

Assessing Effectiveness in Naturalistic Data

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Design Continuum

CAN IT WORK? ←

DOES IT WORK? →

Randomized
Controlled
(Explanatory)

**Pragmatic
Trials**

Observational
(non-
interventional)

Internal
validity

External
validity



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← Randomized

Usual Care Effectiveness Analyses Issues: Randomization?

Yes (Pragmatic)

Medication Switching

Time Varying

Confounders (e.g.
concom. meds)

Missing Data

No (Observational)

- ◉ Selection Bias
- ◉ Unmeasured Confounding



- ◉ Lower on Evidence Hierarchy

Can you get causal inference from observational data?



✗ In Theory (only)

IF:

1. No Unmeasured Confounders

2. No Perfect Confounding

3. Correct Models

EFFECTIVENESS FROM OBSERVATIONAL RESEARCH

× Guidance Documents

- + ISPOR (3 manuscripts:

 - http://www.ispor.org/workpaper/practices_index.asp)

- + GRACE Principles (<http://www.graceprinciples.org/>)

- + PCORI draft (<http://www.pcori.org/what-we-do/methodology/>)

× Key Publications

- + Rubin (2007): mimic clinical trial approach

× Often Ignored Key Points

- + Multiple Testing / Sensitivity / Prospective / Transparency

Assessing Effectiveness using Observational Data

✘ Common Methods

- + Propensity Score Based Analyses
- + Various forms of Matching & Re-Weighting Analyses

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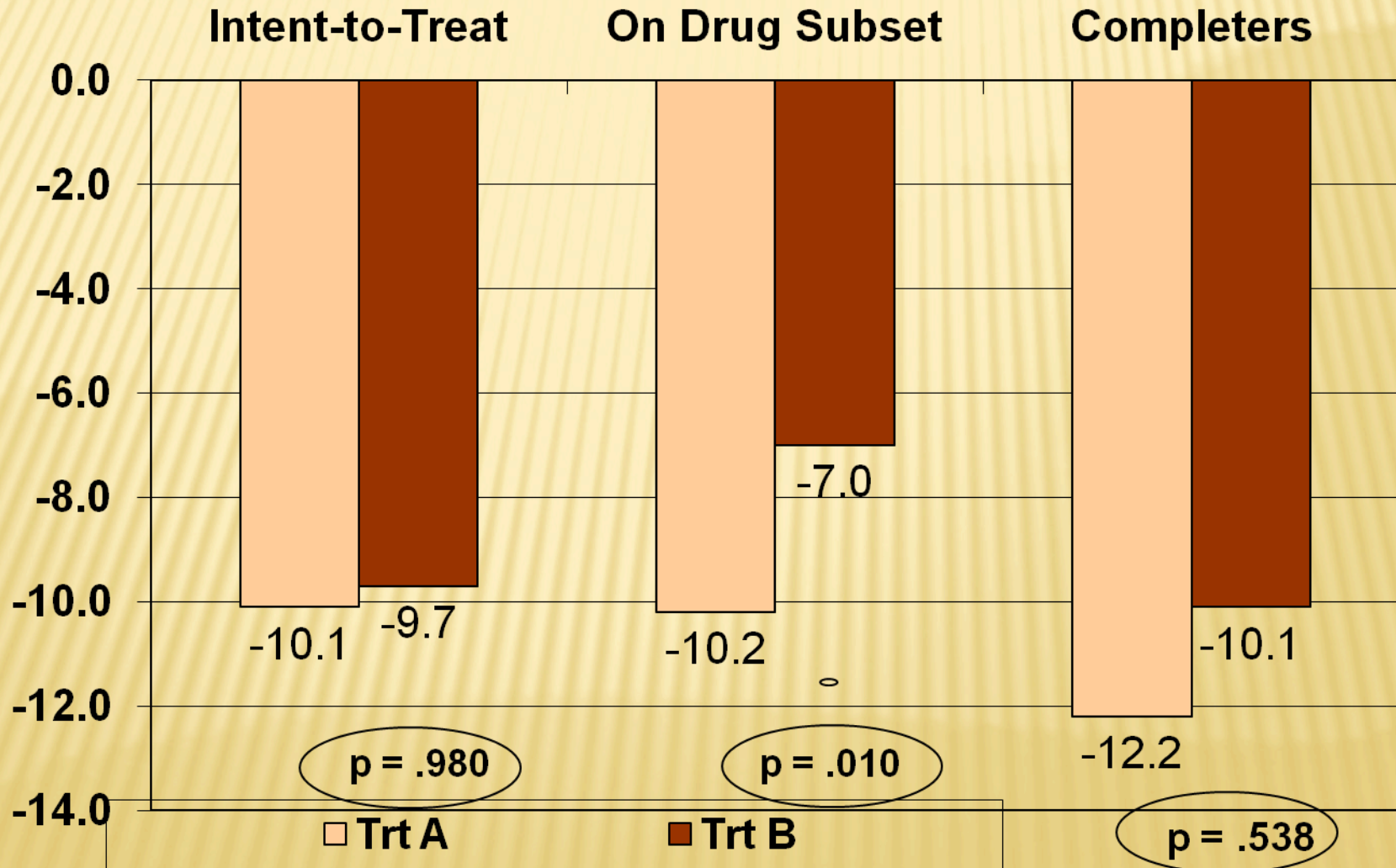


- Lower on Evidence
Hierarchy

Schizophrenia Pragmatic Trial Example (Tunis 2006)

- ❖ Randomized, Open Label, 1-Year, Cost Effectiveness Study
- ❖ 3 treatment regimens (total N = 664)
 - Olanzapine / Risperidone / Conventionals
- ❖ Naturalistic: patients may switch, stop, augment, change doses ... and remain in study
- Primary Analysis: Cost Effectiveness
- Effectiveness Outcome: BPRS Total Score

Methods Matter! BPRS Changes



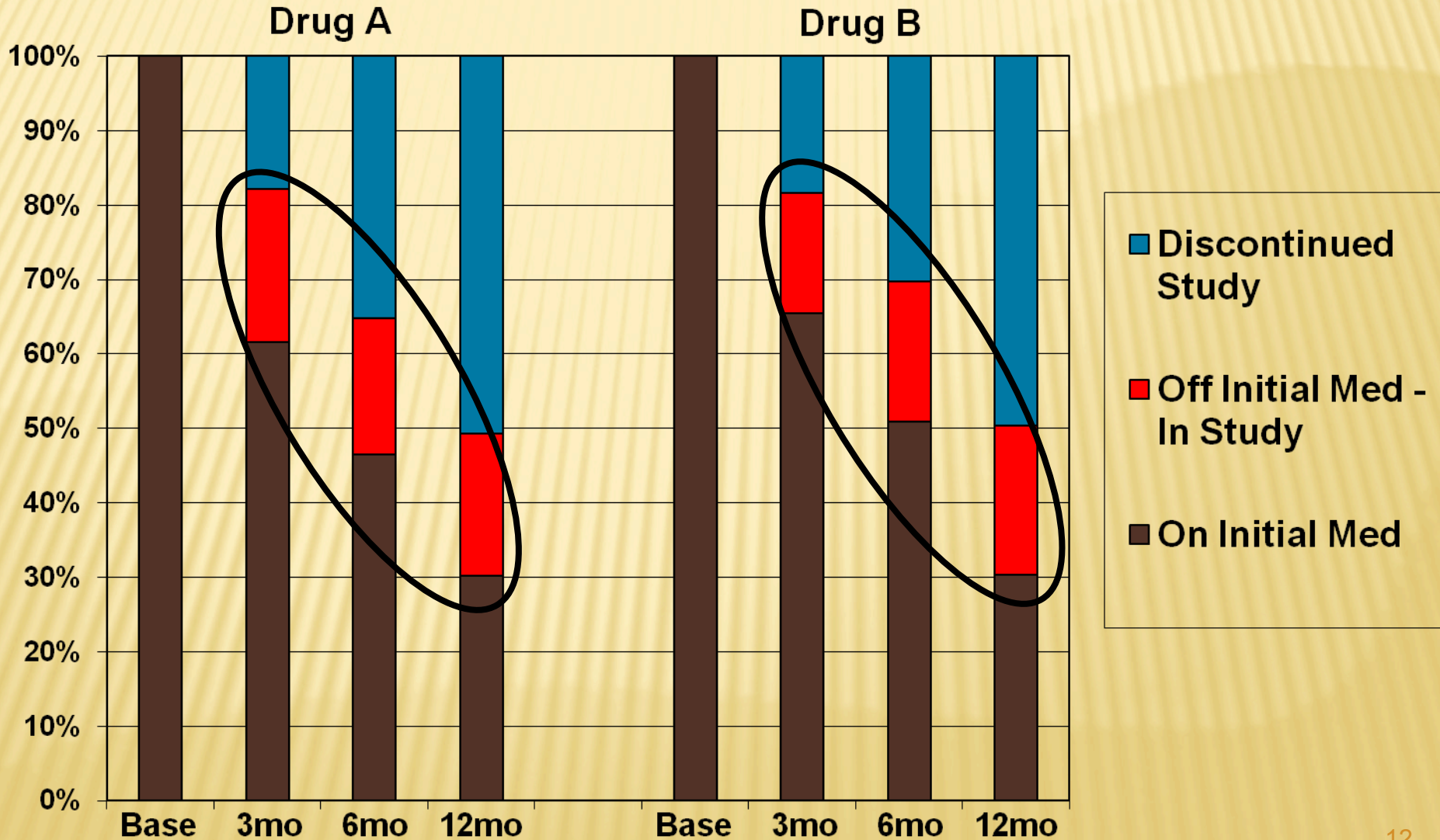
Simplified Patient Disposition

Initial Treatment Group

	<u>Trt A</u>	<u>Trt B</u>
Completed 1 Year on Initial Med.	60.5 %	33.8 %
Switched Meds	13.0 %	47.6 %
Discontinued/Other	26.5 %	18.6 %

Note: this ignores details such as augmentations, multiple switches, treatment gaps, stop/re-starts of same meds ...

Information 'Post Switch'



Addressing Medication Switching

- Ignore the Switching
 - Intent-to-Treat
- Eliminate the Switching
 - Subset Analyses such as
 - Completers (non-switchers)
 - On-Drug (throw out data post-switch)
- Incorporate the Switching
 - Marginal Structural Modeling

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What is the
Correct
Analysis?

Of course it
depends on
the clinical
question

Addressing Medication Switching – Analysis Question

- Ignore the Switching

- “Intent-to-Treat”

Policy Question:

Is there a difference in costs over 1 year if schizophrenia patients are required to start with a generic Typical as opposed to initiating with an Atypical Antipsychotic?

Addressing Medication Switching – Analysis Question

- Can we have it all?
 - Pragmatic Design for generalizability
 - Causal Inference (Question: is the effect of Treatment A different from the Effect of Treatment B)
 - Use all of the data (not drop data after switching)



Marginal Structural Models - Overview

- ❖ Robins (2000) – under a set of unprovable STRONG assumptions – MSMs estimate the causal effect of treatments even when patients switch treatments and time-dependent confounders exist.
- ❖ MSMs are basically weighted repeated measures analyses with treatment as a time-varying variable (“longitudinal propensity scoring”)

MSM Basic Assumptions

Sounds Great ... but
now for the bad news!

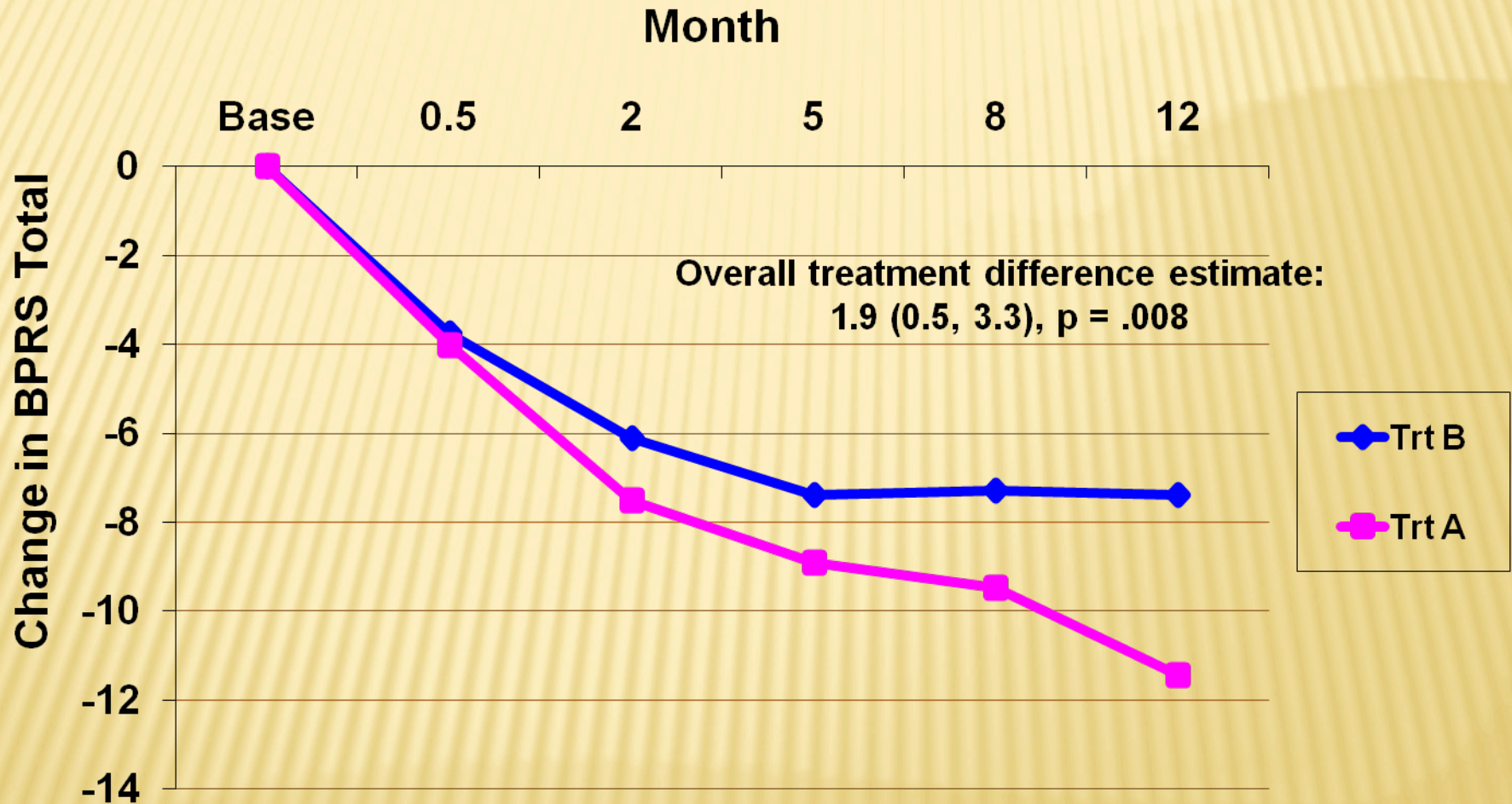
- No unmeasured confounders
- Positivity
 - Positive probability of treatment choice given any set of observed covariates
- Correct Model

Schizophrenia Study: MSM Results (BPRS Total)

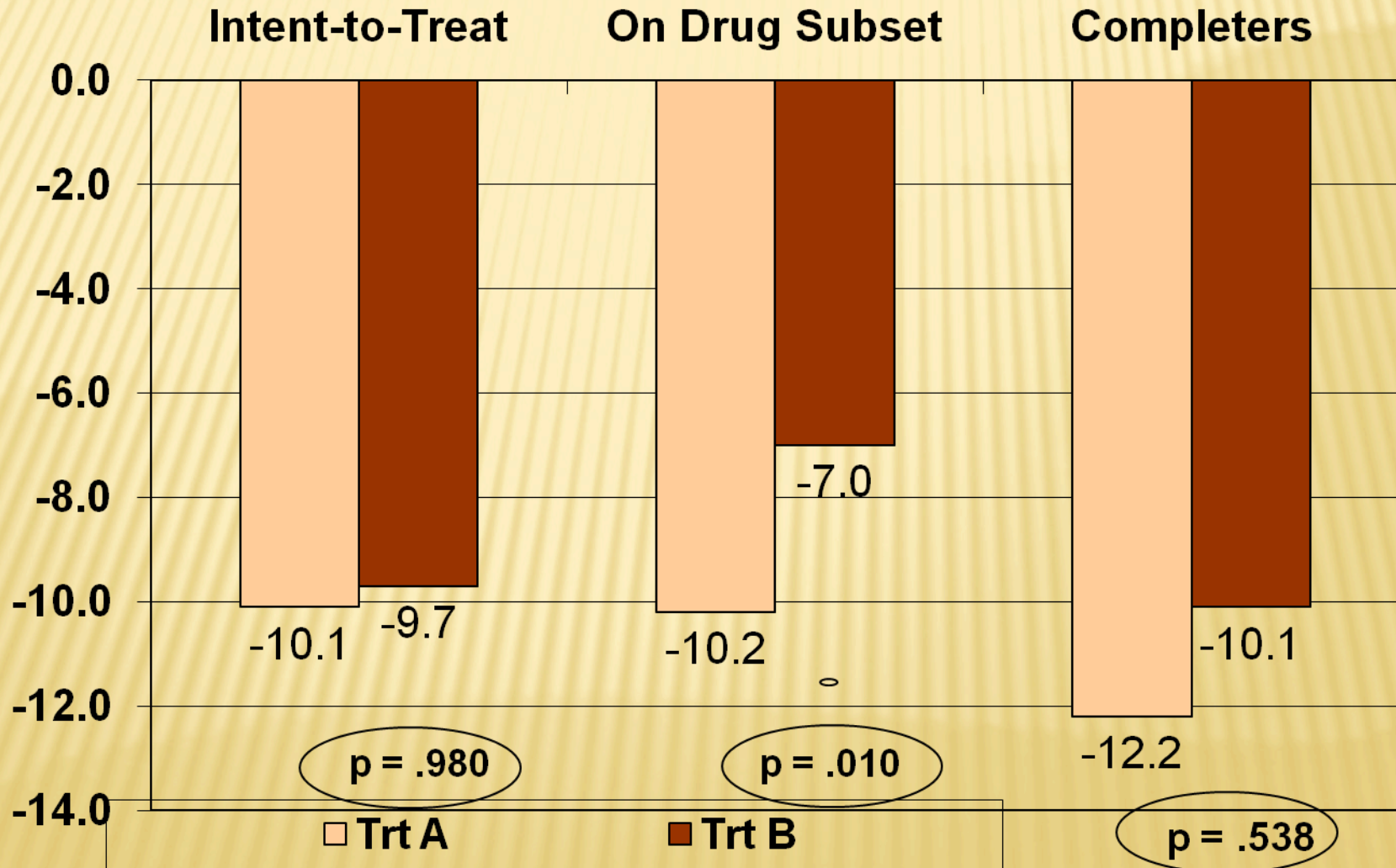
Assessing Change from Baseline to 1-year

<u>Trt A</u>	<u>Trt B</u>	<u>DIFF (CI)</u>	<u>P-val</u>
-13.0	-9.4	-3.6 (-6.9, -0.3)	.030

MSM Analysis: BPRS Data



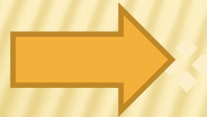
Methods Matter! BPRS Changes



Discussion / Summary



Usual Care studies provide valuable information – but are fraught with major analytical challenges when the interest is in causal treatment comparisons



❖ For Pragmatic Studies ...

❖ Randomization overcomes the biggest hurdle - though analysis challenges remain



Discussion / Summary

Pragmatic Analysis Keys



Match the Analysis to the Question

Simple ITT or 'On Drug' analyses may be OK

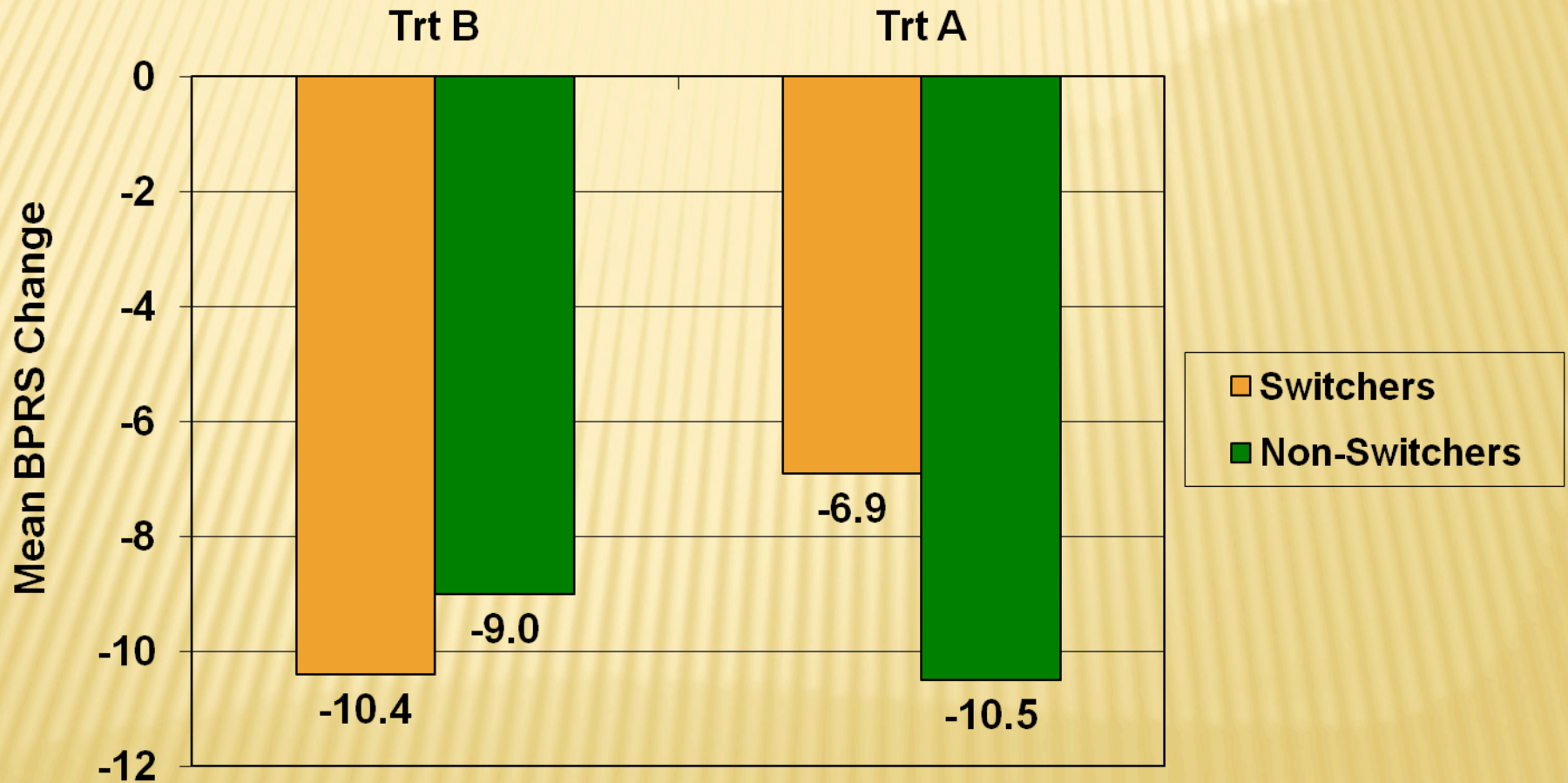
Address Medication Switching and
Concomitant Medication

Marginal Structural Modeling is one
'Causal Inference' Analysis tool

Standard RCT good practices are
critical here as well: Pre-specification,
missing data methods, sensitivity, replication, ...

BACKUP SLIDES

Switching (ITT)



WHY USE OBSERVATIONAL RESEARCH?

- Randomization not possible/practical
 - + Safety (Post Marketing Surveillance)
 - + Rare events / long duration of treatment
- Naturalistic Outcomes are of Interest:
 - + Compliance, adherence, cost, resource utilization / cost, concomitant medications, switching, PROs....
 - + Effectiveness (generalizability of RCT, impact in usual care)
- Questions about Usual Care, Disease, etc.
 - + Prevalence of events while on drug, Natural history of disease, characteristics of population receiving different treatments, risk factors for various outcomes,