Lessons Learned from Conducting a Randomized Controlled Trial in Patients with High Risk for Suicide

Hardy, MS;[1] Wilkinson, ST[1]; Kitay, BM[2];Macaluso, M[3];Santucci, MC[1]; Kumpf, K[1];Voghell, C4; Astorino, L[1,4]; Hershenberg, R[2]; Martinez-Kaigi, V[1] Nowell, T[3];Thase, M[5]; Sanacora, G[1]; Rhee, G[1]

[1] Yale Depression Research Program, Department of Psychiatry, Yale School of Medicine, New Haven, CT; [2] Department of Psychiatry, Emory University School of Medicine, Atlanta, GA[3:] Department of Psychiatry, University of Alabama at Birmingham, School of Medicine, Birmingham, AL [4] Yale Center for Clinical Investigation, Yale School of Medicine, New Haven, CT; [5] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

METHODOLOGICAL ISSUE BEING ADDRESSED

- Clinical trials of depression treatments frequently exclude patients with elevated suicide risk
- Patients with elevated suicide risk are substantially understudied
- As a result, evidence-based clinical treatments for patients with acutely elevated suicide risk are lacking
- The CBT-ENDURE trial addresses the feasibility of recruiting patients at high risk for suicide into a randomized controlled trial and analyzing suicide-related outcomes

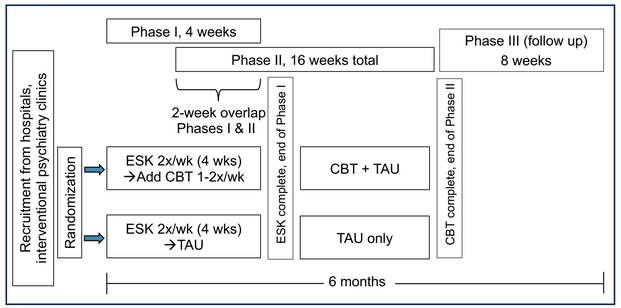
INTRODUCTION

Evidence-based clinical treatments that specifically target suicide risk are limited, due in part to the methodologic and ethical challenges associated with conducting clinical studies in a high-risk population. Recruiting eligible patients while ensuring access to safe clinical care is an important consideration. Selecting appropriate outcome measures is also important. As patient-centered outcomes are becoming more valued, the outcomes which are most meaningful in this clinical group are often event based (e.g., hospitalization, suicide attempt, etc.). We present results from a multi-site randomized controlled trial combining cognitive behavioral therapy with esketamine treatment for relapse prevention in a high-risk clinical population with major depressive disorder with acute suicidal ideation (MDSI). This study demonstrates the feasibility of recruiting patients at high risk for suicide from an enriched sample of treatment-seeking patients in inpatient and outpatient settings and analyzing suicide-related outcomes through a time-to-event analysis. It also provides information valuable to investigators in the design and conduct of future trials recruiting high-risk patients.

METHODS

The CBT-ENDURE trial recruited treatment-seeking patients with MDSI admitted to an inpatient facility for acute SI/suicide attempt, or outpatients with significantly elevated SI referred to an interventional psychiatry service. Patients were randomized to receive 8 treatments of esketamine followed by a 16-week course of CBT, or esketamine with treatment as usual (TAU) only. Feasibility was the primary outcome, as defined by 80% of targeted enrollment (n=100) and 70% retention, with a secondary outcome of group comparisons of suicidal ideation, based on the Columbia Suicide Severity Rating Scale (CSSRS), Beck Scale for Suicidal Ideation (BSSI), and Clinician Global Improvement Scale for Suicide Severity (CGI-S). Change in depressive symptoms was assessed using the Montgomery Asberg Depression Rating Scale (MADRS). We also conducted a time-to-event analysis of a composite of clinical outcomes, including suicide death, attempted suicide, psychiatric hospitalization, or an increase to 75% or worse of baseline in the Beck Scale for Suicidal Ideation.

Figure 1. A schematic of the trial timeline



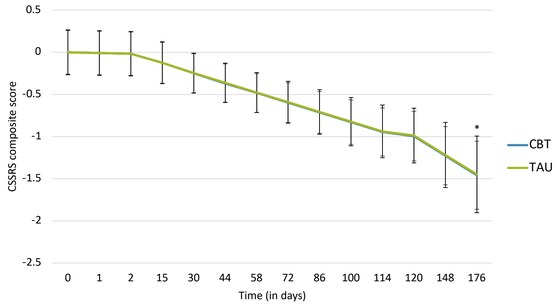
Note: ESK, esketamine; CBT, cognitive behavioral therapy; TAU, treatment as usual. *For those randomized to CBT group, they will begin CBT after 2 weeks of open-label esketamine.

RESULTS

Table 1. Demographic and Clinical Characteristics

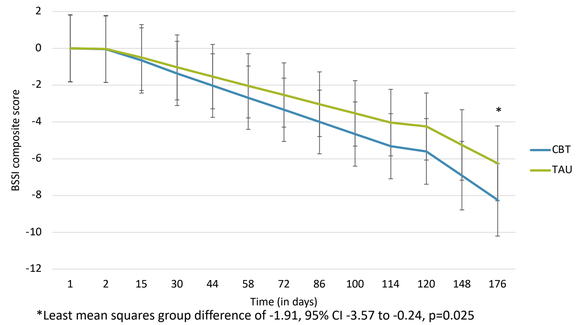
	TAU	CBT	Total	P-value
Sample size	46	47	93	
Age, mean ± standard deviation [SD]	36.6 ± 11.7	39.0 ± 13.9	37.8 ± 12.8	0.38
Gender				
Male	12 (26.1%)	15 (31.9%)	27 (29.0%)	0.45
Female	33 (71.7%)	29 (61.7%)	62 (66.7%)	
Other	1 (2.2%)	3 (6.4%)	4 (4.3%)	
Race and ethnicity				
Non-Hispanic white	33 (71.7%)	39 (83.0%)	72 (77.4%)	0.51
Non-Hispanic black	2 (4.4%)	1 (2.1%)	3 (3.2%)	
Hispanic	7 (15.2%)	4 (8.5%)	11 (11.8%)	
Non-Hispanic other	0 (0.0%)	1 (2.1%)	1 (1.1%)	
Unknown	4 (8.7%)	2 (4.3%)	6 (6.5%)	
Clinical setting				
Inpatient	28 (60.9%)	29 (61.7%)	57 (61.3%)	0.93
Outpatient	18 (39.1%)	18 (38.3%)	36 (38.7%)	
History of psychiatric hospitalizations				
Yes	25 (54.4%)	29 (61.7%)	54 (58.1%)	0.47
Of those with previous psychiatric hospitalizations, number of psychiatric hospitalizations, mean ± SD	2.7 ± 2.2	4.3 ± 5.3	3.6 ± 4.2	0.15
Baseline severity of suicidal symptoms				
Lifetime suicide attempts (per CSSRS)	18 (39.1%)	23 (48.9%)	41 (44.1%)	0.34
Of those with suicide attempts, mean ± SD	2.0 ± 1.2	2.7 ± 2.9	2.4 ± 2.4	0.36
Suicidality in the past 7 days (CGI)				
Not at all suicidal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.36
Mildly suicidal	5 (10.9%)	8 (17.0%)	13 (14.0%)	
Moderately suicidal	18 (39.1%)	16 (34.0%)	34 (36.6%)	
Severely suicidal	21 (45.7%)	17 (36.2%)	38 (40.9%)	
Attempted suicide	2 (4.4%)	6 (12.8%)	8 (8.6%)	

Figure 2. Columbia Suicide Severity Rating Scale (CSSRS) composite score changes over time



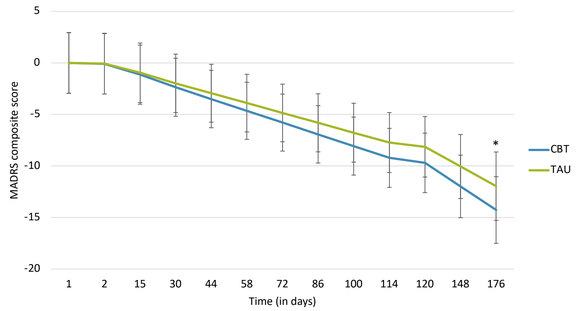
*Least mean squares group difference 0.13, 95% CI -0.39 to 0.65, p=0.623

Figure 3. Beck Suicide Severity Index (BSSI) composite score changes over time



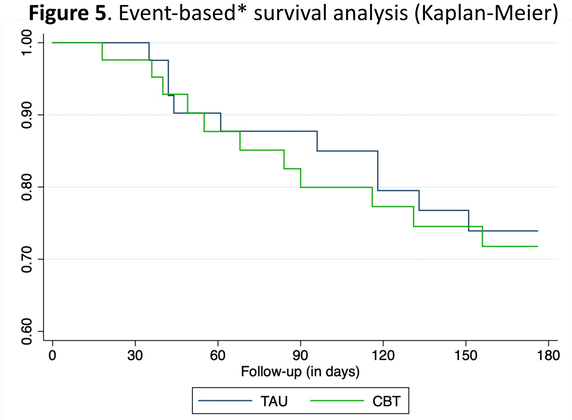
*Least mean squares group difference of -1.91, 95% CI -3.57 to -0.24, p=0.025

Figure 4. Montgomery Asberg Depression Rating Scale (MADRS) composite score changes over time



*Least mean squares mean difference of -3.77, 95% CI -6.62 to -0.93, p=0.009

Figure 5. Event-based* survival analysis (Kaplan-Meier)



*Suicide-related events included including suicide death, attempted suicide, psychiatric hospitalization, or an increase to 75% or worse of baseline in the Beck Scale for Suicidal Ideation. p=0.790

CONCLUSIONS

- Conducting a successful study in a high-risk patient population with MDSI is feasible
- CBT added to intranasal esketamine reduced some, but not all, measures of suicidality, relative to control in patients with MDSI
- Study was under-powered to detect suicide-related events between groups
- Based on total number of suicide-related events, a study powered to detect a moderate treatment effect would need to enroll ~300 participants
- Results suggest that conducting a trial to find group differences in suicide-related events requires enrollment from an enriched sample of high-risk patients (e.g. hospitals, emergency departments)

References

Included separately in a handout, available upon request

Acknowledgements

Funding: This project was funded by a grant from the National Institute of Mental Health (R01MH125205, R01MH125205-02S1, PI Wilkinson). The data for this trial can be accessed through the NIMH Data Archive (NDA).

Disclosures: Dr. Hardy has pending contract research funding from Otsuka Precision Health, administered through Yale University.

Yale University has a financial relationship with Janssen Pharmaceuticals (owner of Spravato) and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

Disclosures for all other authors available upon request

Yale University
School of Medicine