

Subanesthetic IV ketamine rapidly reduces acute suicidal ideation in patients with depression

Kimberly J Jenko, PA-S, Jack Anzilotti, PA-S, Abby Massey, MD
James Madison University Physician Assistant Program, Harrisonburg, VA

INTRODUCTION

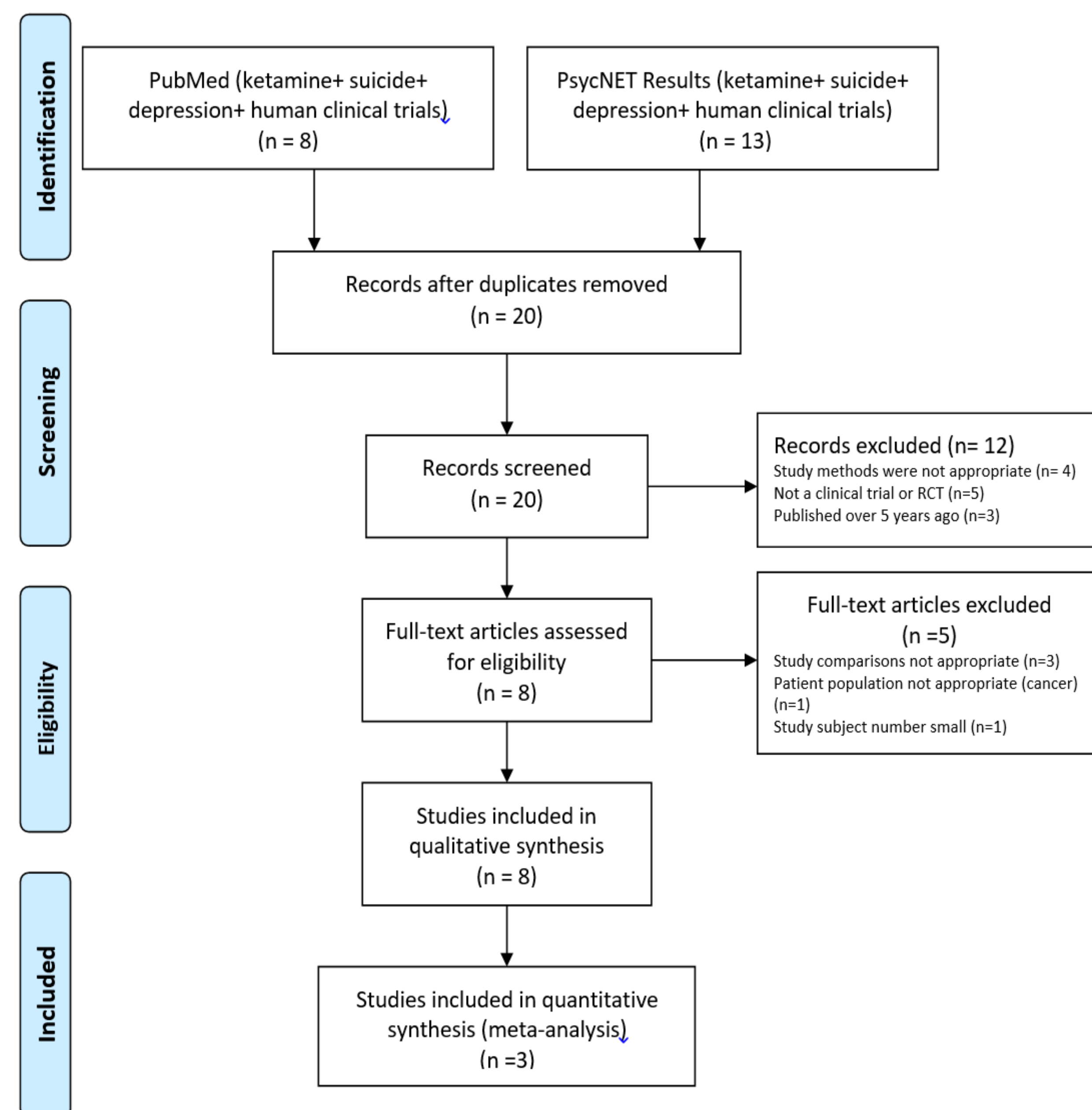
- Roughly 10% of physician office visits every year are due to depression (CDC, 2015). There are approximately 45,000 deaths due to suicide in the US each year, but few options exist for rapid relief of suicidal ideation (SI) for patients with mental health disorders like depression. Current therapies are not effective in treating acute suicidal ideation.
- Ketamine, a glutamate N-methyl- D- aspartate (NMDA) receptor antagonist traditionally used to start and maintain anesthesia, is currently being investigated to reduce acute and prolonged SI.
- Initial studies show acute SI relief for patients with treatment resistant major depressive disorder (TRD), major depressive disorder (MDD), bipolar depression (BD), and post-traumatic stress disorder (PTSD) when treated with ketamine compared to saline placebo.

OBJECTIVE

Does subanesthetic IV ketamine produce a clinically relevant reduction of SI compared to midazolam for patients with mood disorders?

MATERIALS & METHODS

Figure 1. Flowchart depicting methods for selecting eligible studies for review.



Overall Study Design: Patients were randomized and assigned to receive ketamine or midazolam infusion (Table 1) over 40 min. SI was assessed at baseline and 24 hours (day 1) using the Scale for Suicidal Ideation (SSI), Beck Scale for Suicidal Ideation (BSI), and Montgomery-Asberg Depression Rating Scale for Suicide (MADRS-SI). SSI and BSI have a >90% correlation, and were used as the primary measurement of reduction in this review.

RESULTS

Table 1. Study population and dose administration information

	Grunebaum, et al.	Murrough, et al.	Price, et al.
Study style	RCT	RCT	Two Site double blind RCT
Patients (N)	80	24	57
Gender	Midazolam: M= 14, F= 26 Ketamine: M= 18, F= 22	Midazolam: M=4; F= 8 Ketamine: M=4; F=8	Midazolam: M= 11; F= 10 Ketamine: M= 16; F= 20
Mean age (years)	Midazolam: 40.7 Ketamine: 38.4	Midazolam: 39.1 Ketamine: 45.8	Midazolam: 43.8 Ketamine: 48.6
Ketamine dose (mg/kg)	0.5	0.5	0.5
Midazolam dose (mg/kg)	0.02	0.045	0.045

RCT: randomized control trial; M: male; F: female

Grunebaum MF, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *Am J Psychiatry.* 2018; 175(4):327-335.

- Objective:** To test the acute effect of adjunctive subanesthetic IV ketamine on SI in patients with MDD.
- Results:** The average SSI score at Day 1 post-infusion was lower than baseline in both ketamine and midazolam treatments, but the average SSI score was significantly lower in the ketamine group compared with the midazolam group ($p < 0.001$, Cohen's $d = 0.75$).
- Conclusion:** Both treatments reduced SI, but treatment with ketamine showed a statistically significant reduction in SI compared to midazolam.

Murrough JW, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med.* 2015; 45(16): 3571-80.

- Objective:** To assess the rapid antidepressant effects of ketamine in reducing SI in patients with a variety of psychiatric disorders (MDD, PTSD, borderline personality disorder, obsessive compulsive disorder, etc).
- Results:** At day 1, BSI scores were similarly reduced in the ketamine and midazolam groups ($p = 0.32$, Cohen's $d = 0.34$). At day 1, the MADRS-SI scores were significantly lower in ketamine compared to midazolam ($p = 0.05$, Cohen's $d = 0.86$).
- Conclusion:** Treatment with ketamine and midazolam both showed reduction in SI, but a statistically significant reduction was only seen for ketamine using MADRS-SI at 24 hours.

Price RB, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety.* 2014;31(4):335-43.

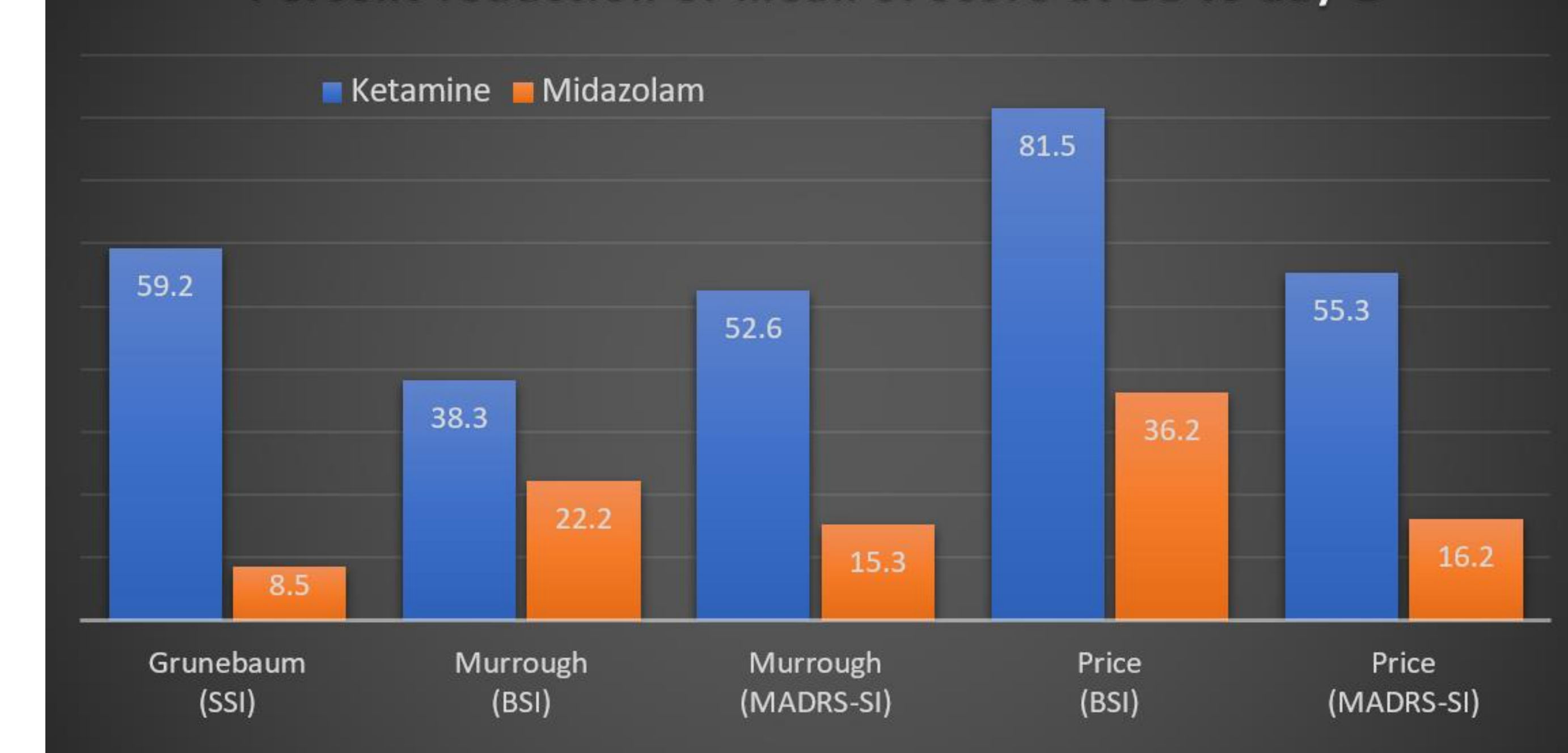
- Objective:** To evaluate the effects of ketamine compared to midazolam to reduce SI in patients with TRD.
- Results:** At day 1, BSI was reduced more in the ketamine group compared to midazolam group ($p = 0.04$). At day 1, MADRS-SI scores were lower in ketamine compared to midazolam (Cohen's $d = 0.86$). When incorporating BSI, MADRS-SI and QIDS-SR results into a $SI_{composite}$ score, a large effect size was seen between ketamine and midazolam (Cohen's $d = 0.82$).
- Conclusion:** Both treatments reduced SI, but treatment with ketamine showed a statistically significant reduction in SI compared to midazolam.

Table 2. Mean SI Scores

	Grunebaum et al.		Murrough et al.		Price et al.		Price et al.		Price et al.	
	SSI	BSI	MADR-SI	BSI	MADR-SI	BSI	MADR-SI	BSI	MADR-SI	
	BL	Day 1	BL	Day 1	BL	Day 1	BL	Day 1	BL	Day 1
Ketamine	14.2	5.8*	17.5	10.8	3.8	1.8*	6.11	1.13*	1.61	0.72
Midazolam	15.8	11.8	18	14	3.9	3.3	6.19	3.95	1.48	1.24

SSI: Scale for Suicidal Ideation; BSI: Beck Scale for Suicidal Ideation; MADRS-SI: Montgomery-Asberg Depression Rating Scale-Suicidal Ideation. * $p < 0.05$

Percent reduction of mean SI score at BL vs day 1



CONCLUSIONS

- Patients treated with IV ketamine exhibited rapid, clinically relevant reductions (>50% reduction) in SI, which were significantly greater than reductions observed in midazolam-treated patients.
- Ketamine significantly reduced SI at day 1 in all studies except when measured by BSI in Murrough. Midazolam did not significantly reduce SI using any measures.
- Midazolam is a better control than saline placebo due to its psychoactive properties which more strongly blinds patients to treatment. However, Grunebaum et al. noted raters correctly guessed the drug they were administered approximately 43% of the time ($p = 0.895$).

DISCUSSION

- Murrough, et al. reported conflicting results between BSI and MADRS-SI. The BSI scale may be less sensitive for a variety of mental disorders other than MDD or TRD.
- There a wide variety of suicide and depression scales available, making it difficult to consistently assess SI in depressed patients across different settings. Further research is needed to firmly establish a definition of "clinically meaningful reductions".
- Several authors in all studies reported financial, consulting, pharmaceutical, and investment involvement.
- Ketamine can be used to treat acute SI in patients with MDD or TRD, but more research is needed to make similar conclusions in patients with other co-occurring psychiatric disorders.
- The NMDA receptor is one of the pathological mechanisms implicated in suicidal ideation. This receptor can lead to further treatment developments for depression, borderline personality disorder, PTSD, and other mental health disorders.

Acknowledgements

We thank Dr. Massey for her research and writing guidance, and are grateful for Dr. Kancler's biostatistical instruction.