U.S. FOOD & DRUG ADMINISTRATION

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

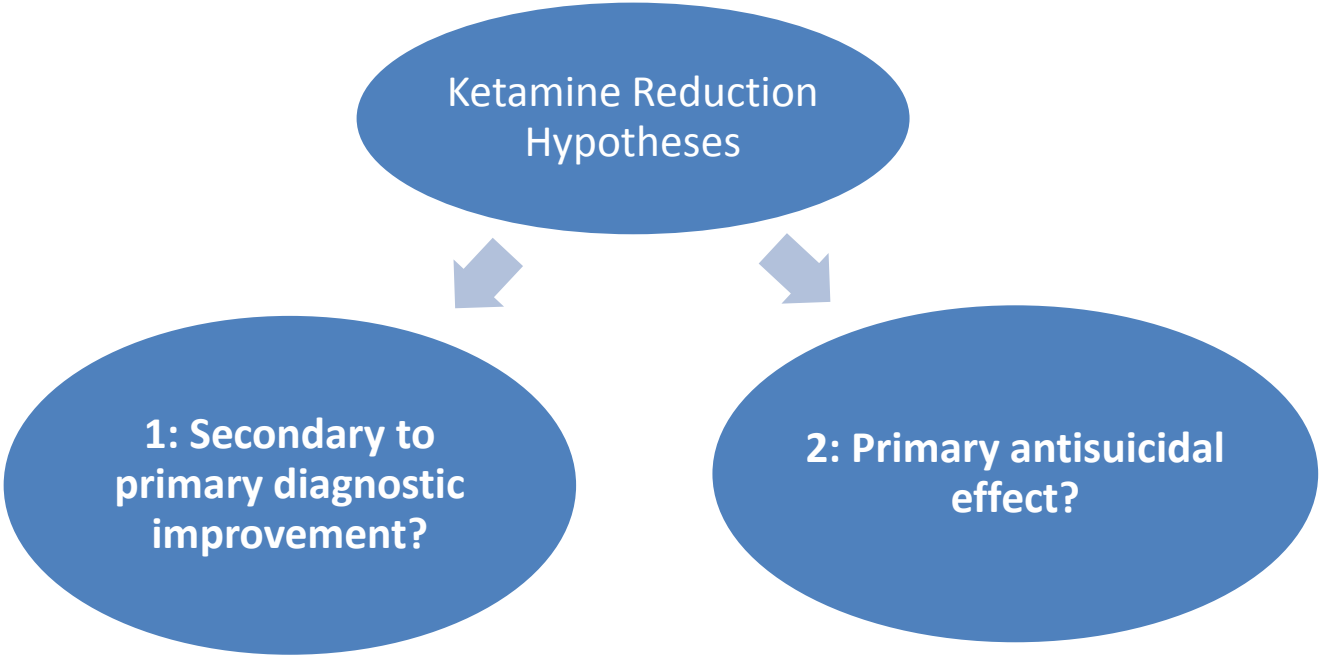
Ketamine SI RCT (Cross-Diagnostic)

- 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



SI Reduction Etiology

- Pro-Hypothesis #1: Correlation between primary outcome measure improvement and secondary SI measures.
- Pro-Hypothesis #2:
  - Ballard et al (2014): SI reduction appeared independent of depression/anxiety reduction (only 19% correlation).
  - 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)

	Day 1	Day 2	Day 25
Esketamine (SD)	-13.4 (9.0)	-19.3 (12.0)	-26.4 (14.5)
Placebo (SD)	-9.1 (8.4)	-12.8 (9.8)	-23.0 (10.8)
LS Mean Difference (SE)	-5.3 (2.1)	-7.2 (2.9)	-4.5 (3.1)
2-sided p-value (compared to 0.05)	**0.015**	**0.015**	0.159

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

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

Source: ClinicalTrials.gov and Canuso C et al, Am J Psychiatry 2018;175(7):620-630.

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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
  - SIBAT Modules: CGI-SS-R, CGI-SR-I, CGJ-SR
  - 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?

Source: ClinicalTrials.gov and Canuso C et al, Am J Psychiatry 2018;175(7):620-630.

SI versus Diagnosis/Condition

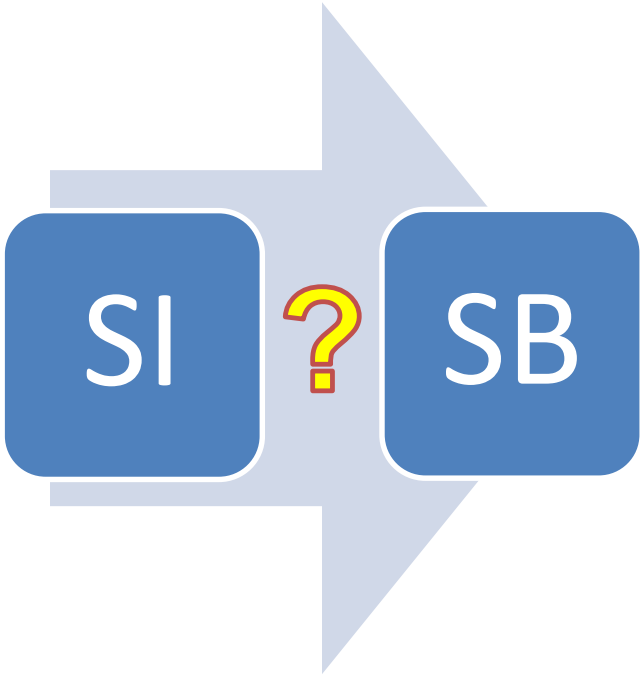
- DPP Position: still important to have data from both perspectives (confirm efficacy of diagnostic endpoint first, then SI) to confirm overall effect.
- We may also eventually consider cross-diagnostic studies with presence of SI or SIB as primary screening criteria to confirm SI reduction effect apart 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)

Summary-Future Directions

- 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.