Some Approaches to Address the Problem of Missing Data in CNS Clinical Trials

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Collaborative Studies Coordinating Center
TICTS Conference, April 2014
Outline

• The missing data problem in CNS trials
• Strategies to minimize impact of missing data at protocol design stage
  – Minimize drop-outs
  – Collect key data after treatment discontinuation

• Designs which incorporate these strategies
  – Cross-over and re-randomization designs
  – Time to all-cause discontinuation
The Problem
## Drop-out Problem in CNS trials

<table>
<thead>
<tr>
<th>Indication</th>
<th>Discontinuation Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-tier Journals</td>
<td>Overall 10%</td>
<td>Wood 2004</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>23% Active 40%</td>
<td>Moore 2008</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>39% Active 39%</td>
<td>Kahn 2001</td>
</tr>
<tr>
<td>Antipsychotics – active controlled</td>
<td>30% Active ---</td>
<td>Kemmler 2005</td>
</tr>
<tr>
<td>Antipsychotics – placebo controlled</td>
<td>49% Active 60%</td>
<td>Kemmler 2005</td>
</tr>
</tbody>
</table>
Impact of Missing Data

• High rates of missing data due to patient discontinuation pose substantial complications for addressing bias and interpretation of results.
  – Statistical methods more developed, widely used
  – Yet the complications increase with the % of missing data

• Study designs aimed at reducing participant drop-out (or it’s impact) are warranted
Recommendations
Recommendation (2):

Investigators, sponsors, and regulators should design clinical trials consistent with the goal of maximizing the number of participants who are maintained on the protocol-specified intervention until the outcome data are collected.
NAS Missing Data Panel: Design Elements to Minimize Dropouts

**Patients:**

- run-in period or enrichment to identify participants who can tolerate or respond to study treatment
- limit to target population (i.e., those who need a new treatment)

**Treatments:**

- flexible doses (titration)
- “add-on” treatment to standard of care vs. standard of care (no placebo)
NAS Missing Data Panel:
Design Elements to Minimize Dropouts

Treatment Period:
• short treatment period (or measure primary efficacy early-on and continue following for safety)
• rescue medications (in combination with time to treatment failure)
• determine long-term efficacy with randomized withdrawal

Outcome:
• define outcomes ascertainable in a high proportion of participants (e.g., composite outcome)

Nat. Res. Council 2010
Recommendation (3):
Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol-specified intervention in the course of the study, except in those cases for which a compelling cost-benefit analysis argues otherwise, and this information should be recorded and used in the analysis.
Collecting Key Information After Drop Out

The benefits of collecting key outcomes after treatment discontinuation often outweigh costs

- Gain Further safety and efficacy information
  - Mortality, Hospitalization
  - Relapse
- Inform Missing data imputation:
  - Directly in the imputation
  - Evaluate consistency of imputation

Design Solution 1:
Multi-sequence 2-period Design
Multi-sequence 2-period Design

A family of designs that addresses both issues:

• Minimize drop-outs
• Collect data after drop-out

Good design choice for:

• Chronic diseases
• Treatments without long-term efficacy effects

CNS: depression, bipolar, schizophrenia, pain, etc.

Koch et al 1998
3-Sequence 2-Period Design

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:A</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>A:P</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>P:A</td>
<td>Placebo</td>
<td>Active</td>
</tr>
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</table>

Enhanced Retention

• Everyone receiving Placebo in Period 1 will receive Active in Period 2.

• Some participants receiving Active in Period 1 will stay on Active in Period 2.

• **If discontinue treatment, do not discontinue study. Immediately cross-over to next arm.**

Koch et al 1998
# Role of Period 1: Primary Efficacy

## Sequences (AA+AP) vs. PA

<table>
<thead>
<tr>
<th>Sequence Rand Ratio</th>
<th>A/P TRT Bal. in P 1</th>
<th>A/P TRT Bal. in P 2 *</th>
<th>A vs. P Power</th>
<th>Period 1 Retention:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1:2</td>
<td>50/50</td>
<td>75/25</td>
<td>larger</td>
<td>Favors premature transition to Period 2</td>
</tr>
<tr>
<td>1:1:1</td>
<td>66/33</td>
<td>66/33</td>
<td>smaller</td>
<td>Reduced advantage of premature transition to Period 2</td>
</tr>
</tbody>
</table>

* Assuming equal continuation from period 1 across sequences

Koch et al 1998

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**Table:**

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Role of Period 2

Continued Safety and Efficacy Measures
• Data collection of key outcomes after primary treatment period

AA vs. AP: Randomized Withdrawal
• Is Period 1 benefit preserved, or is there a loss/reversal?

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<tr>
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<td>Active</td>
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Koch et al 1998
Role of Period 2

AA vs. PA: Delayed Start

• What is the effect of delaying treatment for 1 period?
• Note: reduced power and weaker generalizability if many on P do not complete Period 1

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<td>Active</td>
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<tr>
<td>A:P</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>P:A</td>
<td>Placebo</td>
<td>Active</td>
</tr>
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Koch et al 1998
Role of Periods 1 and 2 Together

AP vs. PA

• Usual crossover analysis of Active vs. Placebo
• If no carryover, serves as supportive analysis comparing the 2 treatment groups

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<td>Active</td>
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<tr>
<td>A:P</td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>P:A</td>
<td>Placebo</td>
<td>Active</td>
</tr>
</tbody>
</table>

Koch et al 1998
Example: Tesamorelin for excessive abdominal fat in HIV

Phase 1 disc. rate similar for placebo and active

<table>
<thead>
<tr>
<th>Sequence</th>
<th>26 weeks</th>
<th>26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>T:T</td>
<td>Tesamorelin</td>
<td>Tesamorelin</td>
</tr>
<tr>
<td>T:P</td>
<td>Tesamorelin</td>
<td>Placebo</td>
</tr>
<tr>
<td>P:T</td>
<td>Placebo</td>
<td>Tesamorelin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seq</th>
<th>Disc. P1</th>
<th>Continued</th>
<th>Disc. P2</th>
<th>Total Disc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T:T, T:P</td>
<td>25%</td>
<td>Eligible completers</td>
<td>15%, 25%</td>
<td>43%</td>
</tr>
<tr>
<td>P:T</td>
<td>22%</td>
<td>Eligible completers</td>
<td>21%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Falutz et al 2010

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### Example: 2 Period X-over of two Active Treatments for Osteoarthritis

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1 (6 wks)</th>
<th>Period 2 (6 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:DM</td>
<td>Acetaminophen</td>
<td>Diclofenac Plus Misoprostol</td>
</tr>
<tr>
<td>DM:A</td>
<td>Diclofenac Plus Misoprostol</td>
<td>Acetaminophen</td>
</tr>
</tbody>
</table>

Some who disc. from Phase 1 continued in Phase 2

<table>
<thead>
<tr>
<th>Seq</th>
<th>Disc. P1</th>
<th>Continued</th>
<th>Disc. P2</th>
<th>Total Disc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM:A</td>
<td>21%</td>
<td>Completers + 42% d/c</td>
<td>23%</td>
<td>32%</td>
</tr>
<tr>
<td>A:DM</td>
<td>22%</td>
<td>Completers + 32% d/c</td>
<td>21%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Pincus et al 2001

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Example: CATIE multiphase comparison of antipsychotics for schizophrenia

18-month double-blind comparative effectiveness trial of 5 randomized active treatments

Followed many NAS Recommendations

Patients:
• Target population: broad inclusion criteria, but all in need of med improvement

Treatments:
• Flexible dosing (titration)
• No placebo

Lieberman et al 2005
Example: CATIE multiphase comparison of antipsychotics for schizophrenia

**Treatment Period:**

- 2 main phases
- **Rescue:** Re-randomized in next phase when current treatment is discontinued

**Outcome:**

- **Measurable for everybody:** Time until all-cause discontinuation

75% discontinued Phase 1 early, yet 56% of them continued into next phase

Lieberman et al. 2005
Design Solution 2:

Time to Discontinuation as Primary Outcome
CATIE Primary Outcome: Time Until All-Cause Discontinuation

- Efficacy
- Tolerability

All-Cause Discontinuation

- Clinician Input
- Patient Input
Time to Discontinuation - Benefits

• Combines efficacy, safety, non-compliance, and general dissatisfactions otherwise hard to measure
  • reason for discontinuation (efficacy, safety, patient decision) collected for supportive analyses
  • note: efficacy and safety can cancel each other out

• Good for:
  • incurable diseases requiring long-term treatment
  • when staying on drug is an indication of success of drug
  • schizophrenia, bipolar, major depression, arthritis, diabetes, HIV
Time to Discontinuation - Benefits

• **Simple measure of effectiveness**
  - Easy to comprehend (for some)
  - Easy to calculate
  - Transparent
  - Not impacted by assumptions or data handling rules

• **No missing data!**
  - **Discontinuation is the outcome instead of the problem**
Time to Discontinuation - Drawbacks

• Some side effects take longer to develop
  • Weight gain, metabolic effects
  • TRTs may have different side effect profiles
  • By definition, time to discontinuation concentrates on the time until the AE leads to discontinuation, not on the severity of specific AEs
  • Evaluations of Safety and Efficacy outcomes are needed

• Loss of power could be caused by loss to follow-up that is unrelated to drug (especially early dropouts for patient decision)
Time to Discontinuation - Drawbacks

• Is it directly interpretable into a context meaningful to a specific patient?
  • Growing evidence that switching is destabilizing
  • Easier to interpret than QALY?
Time to Discontinuation - CATIE

![Graph showing the time to discontinuation for different medications. The graph illustrates the proportion of patients without an event over time for Olanzapine, Perphenazine, Quetiapine, Risperidone, and Ziprasidone.]

- Overall p-value = 0.004*
- P<0.001 for olanzapine vs. quetiapine
- P=0.002 for olanzapine vs. risperidone

Reference: Lieberman et al 2005

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All-Cause vs. Treatment Failure

• Single primary integrative outcome is good
  – Combines multiple benefits and multiple harms

• Time to Treatment Failure
  – Defined rigorously through adjudication
    – In order to reduce site effects/variation
  – Censor reasons for discontinuation other than lack of efficacy or intolerability
    – Reduces noise; may reflect dissatisfaction with study, not drug failure
    – But may likely be censoring informative data
Time to Discontinuation - CATIE

- Some things we learned from CATIE:
  - Reason for patient discontinuation (efficacy, safety, patient decision) is informative about treatment effectiveness
  - Providing treatment options after discontinuing tends to keep patients with treatment dissatisfaction in the study for further evaluation.
Summary

(1) Minimize impact of missing data at design stage

(2) Cross-over or Re-randomization Designs:
  • Aid retention in Period 1
  • Provide Supportive or secondary Aims in Period 2

(3) Time to discontinuation is useful outcome and avoids missing data problem
References


References


