Methodological Issues for Clinical Trials of Drug Treatments for Suicidality

ISCTM: Workshop Session 2b

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Disclosure (L Greenhill)

	Consultant	*Advisory Board*	*Data & Safety Monitoring*	*Honorarium or Travel Support*	*Gift*	*Research Contract*
Pfizer			X			
J & J						X
Otuka						X
NIMH						X
AACAP		X		X		
Lilly				X		
Caremark	X					

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Educational Goals of Workshop

By the end of this presentation, participants should be able to discuss:

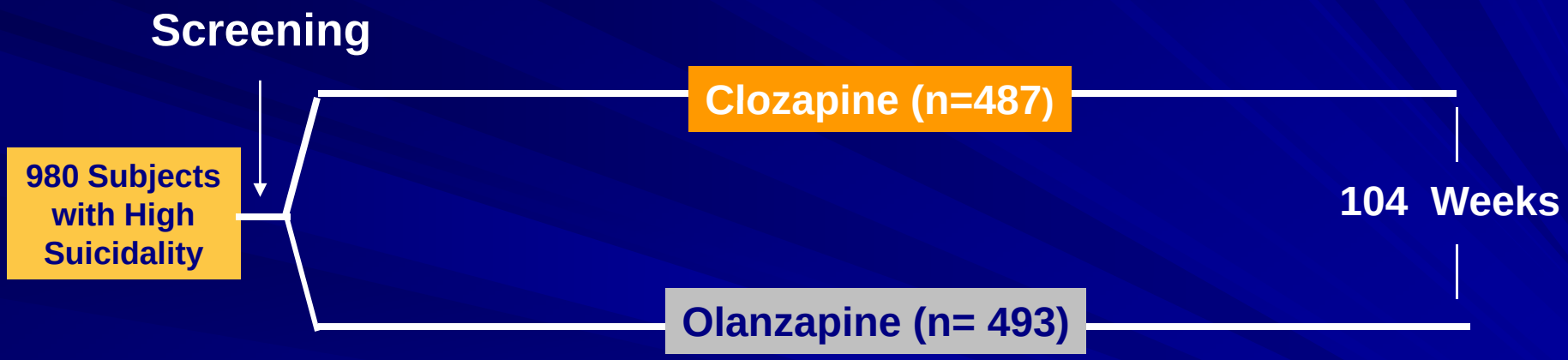
1. **Design features of published clinical trials for the treatment of suicidal behavior**
2. **Key methodological issues in trial design to determine the efficacy of interventions to mitigate suicidal behavior**
3. **Obstacles that face the researcher intent on studying the efficacy and feasibility of mounting a clinical trial in adults or youth with suicidal behavior**

Process

1. Review published RCT trial designs
   a) InterSePT study of clozapine versus olanzapine
   b) Treatment of Adolescent Suicide Attempters (TASA)
   c) Cognitive therapy to prevent attempts: Brown & Beck
2. Discuss key concepts related to the establishment of efficacy
3. Discuss key obstacles for conducting a clinical trial to treat suicidality – report back to main meeting
4. Consider the nature of the publication that might come out of this conference

Meltzer et al, Archives of General Psychiatry, 60(1): 82-91, 2003

InterSePT Study Design



- No concomitant therapy is excluded, including other antipsychotics
- Switch to alternative treatment is not permitted

Alphs L et al, Schizophrenia Bull, 30(30): 577-586, 2004

Cognitive Therapy Trial (Brown et al, 2005, JAMA)

- Single site study, N=120
- Inclusion: consecutive ER visits of adults, 18-55 years, with prior suicide attempt in past 3 months.
- Endpoint: incidence of re-attempt and time to event.
- Design: CBT versus Treatment as Usual (TAU) for 10 sessions, 18 mo F/U
- Results: 120/186 recruited, 24% of CBT versus 42% of TAU re-attempted, no difference in rates of ideation

Brown GK et al, JAMA, 294 (5): 563-570, 2005

Treatment of Suicidal Adolescent NIMH Trial (Brent et al, 2009, JAACP)

- Five site open study, N=124
- Inclusion: consecutive ER visits of adolescents, 12-18 years, with prior suicide attempt in past 3 months.
- Endpoint: incidence of re-attempt and time to event.
- Design: Patient preference: CBT (17) versus Medication Algorithm (14) Versus Combined (93) for 16 sessions, 6 mo F/U
- Boards: Ombudsmen, DSMB, Suicidal Event Determination.
- Results: Morbid risk of suicidal events (0.19) and reattempts on follow-up for 6 months (0.12) with median time to event 44 days. Higher self-rated depression, prior history of multiple attempts, history of sexual abuse, higher rates of ideation, lower family cohesion predicted re-occurrence and earlier time to event.

Brent D et al, JAACP, 48 (10): publish before print, 2009

RCT Planning Challenges

- Definitions, Scales
  - Suicidal behavior
- "Intent"
- Patient selection
- Study Design
- Inclusion/Exclusion
- Managing Suicidality
- Site Selection

- **Oversight**
- **Recruitment**
- **Training, supervision**
- **Differential drug effects**
- **Choice of comparator**
- **Study duration, visit #**
- **Open label vrs DB**
- **Sample Size Estimation**

Question 1: What definitions should be used to guide inclusion / exclusion criteria?

a. What are the criteria for selecting the subjects?
b. What type of control subjects may be recruited : for example, is treatment as usual considered ethical?

Definitions and Scales

- Need good definitions of key terms to obtain optimal inclusion /exclusion criteria so communicate between studies:
  - Suicide attempts
  - Suicide gestures
  - Suicide thinking
  - Intent
- Need optimal scales that are sensitive and selective which measure severity and change?

InterSePT Definitions

Suicide

- Willful death by one's own hand; a "successful" suicide attempt

Parasuicide/Attempted suicide

- Many suicidal people engage in suicidal activities that do not result in death.
  - >20 times more likely to eventually end their own lives than those who don't participate in such activities.

Suicidal ideation

- Considering or fantasizing about taking one's own life. May range from vague or unformed urges to meticulously detailed plans and posthumous instructions.

Suicidal gestures ("cry for help")

- Actions resembling suicide attempts but without full commitment, or in a deliberate attempt to have others notice, e.g., by a non-lethal method of self-harm that leaves obvious signs of the attempt, or simply a lethal action at a time when the person considers it likely that he/she will be rescued.

2. Intent Definitions

- Is there full “intent” if the subject genuinely wishes to die but fail because of
  - lack of knowledge about lethality?
  - cognitively impairment and think it would be successful even if little likelihood?
  - unwillingness to try methods that may end in permanent damage if they fail or harm others?
  - an unanticipated rescue.
  - Plan a rescue but non occurs
- Is suicide-related death driven by delusional thinking the same as “intent?”
- How define and discern the intent?

Question 3: What type of patients should be included?

- a. Given the success of the InterSePT study, and the relatively poor predictive power of suicidal ideation in predicting serious suicide attempts, should clinical trials designed to assess the efficacy of drugs or psychotherapy in reducing the risk of suicide recruit patients with severe and recent suicidal behavior (rather than relying exclusively or in part upon scales of suicidality)?

b. Should a prior suicide attempt be an inclusion criterion, and if so, within what period of time prior to study entry?

c. Should the recurrent behavior (endpoint) always be another attempt, or might it include severe (to be defined and oprationalized) ideation?

Question 4: What study designs should be considered for mounting a RCT to prevent suicidal behavior?

a. What are the criteria for selecting the medications or psychological interventions to be compared?

b. What control arm options are both ethical and adequate : for example, is treatment as usual considered ethical?

d. How do you incorporate associated supportive and attrition prevention (ASAP) measures to enable subjects to remain in study?

Question 5: What endpoint is optimal to measure changes in suicidal behavior?

1. How do the existing group of endpoints compare in relationship to existing RCT endpoints in reliability of measurement, training requirements for measurement, and validity across age groups?

2. How does “time to recurrent of suicidal event” compare with a change on a scale?

3. Are “independent evaluators” who are kept blind as to the treatment assignment of the patient acceptable methods of controlling for study biases?

Endpoint Selection in InterSePT Trial

Specific Aim: To demonstrate decreased risk for suicide among schizophrenic patients treated with Clozaril compared to that for patients treated with Zyprexa, as measured by time (in days, after randomization) to either an

EndPoint: defined as the Time To:

a)Type I Event (time to suicide attempt or intervention to prevent suicide)

or

b)Type II Event (related to blinded psychiatrist-determined changes in the CGI-SS (significant worsening)

Question 6: How is Suicidal Behavior Managed?

- Unethical not to try to prevent suicide
- Impossible to power to study using suicide as only endpoint
- Must use surrogate endpoints related to suicidal behavior (risk of suicidality)
  - suicide attempts (including death from suicide)
  - hospitalization to prevent imminent risk of suicide
  - increased surveillance for imminent risk of suicide

Question 7: What types of sites should be recruited for participation?

- 1. Sites that have successfully recruited patients with severe mood disorders.
- 2. Sites with easy access to inpatient units.
- 3. Sites with unified control over both outpatient and inpatient treatment facilities so that flow can be smooth between emergency room, inpatient units, and outpatient research clinic.
- 4. Sponsors willing to invest heavily in recruitment .
- 5. Research clinic sites with easy access to patients in terms of location and parking.

Question 8: Oversight: what types of monitoring boards are needed?

- 1. A data and safety monitoring board (DSMB) can oversee recruitment and retention, and will use stopping rules.
- 2. Should the new study follow the InterSept and TASA studies, which used independent evaluation boards to determine which events met the criterion of being a recurrent suicidal event?
- 3. Should the DSMB be empowered to require ombusdmen interventions?

Question 9: How can recruitment and retention stay on track?

- a. Parents of depressed adolescent attempters refused study participation in TASA if randomization was involved – is an RCT feasible for suicidal adolescents?
- b. Can patient-choice models be developed that allow for double-blind, controlled study designs?
- c. More youth were retained in the clinical trial who were in psychotherapy; how to boost retention in medical treatment arms?

Question 10: What type of training and ongoing supervision are needed?

- a.Initial training and ongoing regular supervision are needed to prevent rating drift and maintain fidelity to the protocol. What frequency of direct supervision of CBT therapy sessions is required?
- b.Does evidence from similar studies show that frequent staff supervision prevents attrition of subjects?

Question 11: Differential Drug Effects

- What are drug treatment effects on suicidal ideation versus behavior?
- What are interactions between age and drug response?
- What is the earliest onset of drug effects on suicidal ideation or behavior?
- Is there a differential response to drugs for suicidal gestures versus attempts?
- Is there a complex response to drugs over time (some Ss get better, some Ss get worse)?

Next Steps

- Complete the summarization of notes taken during workshop
- Thoroughly review more existing studies
- Identify RCT trial design issues that might deal more effectively with factors that can lead to a failed study