FDA Regulatory Perspective

Suicidal Ideation and Behavior as Efficacy Endpoints in Clinical Trials

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Regulatory Overview

• Prior Research Using SI as Efficacy Endpoint
  – Ketamine, Esketamine, Clozapine, Lithium, etc.

• Considerations Around SI as Efficacy Endpoint
  – Cross-Diagnostic vs. Within Diagnosis
  – Clinical Etiology and Implications
  – Scales/Endpoints in Use

• Future Directions
Disclaimer

• This presentation represents the views of the author and does not represent FDA position or policy.
Ketamine: Literature Review of SI as Endpoint

• Early evidence of reduction of suicidal ideation (SI) has been promising (but not FDA-approved for this indication). Meta-analyses and reviews from research literature confirm possible consistent effect.*

• Quality of evidence remains limited:
  – Small sample size
  – Mostly open-label
  – Screened for diagnosis, not presence of SI
  – SI mainly secondary endpoint

• Larger-scale trials of longer duration needed.

* Bartoli et al, 2017; Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015

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Ketamine SI RCT (Cross-Diagnostic)

• One small RCT (24 subjects) by Murrough et al (2015) used SI as primary endpoint for single-dose IV ketamine versus midazolam (augmentation to existing antidepressant therapy), with multidiagnostic population.

• Patients (both inpatient and outpatient) with current SI were included (MADRS-SI≥4); but outpatients with SI with *active* intent were excluded (C-SSRS=4,5).

• Primary Diagnoses: MDD (54%), bipolar (non-manic), PTSD, and nonpsychotic (anxiety) disorders.
Ketamine SI RCT Results

- Showed possible efficacy for SI reduction (but sample size is small):
  - Beck Scale for Suicidal Ideation (BSI) (primary endpoint) significant at 48 h only (not at 24 h or 72 h or 7 days) (8.8±8.3 on ketamine versus 15.3±10.9 midazolam)
  - MADRS-SI reduction significant at 24 h but not other timepoints. (1.8±1.9 vs. 3.3±1.6).
  - Both not significant at 72 h or Day 7.
- Secondary implicit measures showed improvement as well (particularly on panic and irritability).
- Suicidal behavior (SB, aka suicide attempts and suicide) was not looked at as endpoint measure
- Proof-of-concept study for SI reduction as endpoint using cross-diagnostic population
SI Reduction Etiology

Ketamine Reduction Hypotheses

1: Secondary to primary diagnostic improvement?

2: Primary antisuicidal effect?
SI Reduction Etiology

• **Pro-Hypothesis #1**: Correlation between primary outcome measure improvement and secondary SI measures.

• **Pro-Hypothesis #2**:
  – Peak reduction correlates with peak dissociation.
  – Ketamine works on NMDA and BDNF modulation, but also opioid, amphetamine, and kynurenine pathway via cytokines.*

* Al Jurdi, 2015; Iadarola, 2015
Acute SI Reduction: Clinical Effect

• Time considerations:
  – Rapid but short effect for ketamine or esketamine (different than clozapine, lithium, etc.)
  – Abuse and safety concerns with longer-term use
• Benefit of acute intervention for emergency SI with advantage of rapid onset: stop/prevent imminent SB?
• Open window for other interventions (modifying cognitions, starting other meds, etc.) that may have longer-lasting clinical benefit and/or SB prevention?
  – Consider exploratory outcome measures along these lines to confirm clinical meaningfulness of endpoint
Other SI/B Drug Endpoint Data

- **Clozapine** - 2-year International Suicide Prevention Trial (Meltzer et al, 2003). Drug is administered daily and long-term unlike ketamine.
- **Lithium** has had several meta-analyses showing likely reduced risk of suicide, particularly in depressed patients. (Cipriani et al, BMJ 2013)
- **Antidepressant** meta-analyses have shown equivocal data, with possible increase in SI/B in children/young people up to age 25 (leading to FDA boxed warning) but reduction in adults and the elderly. (Stone et al, BMJ 2009)
Other SI/B Endpoint Data

- ECT (and maybe TMS) may be most analogous to ketamine/esketamine treatment timing.
- ECT showed reduction in SI on HRSD-24 in one review (15% baseline reporting score of zero, and 76% after 9 treatments). But longer-term SI/B reduction study data for ECT unavailable. (Fink et al, 2014)
- TMS shows some preliminary SI improvement in some small studies. (Sun et al, 2016; Desmyter et al 2014)
Esketamine for MDD-SI

• Esketamine approved (in conjunction with an oral antidepressant) in March 2019 for treatment-resistant depression
• Also being studied for reduction of SI in subjects with MDD*
• Phase 2 study for reduction of SI in MDD (SUI2001)*: Study population all had imminent SI and initial inpatient hospitalization at start of study, up to 4 weeks treatment
• Phase 3 studies recently completed (SUI3001 and SUI3002)*: same design, around 225 to 230 subjects each study, up to 4 weeks treatment
• Phase 2 adolescent study pending (SUI2002)*

*ClinicalTrials.gov NCT02133001, NCT03039192, NCT03097133, NCT03185819
Esketamine Study SUI2001

- Placebo-controlled 25-day parallel-group design
- 68 subjects
- IN esketamine (56 and 84 mg) versus placebo twice weekly
- Also receiving standard of care (hospitalization, other medication) for imminent suicidal risk

### MADRS Change from Baseline Results (Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esketamine (SD)</td>
<td>-13.4 (9.0)</td>
<td>-19.3 (12.0)</td>
<td>-26.4 (14.5)</td>
</tr>
<tr>
<td>Placebo (SD)</td>
<td>-9.1 (8.4)</td>
<td>-12.8 (9.8)</td>
<td>-23.0 (10.8)</td>
</tr>
<tr>
<td>LS Mean Difference (SE)</td>
<td>-5.3 (2.1)</td>
<td>-7.2 (2.9)</td>
<td>-4.5 (3.1)</td>
</tr>
<tr>
<td>2-sided p-value (compared to 0.05)</td>
<td><strong>0.015</strong></td>
<td><strong>0.015</strong></td>
<td>0.159</td>
</tr>
</tbody>
</table>

**Source:** Canuso C et al, Am J Psychiatry 2018;175(7):620-630 and FDA Briefing Document for PDAC-DSaRM Advisory Committee Meeting February 12, 2019.

SE – standard error
SD – standard deviation
Esketamine Study SUI2001

- **Secondary Endpoints:**
  - MADRS suicidal thoughts item (MADRS-SI)
  - SIBAT CGJ-SR
  - Beck Scale for Suicidal Ideation

- **Use of single-item anchoring with multiple-item scale**

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**SI Results**

- **MADRS-SI**
  - Median CFB difference between drug and placebo at Day 1 significant but not at Day 2 and beyond

- **CGJ-SR**
  - Median CFB difference not significant at any timepoint


SE – standard error
SD – standard deviation
Perspectives on Esketamine MDD-SI

• Study design developed to ensure ethical access to standard of care (inpatient hospitalization, medication, therapy) for patients with imminent SI/B in clinical trial setting

• Endpoint features
  – Beck Hopelessness Scale, Beck Scale for Suicidal Ideation
  – Patient vs. Clinician-Rated

• Some issues raised
  – Is single vs. multiple item more sensitive to change for efficacy comparison?
  – Does improvement of underlying MDD correlate at all to SI/B?

SI versus Diagnosis/Condition

• DPP Position: still important to have data from both perspectives (confirm efficacy of diagnostic endpoint first, then SI) to confirm overall effect.

• We may also eventually consider cross-diagnostic studies with presence of SI or SIB as primary screening criteria to confirm SI reduction effect apart from diagnosis.

• Challenge in determining appropriate efficacy endpoint sensitivity for rare events
Validity of SI as Endpoint

- SI Reduction: any actual clinical correlation to reduction in SB (i.e., suicide attempts/suicides)?
- Conventional psychiatric knowledge says presence of SI elevates SB risk, but there is controversy.*
- FDA plans to analyze data collected for SI/B prospective trial safety monitoring per our Guidance to Industry from 2009 (revision 2012) for any trends re: SI and its relationship to actual SB events.

* Large et al, 2016; Bolton et al, BMJ 2015
Si and SB Relationship

- Suicide remains difficult to prevent and understand on systematic level
- Suicide is heterogeneous
- Screening/monitoring relies heavily on self-report but SI/SB often occurs privately and is minimized or not disclosed
- SI in most cases doesn’t necessarily lead to SB but is considered a risk factor in several studies
- SB (especially suicide) is rare in studies
- Screening will always have major limitations
Measures to Boost SI Endpoint Clinical Correlation

• Sponsors/researchers should consider SB analysis (as exploratory outcome measure) alongside SI in their trials. (Although sensitivity will be limited due to paucity of events, so likely cannot be a primary measure.)

• Consider other potential correlative factors (depression, impulsivity, insomnia, anhedonia, associated implicit cognitions) for scales and analysis.
SI/B Scales: What to Consider

• Shorter versus multiple-item scale
• More granular (detailed item) scales less sensitive to change in brief time period while shorter scale still shows same efficacy trends in placebo-controlled post-hoc study by Ballard (2015).
• More granular scales already in use for safety monitoring (different goals)
  – AEs can be used as efficacy data
• Ease of correlation with underlying factor scales
SI/B Scales in Use

– Beck Scale for Suicidal Ideation (BSSI)
– Montgomery-Asberg Depression Rating Scale (MADRS)-SI
– Scale for Suicidal Ideation (SSI)
– Hamilton Rating Scale for Depression (HAMD)-SI
– Beck Depression Inventory (BDI)-SI
– Quick Inventory of Depressive Symptomatology (QIDS)-SI
– Sheehan Suicidality Tracking Scale (S-STS)
– Columbia-Suicide Severity Rating Scale (C-SSRS)
– InterSePT Scale for Suicidal Thinking (ISST)
– Suicide Ideation and Behavior Assessment Tool (SIBAT)
– Clinical Global Impression of Severity of Suicidality Scale (CGI-SS)
Other SI/B Trial Outcome Measures

• Adverse event reporting
• Digital/real-time longitudinal monitoring of SI/B during study
• Larger-scale real-world medical chart data collection (Kaiser Permanente study)
• Reduction of SI may be a potential clinical drug target but support for its approval could be strengthened by concomitant analysis of reduction of SB, and examination of drug effects on other contributing factors:
  – Underlying diagnosis/condition (depression/anxiety)
  – Impulsivity/irritability/anhedonia, etc.
  – Implicit factor/underlying cognition modification
  – Other clinical outcome measures: fewer/briefer hospitalizations, etc.
  – Efficacy in cross-diagnostic population
Summary-Future Directions

• Acute SI intervention may provide innovative clinical utility.
• Need to consider how this can be assessed and quantified in clinical research.
• Detection of rare events may merit consideration of innovative methods for data collection, but will still need statistical consideration of how to control/compare/prespecify that data.
• SI/B scales may have different considerations for efficacy versus safety, but there may be novel ways to coordinate each purpose.