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

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Methodological Issue Being Addressed Clinical trials of depression treatments frequently exclude patients with elevated suicide risk, resulting in this population being substantially understudied. The CBT-ENDURE study 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). 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.

Results Ninety-three subjects were enrolled, with 47 randomized to CBT and 46 to TAU. Of these, 69 (74%) were retained through the end of the study. Thus, the study met its primary endpoint for feasibility. Change in suicidal ideation from baseline through end-of-study (week 26), based on the

Beck Scale for Suicidal Ideation (BSSI) and Clinician Global Improvement Scale for Suicide Severity (CGI-S), favored the CBT group over the TAU group (BSSI mean difference of -1.91, 95% CI -3.57 to -0.24, p=0.025; CGI-S mean difference of -0.33, 95% CI -0.58 to -0.08, p=0.011). C-SSRS was not sensitive to difference between groups (group difference 0.13, 95% CI -0.39 to 0.65, p=0.623). Suicide-related events did not statistically differ between groups (hazard ratio = 0.64, 95% CI 0.17 to 2.47, p=0.51). Almost all such events (14/18, 78%) occurred among the patients who were hospitalized at the time of enrollment.

Conclusion This study demonstrates the feasibility of conducting a successful study in a high-risk patient population with MDSI. The results of this study suggest that conducting a trial that intends to find group differences in suicide-related events but enrolls primarily from outpatient settings is infeasible. Based on the total number of events that occurred during the trial, a study powered to detect a moderate treatment effect would need to enroll ~300 participants from hospitals or similar settings (e.g., emergency department settings). It also suggests the effectiveness of combining CBT with esketamine to reduce suicidal ideation and prevent relapse in patients with MDSI.

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Dr. Sanacora has served as consultant to AbbVie, Ancora, Aptinyx, Atai, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Denovo Biopharma, Douglas Pharmaceuticals, EMA Wellness, Embark, Engrail Therapeutics, Freedom Biosciences, GH Research, Gilgamesh, Holmusk, Intra-Cellular Therapies, Janssen, Levo therapeutics, Lilly, Merck, Navitor Pharmaceuticals, Neumora, Neurocrine, Newleos Therapeutics, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Relmada Therapeutics, Seaport, Pharmaceuticals, Sage Pharmaceuticals, Seelos Pharmaceuticals, Supernus, Taisho Pharmaceuticals,Transcend Therapeutics, Usona Institute, Vistagen Therapeutics, and XW Labs; and received research contracts from Johnson & Johnson/Janssen, Merck, and the Usona Institute over

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Dr. Hardy, Ms. Santucci, Ms. Kumpf, Ms. Voghell, Ms. Astorino, Dr. Martinez-Kaigi and Dr. Nowell report no disclosures.