An Ounce of Prevention is Worth a Pound of Cure

Implications of the National Research Council Report on Missing Data in Clinical Trials

Michael P. McDermott, Ph.D.

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Elements of Good Clinical Trial Design

- Randomization
- Blinding
- Appropriate control/comparison group(s)
- Adequate sample size
- Appropriate outcome variable(s)

Problem of Missing Data

- Amount of missing data due to dropout can be high, particularly in long-term trials
  - Antipsychotic trials (Kemmler et al., 2005; Rabinowitz et al., 2009)
  - Dementia trials (Molnar et al., 2009)
  - Post-traumatic stress disorder (Lurie and Levine, 2010)
  - Heart failure (Lipinski et al., 2009)
- Can reduce the benefits of randomization by introducing substantial bias
- Lamotrigine example

A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy

D.M. Simpson, MD; R. Olney, MD; J.C. McArthur, MBBS, MPH; A. Khan, MD; J. Godbold, PhD; and K. Ebel-Frommer, BA, for the Lamotrigine HIV Neuropathy Study Group*

Article abstract—*Objective:* To investigate the analgesic efficacy of lamotrigine in the treatment of painful HIV-associated distal sensory polyneuropathy (DSP). *Background:* The pathogenesis of HIV-associated DSP is unknown and there is no effective treatment. A novel anticonvulsant, lamotrigine, blocks voltage-sensitive sodium channels and inhibits the release of glutamate and aspartate. There have been anecdotal reports of efficacy of lamotrigine in the treatment of painful neuropathy and trigeminal neuralgia. *Methods:* In a multicenter, randomized, double-blind, placebo-controlled study, lamotrigine was initiated at 25 mg per day and slowly titrated over 7 weeks to 300 mg per day. Study duration was 14 weeks. The primary outcome measure was change in pain on the modified Gracely scale with secondary outcome measures including change in neurologic examination, use of concomitant analgesic medications, and global pain relief. *Results:* Of 42 enrolled subjects, 13 did not complete the 14-week study endpoint. In five of these, rash was the cause for dropout. In the remaining 29 evaluable subjects, 20 patients received placebo and 9 received lamotrigine. The pain scores at baseline were not significantly different. The reduction in average pain from baseline to week 14 was greater ($p = 0.03$) in the lamotrigine group (−0.55) than in the placebo group (−0.18), adjusting for baseline levels of pain. There was no difference between the groups on the change in peak worst pain. *Conclusions:* In this small trial, lamotrigine showed promise in the treatment of pain associated with HIV-related DSP. The frequency of rash was greater than in lamotrigine studies in epilepsy. A larger controlled study of lamotrigine is warranted. **Key words:** HIV—AIDS—Lamotrigine—Neuropathy.

NEUROLOGY 2000;54:2115–2119

Dealing with Missing Data

- Avoid the problem – Don't have missing data!
- The problem is unavoidable, so just live with it!
- Let the statistician's figure it out!
  - Literature is filled with statistical methods to deal with missing data
  - No single method or class of methods is suitable for all situations
  - Validity of any particular method depends on assumptions which, in general, cannot be verified using the observed data, i.e., are *untestable*

Some Commonly Used Methods

- Complete case analysis
  - Include only those with complete data in the statistical analysis
  - Introduction of bias (lamotrigine example)
  - Loss of power
- Carrying forward the last (or baseline) observation
  - LOCF (or BOCF)
  - Usually unrealistic imputation model (bias)
  - Introduction of false precision
    - Increase in probability of Type I error

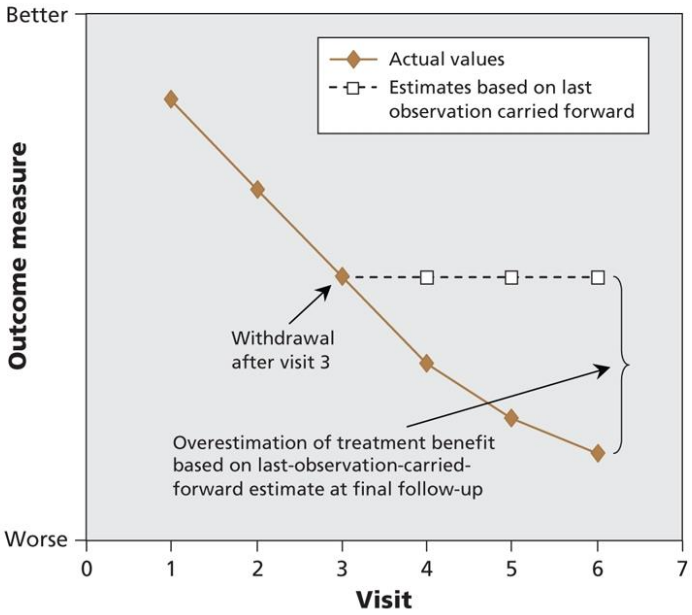
LOCF in Dementia Research

COMMENTARY

Research methods

Does analysis using "last observation carried forward" introduce bias in dementia research?

Frank J. Molnar MSc MDCM, Brian Hutton MSc, Dean Fergusson MHA PhD



Reasons for Popularity of Complete Case/LOCF Analyses

- Simplicity
- Unavailability of software to implement state-of-the-art methods
- Comfort of FDA with older, better understood methods
- Risk-averse behavior of drug developers in the face of the regulatory process
- Non-specific and insufficiently prescriptive nature of existing regulatory guidances
- Education of biostatisticians in the use of state-of-the-art methods

National Research Council Report

- At the request of the FDA, the National Research Council convened panel of experts to prepare "a report with recommendations that would be useful for FDA's development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and on appropriate statistical methods to address missing data for analysis of results."
  - The Prevention and Treatment of Missing Data in Clinical Trials (2010)

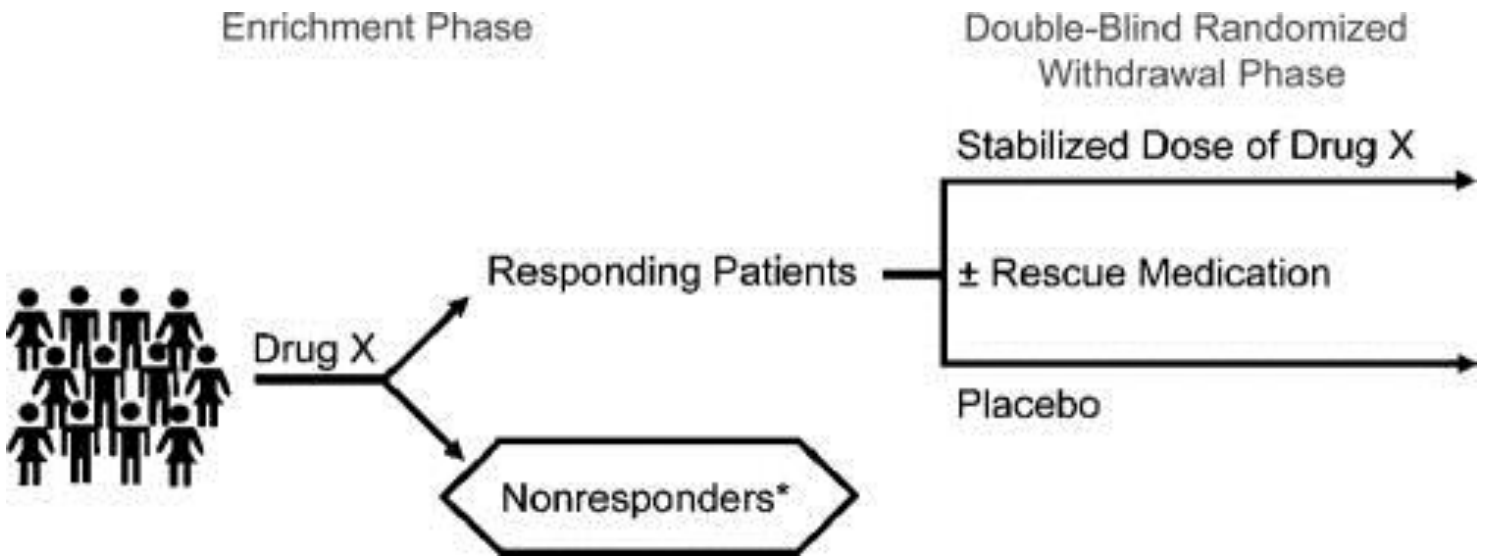
National Research Council Report

- Report is divided into six parts
  - Introduction/Background
  - Trial designs to reduce the frequency of missing data
  - Trial strategies to reduce the frequency of missing data
  - Drawing inferences from incomplete data
  - Principles and methods of sensitivity analyses
  - Conclusions and recommendations

Ideas for Clinical Trial Design to Limit Missing Data

- Target a population not adequately served by current treatments and has an incentive to remain in the trial
- Consider the use of enriched randomized withdrawal designs
  - Enrichment based on short-term or long-term improvement/tolerability
- Allow individualized, flexible treatment regimens
- Consider the use of add-on designs for treatments with different mechanisms

Enriched Randomized Withdrawal Design



Katz N. Clin J Pain 2009; 25:797–807

Ideas for Clinical Trial Design to Limit Missing Data

- Shorten follow-up duration
- Allow use of rescue medications that are designated components of a treatment regimen
  - Time to rescue or composite outcome
  - Decision to use rescue medication
- Avoid outcome variables that are likely to lead to a substantial amount of missing data or that may become unmeasurable in study participants

Ideas for Clinical Trial Conduct to Limit Missing Data

- Target sites with a good track record for recruitment and retention
- Set acceptable targets for missing data and monitor the progress of the trial with respect to these targets
- Provide incentives (monetary and otherwise) to investigators and participants for completeness of data collection (subject to ethical requirements)
- Limit participant burden and enhance the experience of participation
  - Remote data collection
- Provide continued access to effective treatments prior to their approval

Ideas for Clinical Trial Conduct to Limit Missing Data

- Train investigators and coordinators that keeping participants in the trial is important, regardless of whether they continue to receive the study intervention
  - Convey this to study participants as well (informed consent)
  - May depend on estimand (ITT vs. compliers)
  - Collect information on ancillary treatments
  - FOR-DMD example
- Collect information from participants regarding the likelihood that they will drop out and use this information to attempt to reduce the incidence of withdrawal
  - "Intent-to-attend" questionnaire (Leon et al., 2007)
  - Useful covariates in missing data models
- Collect information from participants regarding the reasons for withdrawal

Sample Size Planning

- Common practice is to inflate the original sample size N_0 according to the percentage of subjects expected to withdraw (P)
  - $N = N_0 / (1 - P)$
  - Assumes a complete case analysis
  - Does not account for bias
- Improved methods are needed that attenuate the planned treatment effect due to noncompliance
  - Assumptions for proper adjustment may be somewhat arbitrary
  - ERSET trial example (Engel et al., JAMA, 2012)

Missing Data Mechanisms

- Missing completely at random (MCAR)
  - Missingness is independent of past and future values
- Missing at random (MAR)
  - Missingness is independent of future values given the past values
  - Reasonable predictions of future values for those who drop out at a given time can be made from those who have observed data at or after that time
- Missing not at random (MNAR)
  - Missingness may depend on past and future values

Missing Data Methods

- Methods that assume MCAR
  - Complete case analysis
  - Mean substitution
  - Marginal models (generalized estimating equations, or GEE)
- MCAR assumption is rarely valid in practice

Missing Data Methods

- Methods that assume MAR
  - Likelihood-based methods
    - Mixed effects models for repeated measures
    - Random coefficient models
    - Rely on parametric assumptions as well as MAR assumption, which are (jointly) untestable
  - Marginal models with inverse probability weighting (weighted GEE)
    - More weight is given to data from subjects who have a higher probability of withdrawal (i.e., are "underrepresented" among complete cases)
    - Fewer parametric assumptions than likelihood-based methods
    - Requires a model for the probability of withdrawal
    - Can lack stability if there are large weights

Missing Data Methods

- Methods that assume MAR
  - Regression-based imputation
    - Predicts missing values based on observed values
    - Does not account for uncertainty in imputed values
  - Multiple imputation
    - Instead of imputing a single value for each missing datum, impute multiple values reflecting the uncertainty associated with the imputation
    - This yields several complete data sets, each of which is analyzed using standard methods
    - Results are combined across data sets to yield final inference
    - Flexible method, but still generally relies on parametric modeling assumptions

Missing Data Methods

- MNAR methods
  - Selection models
  - Pattern-mixture models
    - Requirements
      - Model for the observed data distribution
      - Assumptions that describe how missing data can be extrapolated given the observed data (unverifiable)
    - Useful for sensitivity analyses
      - Make different assumptions concerning, say, how much the mean response differs between those who do and do not drop out, separately in each treatment group
      - See how the trial results vary according to clinically plausible assumptions

Concluding Remarks

- Software is available to implement state-of-the-art methods for handling missing data
- No methods are perfect, rely on untestable assumptions
  - Sensitivity analyses
  - Ongoing research regarding how to best do these
- Emphasizes the need for prevention of missing data to reduce the reliance of the trial results on untestable assumptions

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