18 ± 1.53). There was a trend association of BMI and remission (OR = 1.17; 95% CI, 0.98–1.39; $P = .07$). When data were categorized into 4-level ordinal variables (BMI categories), there was a significant association between higher BMI category and remission ($P = .03$, Figure 1).

Figure 1. Remission Rate, per BMI Category, in Patients Receiving Ketamine[a]



[a]BMI categories are defined as follows: normal weight: BMI range, 18.5–24.9; overweight: BMI range, 25.0–29.9; obesity class I: BMI range, 30.0–34.9; obesity class II: BMI range, 35.0–39.9. All BMI values are kg/m^2.
Abbreviation: BMI = body mass index.

We found an association between baseline BMI and odds of remission and an effect modification of the relationship between ketamine and remission by BMI category. Our major limitation is very small sample size, especially in the class II obesity category, which drove the BMI association with remission and percentage change in MADRS score; thus, replication of these findings in a larger sample is needed. Nevertheless, these data, alongside those of Niciu et al,[6] suggest that higher BMI may be associated with higher rates of remission regardless of infusion rate. Ketamine is highly lipid soluble and is rapidly transferred across the blood-brain barrier, directly impacting brain lipids. One proposed hypothesis is that patients with higher BMI may very likely have received a clinically effective dose of ketamine, which may have led to greater improvement in depression scores.[6] These data have implications when evaluating merits of actual versus ideal body weight in ketamine dosing and raise an important clinical question in need of an adequately powered randomized trial (probably with restriction as to the upper allowable BMI limit for enrollees for safety purposes). This issue is important as US obesity rates steadily increase.[11] Interestingly, a recent study (Cullen et al[12]) dosed ketamine in TRD adolescents on ideal body weight. However, after observation that most subjects were nonresponders, the study design was switched to dosing on actual body weight, which resulted in significantly increased response rates.

Further consideration is needed before dosing patients based on ideal body weight, as the risk for underdosing this population may exist. Although higher BMI favors efficacy, safety considerations of lipophilic drug use in obese patients should be considered and need further investigation.

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Supplementary Material

Article Title: The Association Between Body Mass Index and Remission Rates in Patients With Treatment-Resistant Depression Who Received Intravenous Ketamine

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List of Supplementary Material for the article

1. Appendix 1 Additional Analysis
2. Table 1 Patient Baseline Characteristics
3. Table 2 Remission rate to IV ketamine with subsequent infusions

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Appendix 1: Additional Analysis. Quantitative percent change in MADRS score from baseline to final assessment was modeled using linear regression, with log (BMI) or BMI obesity category as the predictor and with baseline MADRS score included as a covariate.
Quantitative percent change in MADRS score adjusted for baseline MADRS was not significantly associated with log (BMI) ($p=0.15$), but showed marginally significant association with ordinal BMI obesity categories ($p=0.064$) and a significant difference between the normal BMI and class II obesity categories ($p=0.017$).

Supplementary Table 1. Patient Baseline Characteristics

	N=22	Remitter n=10	Non-remitter n=12	p-value
Age, mean (SD)	46.43 (11.49)	46.29 (10.67)	46.56 (12.60)	0.96
Female, n (%)	17 (77.27)	6 (60)	11 (9.67)	0.14
Caucasian, n (%)	21 (95.46)	10 (100)	11 (91.67)	1.00
BMI, mean (SD)	30.73 (6.59)	33.70 (7.29)	28.3 (5.00)	0.053
Height, mean (SD)	166.64 (7.36)	166.7 (7.93)	166.6 (7.21)	0.97
Weight, mean (SD)	85.65 (21.01)	94.36 (24.23)	78.39 (15.37)	0.07
Baseline MADRS	31.18 (7.20)	29.8 (7.18)	32.33 (7.32)	0.42
MADRS at 100 min	18.36 (9.59)	12.3 (6.68)	23.42 (98.83)	0.004
MADRS at 24 hr	18.86 (9.76)	12.6 (7.25)	24.08 (8.58)	0.003
MADRS, Q10, baseline	2.86 (1.61)	3.6 (1.17)	2.25 (1.71)	0.048
MADRS, Q10, 24hr	1.50 (1.26)	1.5 (1.18)	1.5 (1.38)	1.0

Abbreviations
3 patients who responded at 1 hr, did not meet response criteria at 24 hr
4 patients met remission criteria at 1 hr, of whom 3 continued to meet remission (1 did not)
8 patients met response criteria at 1 hr, of whom 4 met criteria at 24 hr (4 did not)
3 additional subjects met response criteria at 24 hr

P-value is comparing patient characteristics between remitters and non-remitters.

Supplementary Table 2. : Remission rate to IV ketamine with subsequent infusions

Number of infusions administered	Number of patients infused	Number of patients remitted
1[a]	5	4
2	4	4
3[a]	2	1
4	11	1

[a]One patient dropped out after the first infusion and one after the third infusion despite not achieving remission