# Statistical issues in clinical trials with polypharmacy:

## 50 ways to lose your signal

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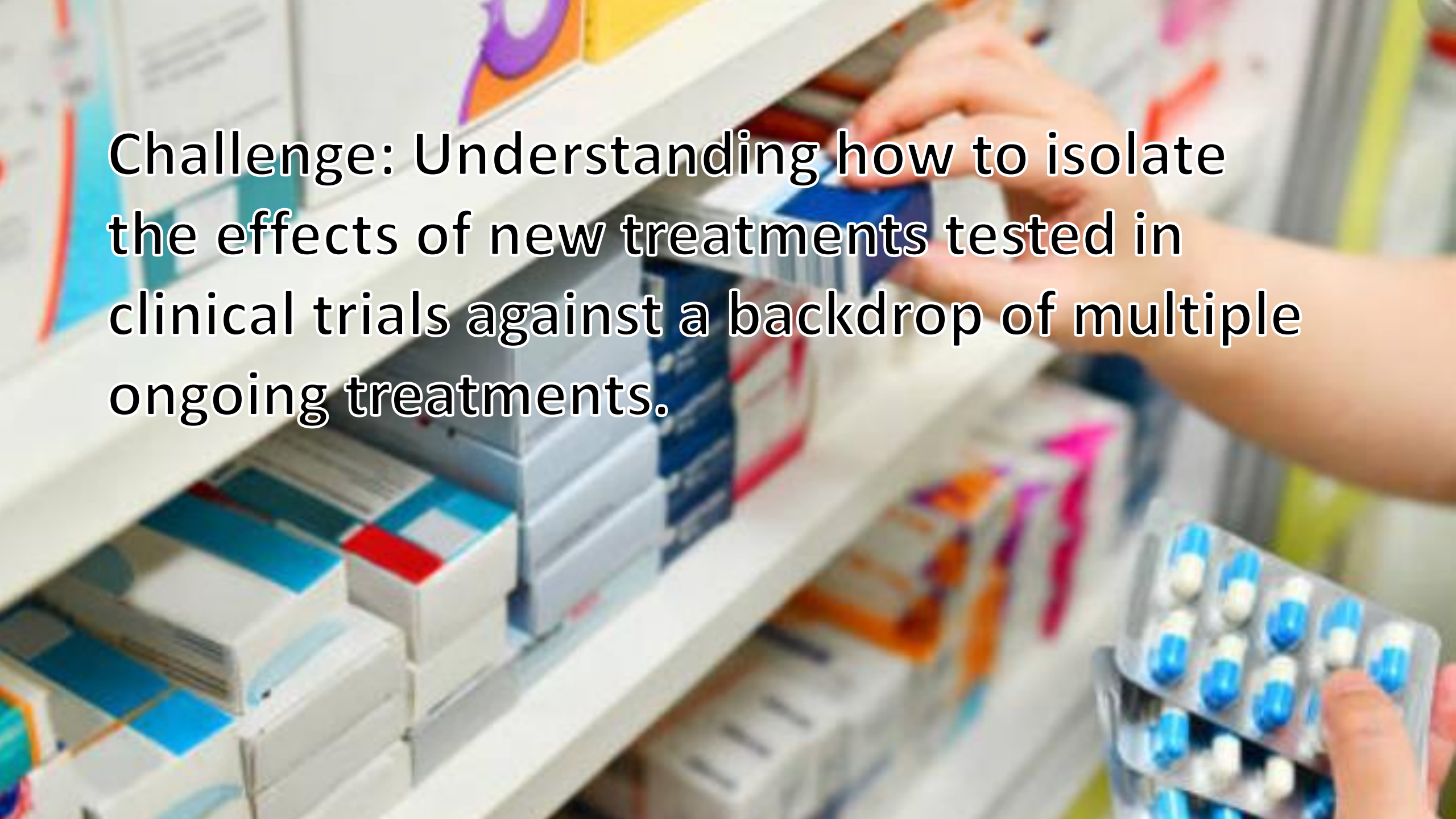


Challenge: Understanding how to isolate the effects of new treatments tested in clinical trials against a backdrop of multiple ongoing treatments.

# Statistical/Methodological Challenges

(I) Collecting accurate data

(II) Operationalizing and capturing concomitant medication treatment episodes

(III) Categorizing compounds into classes, and comparing compounds and dosage (potency) in a class (standard metric; equivalency of compounds)

(IV) Accounting for concomitant meds in statistical analysis

# I. Collecting accurate data

*Screening visit:* All medications administered, indication, daily dose & time of administration

*Subsequent visits:* New meds, changes/discontinuation of previously listed meds and total daily dose or route.

*Medication:* name and indication; for multiple ingredient medications, strength, e.g., carbidopa/levodopa 25/100. Dose: for each administration.

*Date:* Start & Stop (actual or estimated; specify).

**Unanswered need:* Collecting data on self-medication including substance use

→ Lots of data is collected; much of it is underutilized.

# II. Operationalizing and capturing treatment episodes

- Constructing concomitant medication treatment episode
  - Identify each use of medication decide whether they belonging to the same treatment episode
  - Capture dose & changes in dose during the episode
  - Categorize medication by class
  - Use above to derive measures of exposure

Measures of exposure used in statistical analyses for estimating medication effects.

# Operationalizing and capturing treatment episodes

Open access

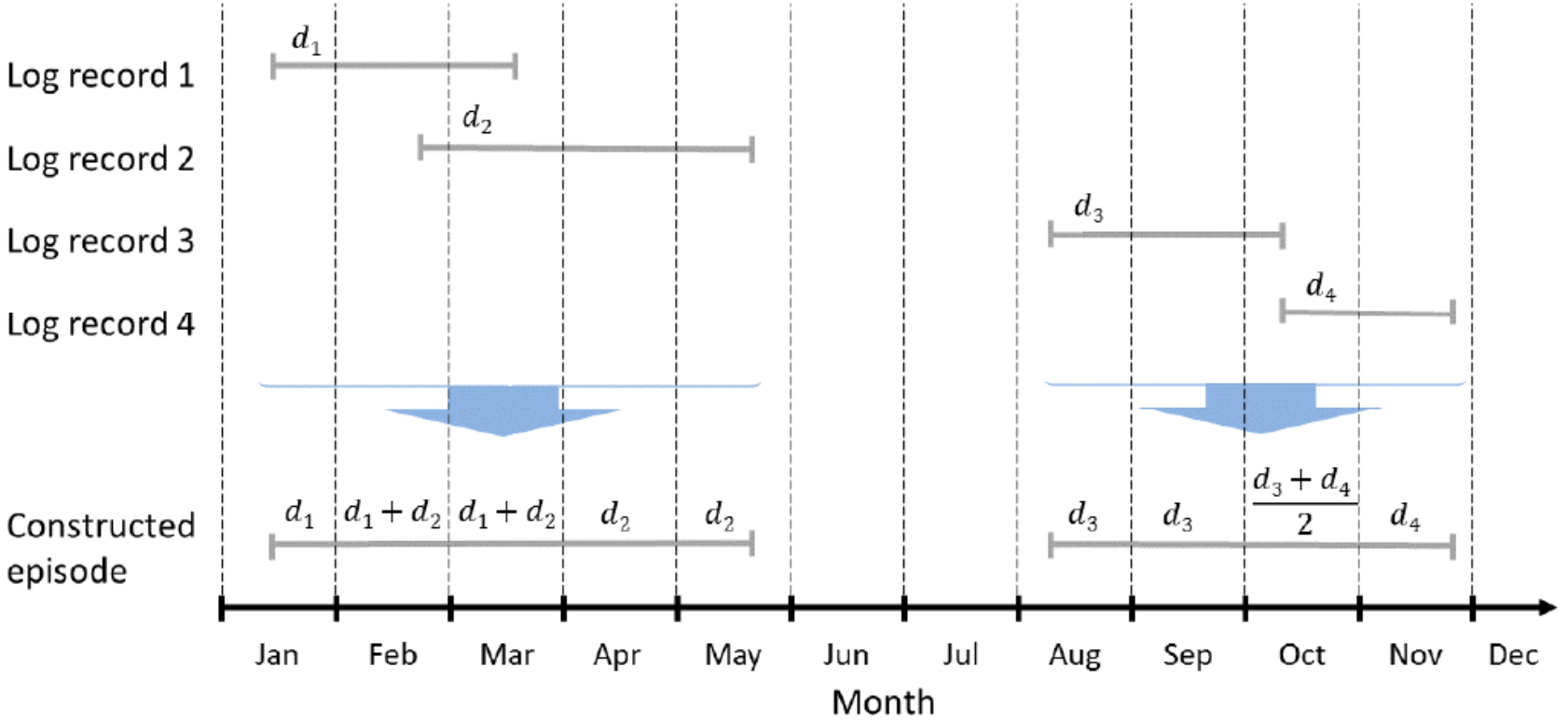



**Figure 1** Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, $d_1$, $d_2$, $d_3$ and $d_4$. Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

Kuramoto LK, Sobolev BG, Brasher PMA, *et al*. Constructing treatment episodes from concomitant medication logs: a prospective observational study. *BMJ Open* 2020;10:e034305. doi:10.1136/bmjopen-2019-034305

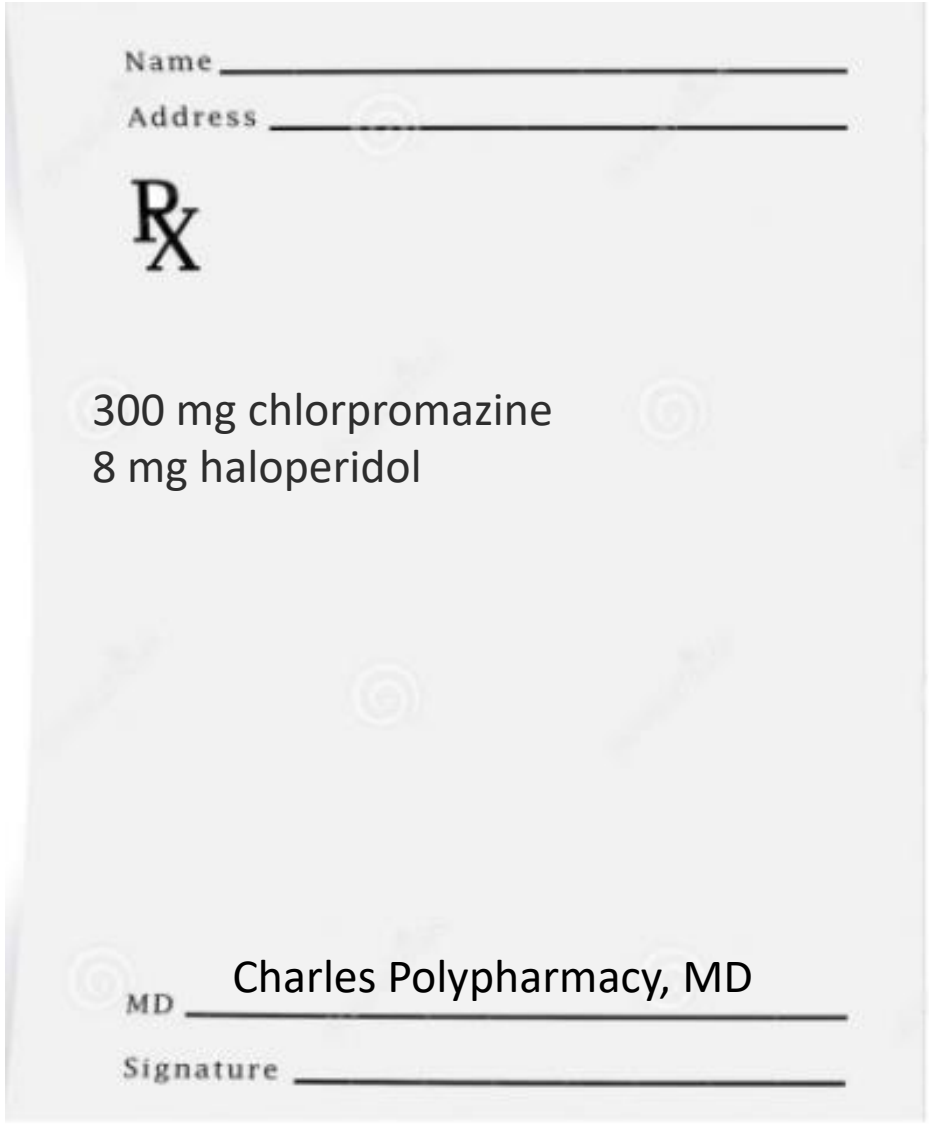
# III. Comparing compounds and dosage (potency) in a class

## Methods used to create cross compound dose equivalency (i.e., common metric)

- Defined daily dose (DDD) equivalent (WHO Collaborating Center for Center for Drug Statistics Methodology), average maintenance dosage.
- Chlorpromazine equivalents from *flexible* dose double blind studies (Davis, 1976)
- Expert consensus equivalents (Gardner et al, 2010)
- Minimum effective dose, systematic reviews of double-blind *fixed dose* placebo-controlled studies (Takeuchi, H. el al, 2020).
- Equivalence relative to % of maximum dose *British National Formulary* (BNF) (Yorston, G., & Pinney, A. (2000)

# Different methods give different equivalences

<u>Olanzapine (mg day)</u>
-WHO DDD 10 mg
-Minimum effective dose (7.5 & 10 mg)
-Expert consensus median 20 mg
-BNF max 20 mg




<u>2 DDD of antipsychotics</u>

1 DDD 300 Chlorpromazine= Haloperidol 8

Davis: 400 Chlorpromazine=Haloperidol 8

# IV. Accounting for concomitant medications in statistical analysis

Basic:  Descriptive  summary of the number and percentage of subjects who took concomitant medications by class.  (standard)

Medium: Include summary of exposure as a covariate. (underutilized)

Advanced approaches:  Modelling for time-varying confounders, cumulative exposure and latency, and treatment switching.  (futuristic)

# Example: add-on trial

Inclusion criteria:  (a) remained symptomatic but without clinically significant fluctuation and (b) antipsychotic doses unchanged for at least 3 months. Dose to be maintained during the period of the 6-week trial

Comparisons made of antipsychotic treatment equivalents at baseline (like comparing age or sex distribution).

“Equivalent” if different can be used as a covariate in analysis.

Lane et al, *JAMA Psychiatry*. 2013;70(12):1267-1275. Add-on Treatment of Benzoate for Schizophrenia A Randomized, Double-blind, Placebo-Controlled Trial of D-Amino Acid Oxidase Inhibitor

# Study using chlorpromazine equivalent

(Gardner et al expert consensus method)

Table 1. Demographic, Clinical, and Antipsychotic Characteristics of Patients Assigned to Placebo or Sodium Benzoate Treatment

| Characteristic | Treatment Groups: Placebo (n = 27) | Treatment Groups: Benzoate (n = 25) | *P* Value |
|---|---|---|---|
| Female, No. (%) | 12 (44.4) | 14 (56.0) | .58[a] |
| Age, mean (SD), y | 36.3 (7.9) | 38.4 (9.7) | .39[b] |
| Age at illness onset, mean (SD), y | 23.4 (6.2) | 22.2 (6.0) | .40[c] |
| No. of hospitalizations, mean (SD) | 3.1 (2.8) | 3.3 (3.2) | .91[c] |
| Educational level, mean (SD), y | 10.5 (2.0) | 11.1 (2.3) | .32[b] |
| Body weight, mean (SD), kg | 64.4 (12.4) | 68.6 (11.7) | .21[b] |
| No. of patients using typical/atypical antipsychotics | 13/14 | 14/11 | .59[a] |
| Amisulpride | 1 | 2 | |
| Chlorpromazine | 1 | 4 | |
| Flupenthixol | 2 | 0 | |
| Haloperidol | 9 | 9 | |
| Quetiapine fumarate | 2 | 1 | .58[a] |
| Risperidone | 7 | 6 | |
| Sulpiride | 1 | 1 | |
| Ziprasidone | 0 | 1 | |
| Zotepine | 4 | 1 | |
| Chlorpromazine equivalent dose, mean (SD), mg/d[d] | 561.3 (308.0) | 587.5 (449.3) | .50[c] |

Lane et al, *JAMA Psychiatry*. 2013;70(12):1267-1275. Add-on Treatment of Benzoate for Schizophrenia A Randomized, Double-blind, Placebo-Controlled Trial of D-Amino Acid Oxidase Inhibitor

Example using concomitant Medication *category* as dichotomous variable in a linear model.

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ORIGINAL RESEARCH

WILEY Brain and Behavior Open Access

# Concomitant medication use and clinical outcome of repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder

Aimee M. Hunter[1,2] | Michael J. Minzenberg[1,2] | Ian A. Cook[1,2,3] | David E. Krantz[1,2] | Jennifer G. Levitt[1,2] | Natalie M. Rotstein[2] | Shweta A. Chawla[2] | Andrew F. Leuchter[1,2]

**TABLE 4** Medication effects in linear mixed model analyses examining clinically based medication categories as predictors of change in symptom severity over time (weeks 2, 4, and 6)[2]

| | Denominator *df* | *F* | *p* |
|---|---|---|---|
| Psychostimulants | 176.74 | 4.94 | 0.03* |
| Benzodiazepine | 178.06 | 3.00 | 0.09 |
| SSRI | 177.48 | 0.00 | 0.99 |
| SNRI | 177.30 | 0.00 | 0.99 |
| Atypical Antidepressant | 177.45 | 0.11 | 0.74 |
| Atypical Antipsychotic | 177.43 | 0.03 | 0.86 |
| Anti-Epileptic | 177.24 | 0.28 | 0.60 |

*Note*. All models included baseline severity as a covariate. Change in symptom severity was assessed using the Inventory of Depressive Symptomatology Self Report (IDS-SR30) (Rush et al., 1996).
*$p \leq 0.05$.

# Example using concomitant antidepressant medication as dichotomous variable in survival analysis.

Effects of Antidepressant Medication on Morbidity and Mortality in Depressed Patients After Myocardial Infarction (Taylor et al, 2005; Arch Gen Psych 2005) (from the ENRICH (Enhancing Recovery in Coronary Heart Disease study, RCT standard care, vs. enhanced with CBT)

Antidepressant use coded as yes/no at baseline, month 6 and yearly thereafter yes/no (1,0) at each time point was time dependent covariate

Survival analysis (Cox regression) time to death or MI.

Separate models examined effects of any antidepressant use and SSRI antidepressant use

Adjustment was made for baseline patient characteristics (age, baseline Beck Depression Index (BDI) score, and severity of medical illness)

Further analysis of the ENRICH study (previous slide)
Method to evaluate whether a concomitant intervention could change a patient's response over time.

A varying-coefficient model for the evaluation of time-varying concomitant intervention effects in longitudinal studies (Wu et al, 2008; Statistics in Medicine)

Question: Did antidepressant (AD) have added benefits for lowering the BDI scores of patients in the psychosocial treatment arm who started to get AD's concomitantly during the trial?

Method:

- Start of AD was defined as a subject-specific 'change-point';
- evaluated the effects of AD on patient's BDI scores over time before and after the 'change-point'
- Use mixed-effects model to evaluate the patient's longitudinal outcome trends before and after the patient's starting of AD.

# Losing your signal

# Association of Concomitant Use of Cholinesterase Inhibitors or Memantine With Cognitive Decline in Alzheimer Clinical Trials: A Meta-analysis*

Question: Are cholinesterase inhibitors or memantine associated with cognitive outcomes in clinical trials for Alzheimer disease?

Findings: Participants receiving cholinesterase inhibitors or memantine had 1.4 points per year difference on the Alzheimer Disease Assessment Scale–cognitive subscale compared with those receiving neither medication.

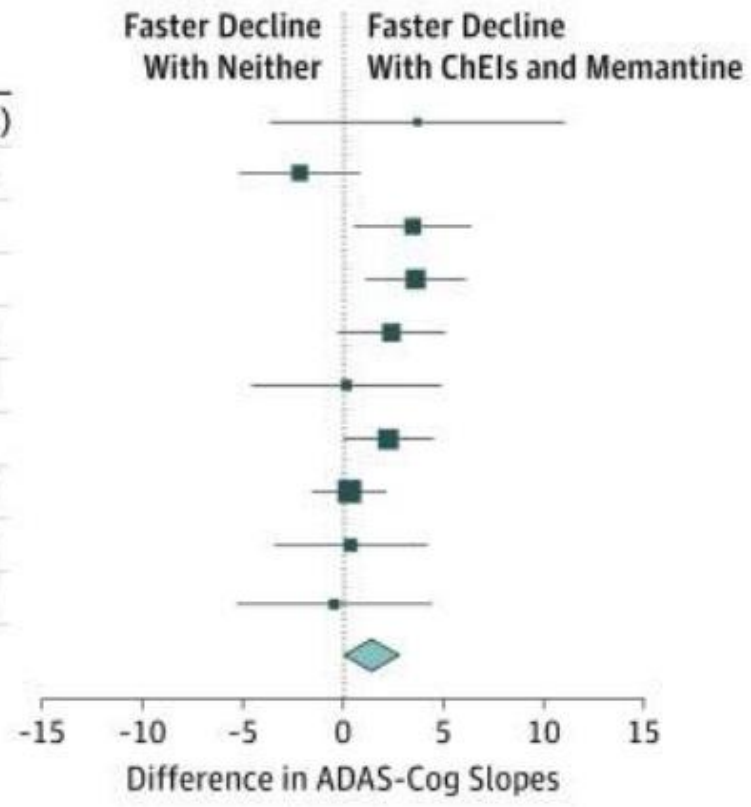
- -Differences were statistically significant
- -Difference is about the same size as the expected effect of new therapeutic drugs being investigated in the clinical trials.

Meaning: ***Differences in the use of cholinesterase inhibitors and memantine*** between treatment and placebo groups of clinical trials **may lead to the conclusion that a treatment is effective when it is not, or vice versa**.

*Kennedy et al, JAMA Netw Open. 2018;1(7):e184080. doi:10.1001/jamanetworkopen.2018.4080

2/2 Association of Concomitant Use of Cholinesterase Inhibitors or Memantine With Cognitive Decline in Alzheimer Clinical Trials (Kennedy et al, 2018)

| Source | Medications | Participants, No. | | Slope Difference (95% CI) |
|---|---|---|---|---|
| | | AD Medications | No AD Medications | |
| Sano et al,[10] 1997 | SL | 2 | 314 | 3.7 (-3.6 to 11.1) |
| Aisen et al,[11] 2000 | PR | 19 | 116 | -2.2 (-5.2 to 0.9) |
| Mulnard et al,[12] 2000 | ES | 31 | 84 | 3.5 (0.5 to 6.4) |
| Aisen et al,[13] 2003 | NS | 288 | 56 | 3.6 (1.1 to 6.1) |
| Aisen et al,[14] 2008 | HC | 361 | 22 | 2.4 (-0.3 to 5.1) |
| Petersen et al,[2] 2010 | ADNI | 173 | 6 | 0.2 (-4.6 to 4.9) |
| Quinn et al,[15] 2010 | DHA | 353 | 33 | 2.2 (0.0 to 4.5) |
| Rafii et al,[16] 2011 | HU | 97 | 92 | 0.3 (-1.5 to 2.2) |
| Sano et al,[17] 2011 | LL | 373 | 13 | 0.4 (-3.4 to 4.2) |
| Tariot et al,[18] 2011 | VN | 275 | 6 | -0.4 (-5.3 to 4.4) |
| | | | | 1.4 (0.1 to 2.7) |




**Rates of Decline for Participants Receiving ChEIs, Memantine, or Both Compared With Rates of Decline for Participants Receiving Neither Medication**

AD indicates Alzheimer disease; size of squares is proportional to the weight of the study in the analysis, ChEIs, cholinesterase inhibitors; DHA, docosahexaenoic acid; ES, estrogen; HC, homocysteine; HU, huperzine; LL, lipid lowering; NS, nonsteroidal; PR, prednisone; SL, selegiline; and VN, valproate neuroprotection.

# Conclusions

- Polypharmacy/concomitant medications can compromise efficacy results.
- Collecting accurate data is challenging.
- Comparing compounds and dosage (potency) in a class is problematic.
- Operationalizing and capturing treatment episodes is complicated.
- Exposure to concomitant meds needs to be accounted for more thoroughly in statistical analysis.
- Contending with polypharmacy in clinical trials needs more attention.