Suicidal Ideation & Behavior Discussion

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2010
Suicidal ideation

2012
• Passive Suicidal ideation
• Active: Non-Specific (no method, intent or plan)
• Active: Method (No intent or plan)
• Active: Method and intent (but no plan)
• Active: Method, Intent and Plan
**FDA Guidance Documents**

Ideation or Behavior (SIB) 2010  
SIB intent unknown

Ideation or Behavior (SIB) 2012  
No equivalent
FDA Guidance Documents

Suicidal Behavior 2010
- Completed suicide
- Suicide attempt
- Preparatory acts toward imminent suicidal behavior (interrupted & aborted)
- Self-injurious behavior: No suicidal intent
- Not enough information (fatal)
- Other: No deliberate self harm
- Not enough information (non-fatal)

Suicidal Behavior 2012
- Completed suicide
- Suicide attempt
- Interrupted attempt
- Aborted attempted
- Preparatory actions
- Self-injurious behavior: No suicidal intent
What are the ramifications of greater granularity (2012 document) re: monitoring for ideation and of preparatory acts?

- Inter-rater reliability
- Self vs rater versions (when a “guide” is or is not present)
- Dealing with lifetime severity in the context of “recency” vs current vs “ever”
  - Suicidal ideation at its lifetime worst is more predictive of suicide than current ideation (Beck, Brown, et al 1999)
- “Worst severity” defined as “lifetime” & (separately) baseline
  - 1) Intent/Plan/Method (Ideation level)
  - 2) Ideation severity defined by intensity in terms of frequency, duration, controllability, deterrents & rationale for ideation
    - Validity of the severity items as a scale?
- Implications for identifying treatment emergent effects in a high risk population
  - What is the scale-based trigger & process to signal SIB as an SAE by FDA criteria (death, life threatening, hospitalization, disability, requires urgent action)
  - Treatment emergent SIB as a paradoxical response to treatment effectiveness as in depression and Alzheimer Disease: How to interpret?
FDA Guidance Documents
2010 & 2012

• What is the experience so far at the site level re: baseline current and lifetime reporting of SIB & identifying treatment emergent SIB effects in Phase 2 and 3 and/or MAD studies in high risk populations?
• Since the FDA credits the C-SSRS rater version as seeking to get data from all sources in assessing SIB, how do both versions of the C-SSRS seek “all sources” in meeting this goal cited by the FDA in its Guidance document?
• What published evidence, apart from the small study in Milwaukee (10 psychiatric inpatients vs 10 staff at the hospital), validates the equivalence or superiority of the eCSSRS vs the rater version?
• Issues as above for the rater and self-rated S-STS
• Can the same scales serve to assess Rx efficacy for drugs designed to reduce risk of self-harm as for monitoring SAEs per FDA Guidance Document in 2012?
From the 2009 Consensus Conference

• Psychometric properties relevant for detecting SAEs:
  – Retest stability
  – Effect sizes from blinded treatment studies
  – Diagnostic accuracy (high specificity)
  – Sensitive to change (from baseline) as a rare event and/or early indicator of change

• Psychometric properties of value in efficacy trials:
  – Internal consistency
  – Reliability
  – Factor structure
  – Convergent validity
A Gold Standard for Treatment Emergent Adverse Events?

• FDA asks for routine monitoring of biological data that might be indicative of an unexpected finding or a signal risk of toxicity, disability or death. **How well do currently available instruments work as a gold standard for emergent severe suicidal ideation/behavior?**

• Ultimately, a gold standard will need to be very sensitive to picking up drug/placebo differences in assessing treatment emergent SIB effects in realistic sample sizes and in relationship to drug exposure (as early as possible). **What do the data say? Are there any advantages in this regard in either version of the current S-STS, the C-SSRS or in the ISST-Plus?**

• Historically, in the area of psychotropic drug development, it has been easier to establish sensitivity to change over time (Study endpoint Vs baseline) than in meeting the stricter criteria of sensitivity to drug placebo differences. **How does this apply to identifying SAEs related to suicide risk in patients whose illness also includes an elevated risk of SIB? (e.g. MDD and BPD)**

• DOD and the VA developed a Self-Directed Violence Classification and an algorithm to match to the C-SSRS items. **Can data that industry has collected with the S-STS or the ISST-Plus be acceptable using relevant algorithms to C-SSRS? If not, what is needed? What is the rationale for rejecting these data collection instruments?**
SIB Assessments in Special Populations

- What modifications (if any) need to be made in baseline, lifetime & follow-up data
  - In patients with cognitive impairment (e.g.: Alzheimer Disease—early and later stage)
  - At different stages of the life cycle (the effects of age in the FDA meta-analyses)
  - In patients with alcohol or other substance dependence disorders (“state dependent effects”)
  - International studies
The 2009 Consensus
Beyond the Assessment Instruments

- FDA should make use of its new **post-marketing authority** to identify a screening instrument that would be valid, systematic and useful in obtaining post-marketing data to identify the potential association between a drug or drug class & the emergence of SIB
- Case control studies in large population-based health care systems
  - How could this be funded? A role for NIH Institutes with CNS portfolio?
- Search for early indicators of SIB associated risk (e.g.: “psychic anxiety”)
- A better understanding of the sequence & timing of emergence of SIB and associated variables
  - Such screening should employ standard time intervals (weeks, months, etc.)
- Genetic studies in high risk families to try to decipher causal mechanisms for treatment emergent and other SIB.
The 2009 Consensus: The Bottom Line

• The FDA, industry and the clinical research community need to evaluate the utility, limitations, costs and benefits of the current Agency requirement that all CNS-active clinical drug trials must include the C-SSRS or equivalent screening instrument for SIB
  – The impact of the mandate on the development of CNS-active drugs
  – The health and safety of the public
    • Studies in patients with varying degrees of SIB
    • More effective post-marketing data
    • Understanding potential mediators, moderators and associated variables
  – Beyond FDA requirements, there is a need for systematic assessment of suicide risk in high risk patients in primary care, mental health and emergency/hotline and urgent care settings & more effective efforts at suicide prevention in and apart from these settings.