THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

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

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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

Indication	Discontinuation Rate			Reference
	Overall	Active	Placebo	
Top-tier Journals	10%			Wood 2004
Musculoskeletal pain		23%	40%	Moore 2008
Antidepressants		39%	39%	Kahn 2001
Antipsychotics – active controlled		30%	---	Kemmler 2005
Antipsychotics – placebo controlled		49%	60%	Kemmler 2005

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

NAS Missing Data Panel

- National Academy of Science Panel on Handling Missing Data in Clinical Trials (2010)

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

NAS Missing Data Panel

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***.

Nat. Res. Council 2010

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

Nat. Res. Council 2010, Koch et al 1998

Design Solution 1:

Multi-sequence 2-period Design

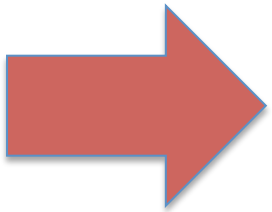
Multi-sequence 2-period Design

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

Sequence	Period 1	Period 2
A:A	Active	Active
A:P	Active	Placebo
P:A	Placebo	Active

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

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

Sequence	Period 1	Period 2
A:A	Active	Active
A:P	Active	Placebo
P:A	Placebo	Active

* Assuming equal continuation from period 1 across sequences

Koch et al 1998

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?

Sequence	Period 1	Period 2
A:A	Active	Active
A:P	Active	Placebo
P:A	Placebo	Active

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

Sequence	Period 1	Period 2
A:A	Active	Active
A:P	Active	Placebo
P:A	Placebo	Active

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

Sequence	Period 1	Period 2
A:A	Active	Active
A:P	Active	Placebo
P:A	Placebo	Active

Koch et al 1998

Example: Tesamorelin for excessive abdominal fat in HIV

Sequence	26 weeks	26 weeks
T:T	Tesamorelin	Tesamorelin
T:P	Tesamorelin	Placebo
P:T	Placebo	Tesamorelin

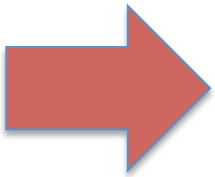
Phase 1 disc. rate similar for placebo and active

Seq	Disc. P1	Continued	Disc. P2	Total Disc.
T:T, T:P	25%	Eligible completers	15%, 25%	43%
P:T	22%	Eligible completers	21%	40%

Falutz et al 2010

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

Sequence	Period 1 (6 wks)	Period 2 (6 wks)
A:DM	Acetaminophen	Diclofenac Plus Misoprostol
DM:A	Diclofenac Plus Misoprostol	Acetaminophen



Some who disc. from Phase 1 continued in Phase 2

Seq	Disc. P1	Continued	Disc. P2	Total Disc.
DM:A	21%	Completers + 42% d/c	23%	32%
A:DM	22%	Completers + 32% d/c	21%	30%

Pincus et al 2001

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

CATIE
Clinical Antipsychotic Trials of Intervention Effectiveness
A Research Program Studying Treatment Effectiveness and Outcomes in Schizophrenia and Alzheimer's Disease

Lieberman et al 2005

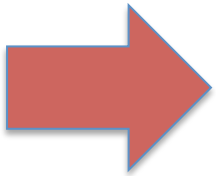
Example: CATIE multiphase comparison of antipsychotics for schizophrenia

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



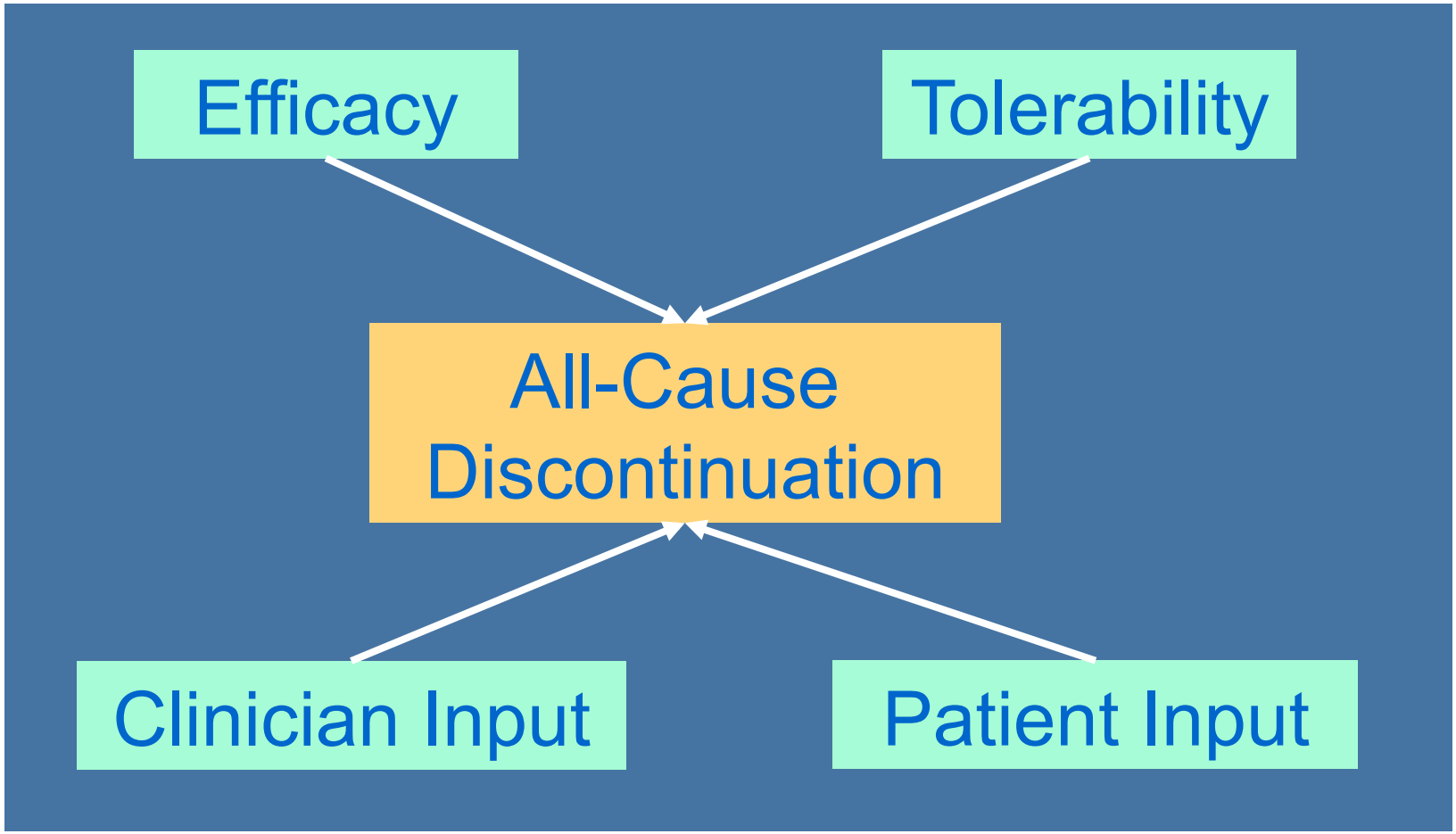
75% discontinued Phase 1 early, yet 56% of them continued into next phase

Lieberman et al 2005

Design Solution 2:

Time to Discontinuation as Primary Outcome

CATIE Primary Outcome: Time Until All-Cause Discontinuation



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

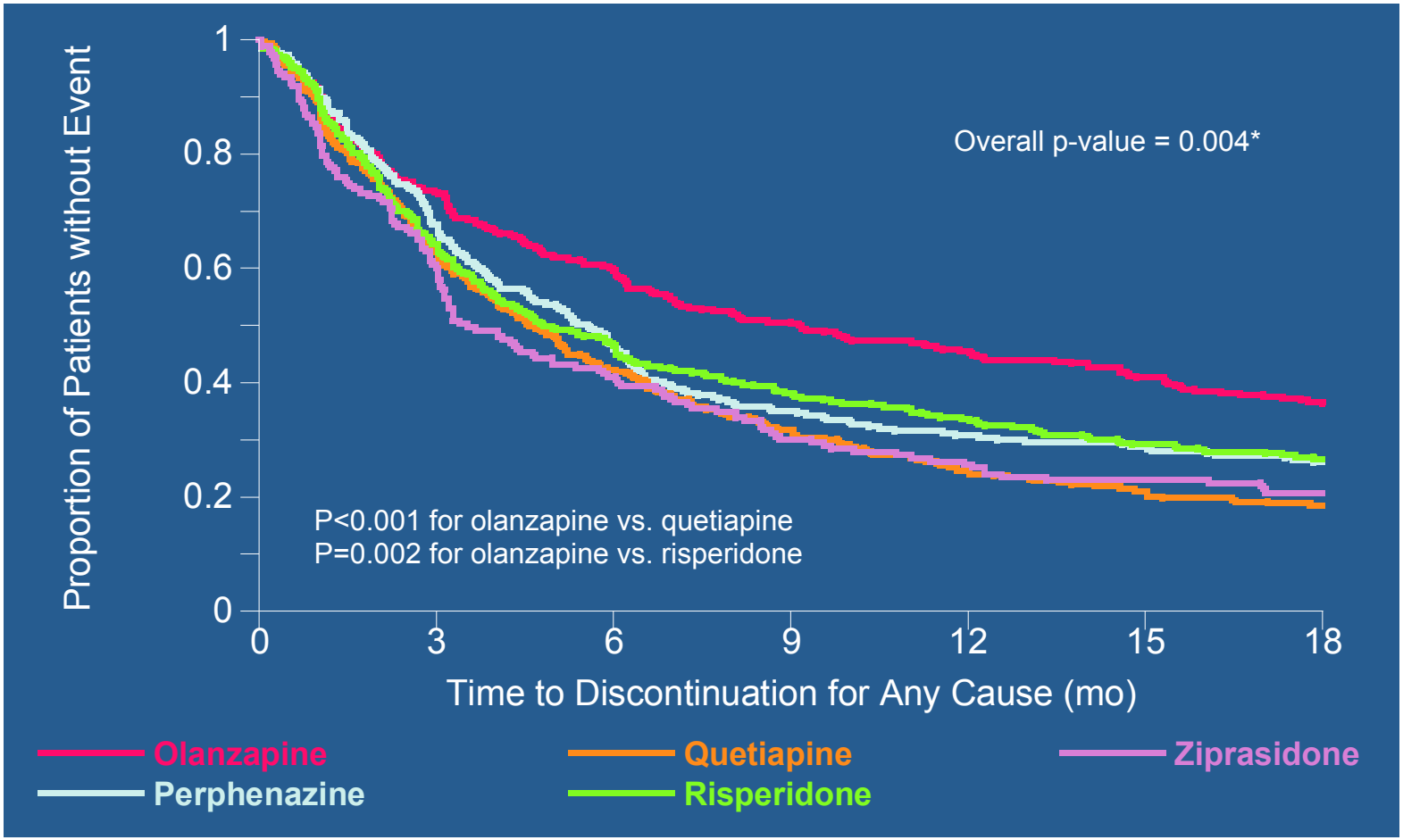
- Some side effects take longer to develop
  - Weight gain, metabolic effects
  - TRTs may have different side effect profiles
  - By definition, time to discontinuation concentrates on the time until the AE leads to discontinuation, not on the severity of specific AEs
  - Evaluations of Safety and Efficacy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



Lieberman et al 2005

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 dis-satisfaction in the study for further evaluation.

Davis et al 2011

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

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