Critical Issues in the Design of Clinical Trials for Neurocognitive Drugs

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FDA-NIMH Workshop: Clinical Trial Design for Neurocognitive Drugs

- Process:
  - Identified major study design issues for which there was a lack of consensus
  - Identified expert in the area to review available empirical data on the issue
  - At Workshop, expert presented review with recommendations for how to proceed
  - Discussion panel, comprised of academic, industry, and FDA representatives, reviewed recommendations
  - If possible, consensus was reached

Study Design Issues

- Clinical Status
  - Medication status
  - Symptom severity
- Medications
  - Antipsychotics
  - Concomitant
- Level of Cognitive Impairment
- Study Design
  - Adjunctive agents
  - Broad spectrum agents

TURNS Study Design

Inclusion Criteria: Clinical Status

- What design approaches should be used to isolate change in cognitive function from changes in other symptom domains, i.e. how to isolate a specific effect on cognition from other concurrent changes in clinical status that may effect cognitive function (Pseudospecificity)

TURNS Study Design

Inclusion Criteria: Clinical Status

- Include subjects who:
  - Are clinically stable and in the residual (non-acute) phase of illness for a specified period of time (e.g., 12 weeks)
  - Have been maintained on current antipsychotic and other concomitant psychotropic medications for a specified period of time sufficient to minimize potential complications of assessment of cognitive status (e.g., 8 weeks) and on current dose for a specified time period (e.g., 4 weeks)
  - Have a predefined level of positive, negative, depressive, and extrapyramidal symptoms

TURNS Study Design

Inclusion Criteria: Clinical Status

- Rationale:
  - Cross-sectional studies have demonstrated:
    - Hallucinations/delusions: no correlations
    - Disorganized behavior: Small to medium correlations
    - Negative symptoms: Medium to large correlations (primary vs secondary)
  - Longitudinal studies have demonstrated:
    - Hallucinations/delusions: Small to medium correlations
    - Disorganized behavior: Medium correlations
    - Negative symptoms: Small to large correlations
  - 12 point change in IQ between medicated and unmedicated condition (Weickert et al, 2003)
    - Medications may enhance test-taking ability

TURNS Study Design

Inclusion Criteria: Clinical Status

- Rationale:
  - Establishing maximum symptom severity reduces baseline within group heterogeneity
  - Pseudospecificity is best dealt with by restricting symptom severity prior to randomization
    - Statistical approaches cannot be used to rule out pseudospecificity
      - Cannot infer causality through statistical adjustment of post-randomization covariates

TURNS Study Design

Inclusion Criteria: Medications

- Second Generation Antipsychotics other than clozapine
  - Further restriction would depend on:
    - Mechanism of action
    - Type of study, e.g. PD/PK
    - Stage of development
  - Exclude subjects treated with multiple antipsychotics
- Concomitant Medications: Yes, but …
  - Further restriction would depend on:
    - Mechanism of action
    - Stage of development
  - PRN anti-anxiety agents would be allowed, but all NP testing must occur 24 hours after last PRN dose.

TURNS Study Design

Inclusion Criteria: Level of cognitive impairment

- Maximum performance level: Performance within 1.0 SD from perfect on the following three measures:
  - Letter-number span (24 or >)
  - HVLT total (31 or >)
  - CPT d-prime (3.47 or >)
- Minimum performance level: subject must be able to validly complete the baseline MATRICS assessment

TURNS Study Design: Adjunctive Agents

- Overall design: parallel group; double-blind comparison of placebo and study drug
  - Lead-in Phase: 2 weeks
  - Double-Blind Treatment Phase: 8 weeks
- Adjunctive agent added to current medication regimen
  - Restriction of antipsychotics and concomitant medications as described above
- Assessments:
  - MATRICS Battery: Primary outcome measure
  - Functional: Co-Primary measure
    - UCSD Performance-Based Skills Assessment (UPSA)
    - Schizophrenia Cognition Rating Scale (SCoRS)
  - Clinical: BPRS, SANS, Calgary Depression Scale

TURNS Study Design: Broad Spectrum Agents

- Evaluation of the cognitive-enhancing effects should be separated from the evaluation of antipsychotic efficacy (Pseudospecificity)
- Major issue is the selection of an appropriate comparator
  - Ideal comparator would be cognitively-neutral or better
- Possible comparator agent options:
  - Placebo
    - Minimizes potential confounding from EPS
    - Potential for significant symptom exacerbation
  - Conventional Antipsychotic
    - Potential of differential EPS and other neurological side effects
    - Commonly used in conjunction with anticholinergics

TURNS Study Design: Broad Spectrum Agents

- Possible comparator agent options (contd):
  - Second Generation Antipsychotic
    - Minimize potential confounding due to neurological side effects
    - Potential problems with interpretation:
      - Broad spectrum improves cognition while SGA comparator either does not or not as much
      - Broad spectrum has no effect, but SGA comparator impairs cognition
      - Both Broad Spectrum and SGA comparator impair cognition, but broad spectrum agent to a lesser degree
    - Requires placebo control to differentiate among possible interpretations