

# **VHA Database Medication Studies: Addressing Confounding & Interpreting Findings of Lithium & Suicide & Non-Suicide Mortality**

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# Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation.
- **Funding:** HSRD CDA 09-216, & to CHOIR & SMITREC
- Work in partial fulfillment of my PhD from UMass Millenium PhD Program
- I will be discussing “off-label” uses of the following medications:
  - Lithium
  - Valproate

# Objectives

- Assess whether Lithium (Li) should be used to **prevent suicide** in Veterans
- Discuss the value of using **an Intent-To-Treat design** in nonrandomized (database) studies
- Discuss **recent innovations** for database studies:
  - for addressing “measured” confounding
  - for assessing “unmeasured” confounding

The image shows the silhouettes of three soldiers against a bright, orange and yellow sunset sky. The soldier on the left is the largest, wearing a helmet and carrying a large backpack. The other two soldiers are smaller and positioned further back. The overall mood is somber and reflective.

What if their biggest risks were after they came home?

# The Imperative

- The Problem: Veteran Suicide Deaths: 22/day
- Could Lithium Be Part of the Solution?
  - Lithium has better evidence of Suicide Prevention benefits than any other routinely-used medication...
- Can we use VHA's national clinical care databases to start to answer this question?
  - SMITREC Role in compiling data

# Patient Cohort

- Incident VHA users, 1999-2008 (6-mo clean period)
- Qualifying Mental Health Dx in past 30d
  - Broad: Bipolar, MDD, Depr NOS, Schizoph, Schizoaff
- Exclude Potential NonMental Health Indications for Use
  - Preexisting Epilepsy, Migraine, Neuropathy, Cancer, Skull Fracture, TBI, Dementia, Nursing Home, Hospice or Rehab Care

**FINAL SAMPLE: n=42,384**  
**(n=21,162 pairs)**

# Prior to Discussing Methods: Poll Question

- **What response best characterizes YOU?**
  - A) Never have done a database study but might do one in the future
  - B) Have done at least one database study
  - C) Have done at least one database study and consider yourself to be an epidemiologist
  - D) Have done at least one database study and consider yourself to be a statistician
  - E) Have not done a database study and may not in the future; just interested in what work other CDA recipients' have done

## 2<sup>nd</sup> Question

- Based on your current knowledge, what do you view as the biggest THREAT TO VALIDITY (i.e., to getting the correct answer) for database studies:
  - 1) Misspecification of your outcome of interest
  - 2) Misspecification of your exposure of interest
  - 3) Confounding
  - 4) Something else

# Innovation: hd-PS Matching

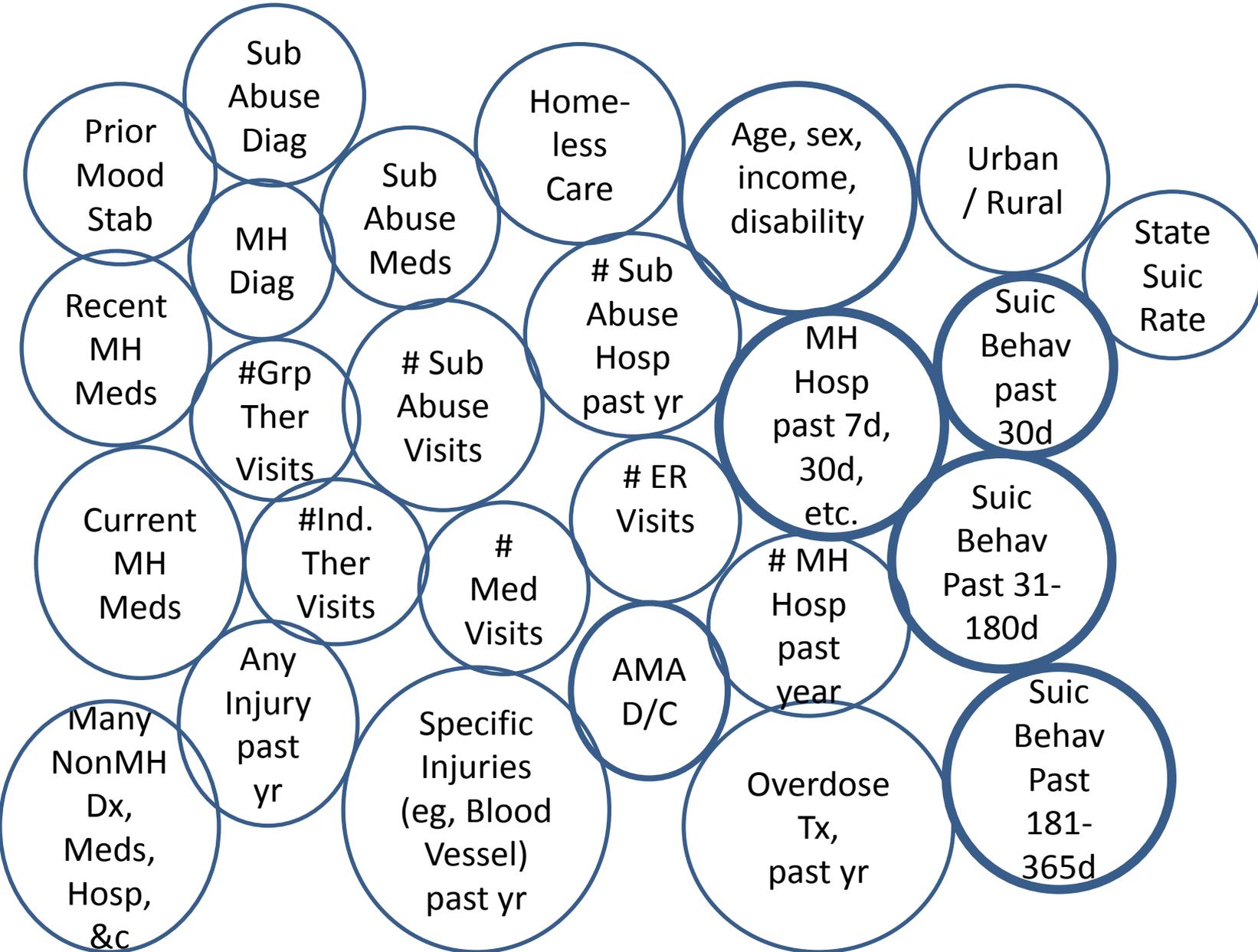
- “High dimensional” propensity scores (hdPS) (Schneeweiss et al., 2009) maximizes a distinct advantage of propensity scores (PS) for Large Database studies
  - Gave us ability to include up to **400X more variables** than standard regression
- Matching w/ a PS = Unusually transparent method
  - Mimics RCT for measured covariates
  - “Table 1” easily shows balance in (measured) covariates

# Our Added Innovation: Optimize the hdPS for Suicide Studies

- Include ESSENTIAL DETAIL re: TIMING (especially important for studies of suicide)
  - **MH Hospitalizations** – Discharged today, D/C in last 7 days, 30 days, 31-180 days, 181-365 days.
  - **Medications: Current Meds**
    - Possibly Discontinued Meds (ran out <30d ago)
    - Recently Discontinued Meds (31-180d ago)
- Can also permit HIGHLY NONLINEAR relationships

**END RESULT: 934 Total Covariates!**

# “Cast a Wide Net”





# TABLE 1 (Patient Characteristics)

	UNMATCHED			MATCHED		
	LITHIUM	VALPROATE	STD DIFF	LITHIUM	VALPROATE	STD DIFF
	%	%		%	%	
<b>Diagnoses</b>						
Bipolar I, past 30d	45.4	31.7	0.28	45.1	45.7	0.01
PTSD	22.8	27.8	0.12	22.8	22.4	0.01
Alcohol Dep	21.0	21.9	0.02	20.9	21.1	0.01
<b>Suicidal Behavior (Attempt) Diagnoses (past 30d, by location of dx)</b>						
NonMH Hosp Dx	0.13	0.17	0.01	0.13	0.11	0.005
	...etc....	...etc...				

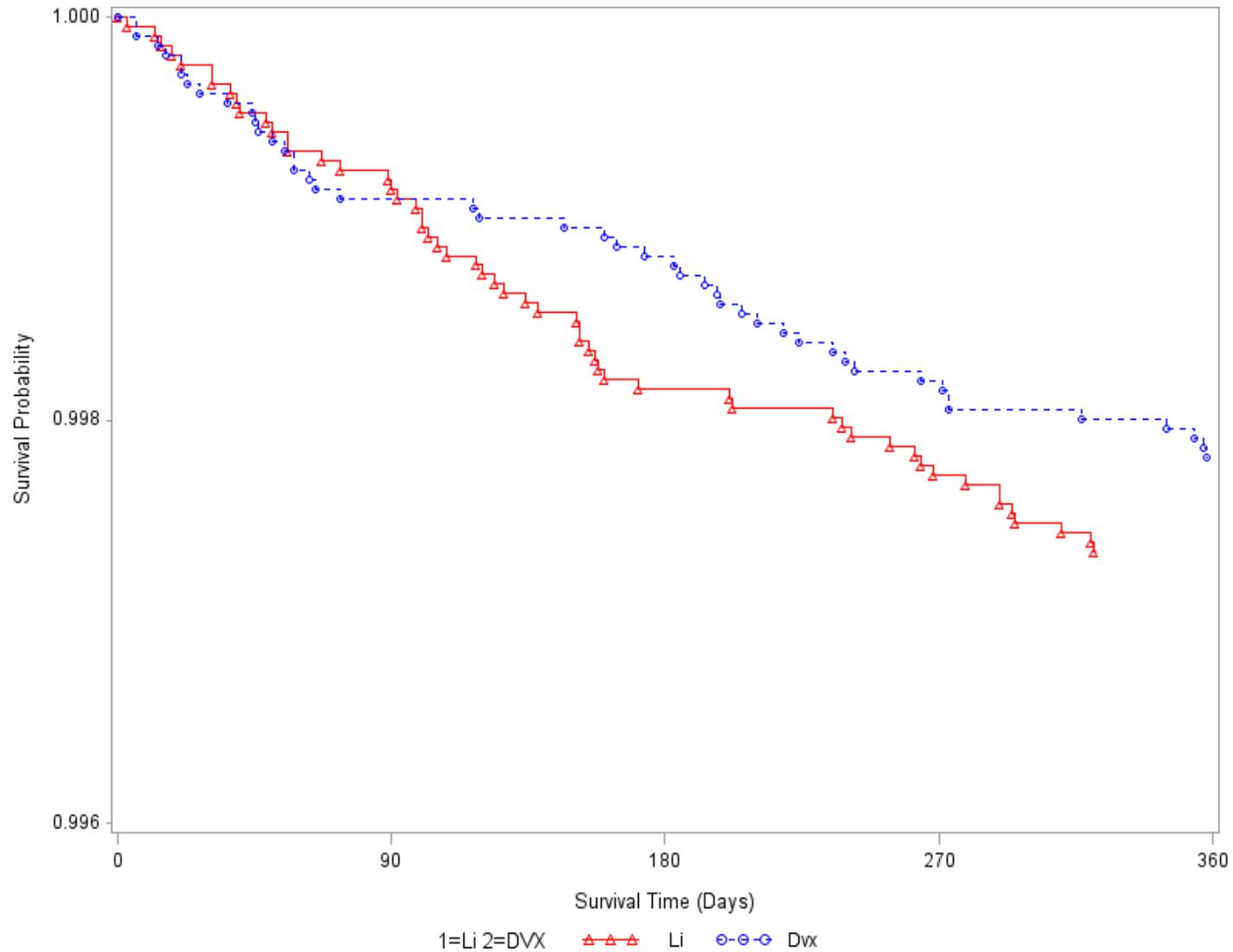
**ALL 934 covariates CLOSELY BALANCED this way**  
**(Std. Diff <0.018)**

# 3rd Innovation: Intent-to-Treat Analysis

- Standard for RCTs but not often used in Database Studies
- Effects Estimate more “conservative,” (b/c includes those no longer on medication and thus no longer experiencing active effects), but ...
  - **Captures possible risks upon treatment discontinuation**
  - **Aids interpretation** by minimizes impact of confounding arising during treatment
- **CONS: More sensitive to baseline confounding, less generalizable**

**SO WHAT DID  
WE FIND?**

# Suicide Deaths over 1 Year...



# Looking Deeper: “Former User Risk” Is Key

- Risk AFTER Initial Treatment Stopped is key...

## Risk of Suicide Death, by Time and Treatment Status, OR

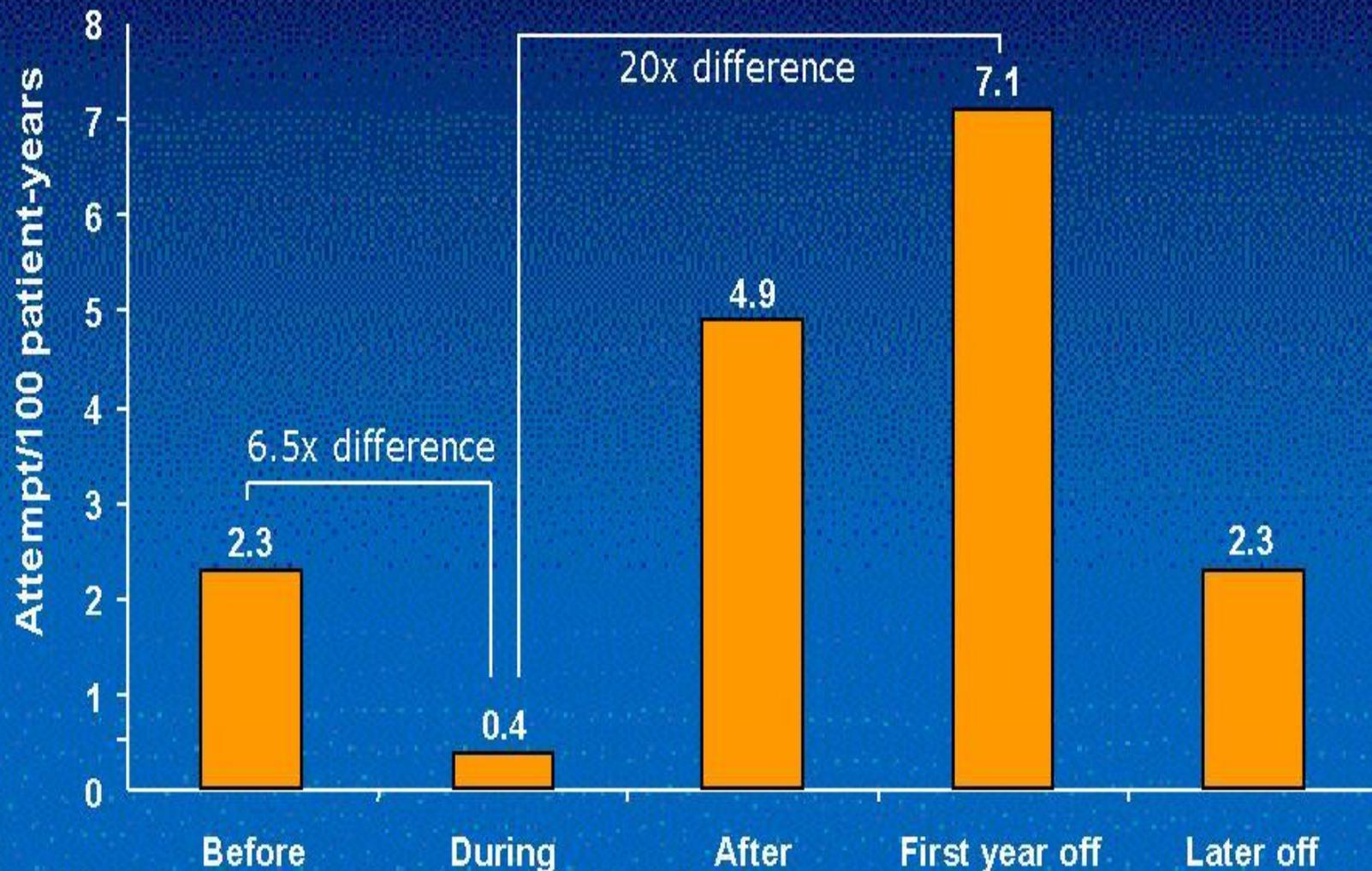
Time Period	Intent-to-Treat (ITT)	As-Treated	After Initial Exposure
0-90d	<b>0.95</b> (0.50-1.81)	0.88 (0.44-1.77)	1.49 (0.25-8.95)
0-180d	<b>1.56</b> (0.94-2.58)	1.00 (0.51-1.96)	<b>2.72</b> (1.21-6.11)*
0-365d	<b>1.22</b> (0.82-1.81)	0.86 (0.46-1.61)	1.51 (0.91-2.50)

\*P=0.015; Conditional Odds Ratio (ITT, As-Tx) or Odds Ratio (After Initial Exposure)

# “Former User” Risk

- “Former User” Risks can reflect up to 5 components:
  - **Risks Triggered by Treatment Discontinuation\***
    - (e.g. “rebound” mood episode, hypertension, hypercoagulability)
  - **Residual Baseline Confounding**
  - **Confounding from Selection During Treatment**
  - **(Persistence of Active Treatment effects)**
    - But should be in same direction as Active Tx effects
  - **(Random Error)** – but results (180d) statistically significant...

# Risk of Suicide Attempts and Lithium Treatment Status



# Survival Analysis: 91-180 days is key

**TABLE 4. Cox Regression Survival Analysis by Time since Medication Initiation**

<b>Intent-to-Treat Cohort</b>	
<b>Time Period</b>	<b>Hazard Ratio (95% CI)</b>
<b>0-90d</b>	0.95 (0.60-1.50)
<b>91-180d</b>	3.50 (1.41-8.66) <sup>a</sup>
<b>181-365d</b>	0.81 (0.43-1.53)

<b>Stratified by Treatment Status</b>		
<b>Time Period</b>	<b>Hazard Ratio (95% CI)</b>	
	<b>During Exposure to Initial Treatment</b>	<b>After Stopping/Modifying Initial Treatment</b>
<b>0-90d</b>	0.93 (0.54-1.58)	1.43 (0.24-8.36)
<b>91-180d</b>	NC <sup>c</sup>	3.14 (1.25 – 7.85) <sup>b</sup>
<b>181-365d</b>	0.26 (0.03-2.35)	0.93 (0.47-1.84)

<sup>a</sup> p=0.007; <sup>b</sup> p=0.015

# 1<sup>st</sup> BOTTOM LINE

- VA should be aware that Lithium may not be as effective against suicide as expected:
  - from past Database studies (of active users) or
  - RCTs with high adherence...
- ...DUE to HIGH RATES of DISCONTINUATION **AND** POSSIBLY INCREASED RISK OF SUICIDE SHORTLY AFTER DISCONTINUATION (even after just a few prescriptions)...

# RECOMMENDATIONS

- Providers should make efforts to maximize persistence with Li once initiated...
- Veterans should be warned of possible suicide risks accompanying Li discontinuation
- Patients on Li should be closely monitored if feasible (early in treatment & after discontinuation)

# BUT THERE'S MORE...

- “Former User” Risks can reflect up to 5 components:
  - **Risks Triggered by Treatment Discontinuation\***
    - (e.g. “rebound” mood episode, hypertension, hypercoagulability)
  - **Residual Baseline Confounding**
  - **Confounding from Selection During Treatment**
  - **(Persistence of Active Treatment effects)**
    - But should be in same direction as effects during Active Treatment
  - **(Random Error)** – but results (180d) statistically significant...

# Is Residual Confounding Plausible?

- ABSOLUTELY!!!!
- SENSITIVITY ANALYSIS:
  - Analysis of Prior Suicidal Ideation Codes (V62.82)
    - Not widely used, & not even introduced until 2005
  - Diagnosed Suicidal Ideation in 30 days Prior to Initiation More Common in Patients Initiating LI than VAL

OR 1.30 (1.09-1.54), p=0.003

# What Was Missing...



# Suddenly a Rude Surprise!

[Am J Epidemiol](#) 2011 Dec 1;174(11):1223-7;

Pearl, J. **Invited commentary:  
understanding bias amplification.**

“In choosing covariates for adjustment or inclusion in **propensity score analysis**, researchers must weigh the benefit of reducing confounding bias carried by those covariates against **the risk of amplifying residual bias carried by unmeasured confounders**. The latter is characteristic of covariates...that are more strongly associated with the exposure than with the outcome...”

# Have We “Amplified” Confounding?

→ Tighter, more extensive control on (less important) covariates **INCREASES** imbalance in unmeasured/unincluded Covariates...



“Squeezing the Balloon”

# +/- 20% Outcome Risk Sensitivity Analysis

- Follows Patrick et al., 2010 (Schneeweiss Group)
  - Uses alternate, outcomes-based selection strategy (different from original hd-PS)
  - For us, +/- 20% criteria was 1<sup>st</sup> systematic variable selection

Model	As-Tx (cOR)	Former User (OR)
Full PS (i.e., potentially amplified)	1.00 <sup>a</sup> (0.51-1.96)	3.60 (1.34-9.73)
Modified PS (+/-20%)	1.00 <sup>a</sup> (0.58-1.72)	3.00 (1.19-7.55)

<sup>a</sup> Conditional HRs, Rate Ratio(not conditional): 1.01 and 1.22, respectively

- Consistent with (but not conclusive of) substantial residual confounding (+ some degree of amplified confounding)...

# What does it mean?

- Both **Former User Risk** ( $\uparrow$  in Li initiators)

and

the **reduction of Former User Risk** when a **less nonselective propensity score model** is used...

and especially the

**External Measure** (SI codes)

are consistent with residual confounding biasing against Li  
... (despite the hdPS success)...

# Implications of Confounding...

- The study results likely UNDERESTIMATE of Li's Suicide Prevention Benefits
- 365-day HR (ITT) =  $> 1.22$
- 365-day HR (active recipients) =  $> 0.86$
- BOTTOM LINE: **Most likely interpretation:** Li has both some genuine benefits (during active treatment) and genuine risks (after discontinuation)...
- ? The signature of many effective medications?

# Highlights of Additional Findings

- Non Suicide Mortality Study – elevated risk at 180 days AGAINST direction of likely confounding bolsters likelihood that Li discontinuation has real deleterious consequences.
- Stratification by Diagnosis (Bipolar Disorder vs other Mood/Psychosis Disorders)
  - Risk after discontinuation seen much more in patients with bipolar disorders: **500% increase vs 70% increase**
  - Reductions in suicide risk more evident in patients actively receiving Li who have other Mood/Psychotic Disorders (inconsistently significant), not Bipolar Disorder
  - *Really revolutionary... but data starts to make sense...*

# Question

- What would your reaction be if Mental Health medications were shown to have an impact on NonMental Health to the extent that could be observed on nonsuicide mortality?
  - 1) Surprised and it would change my view of Mental Health medications
  - 2) Not surprised, but it would still change my view of Mental Health medications
  - 3) Surprised, but it would not change my view of Mental Health medications
  - 4) Not surprised, and it would not change my view of Mental Health medications

# Both Li and VAL have myriad systemic effects...

Physiological Effect	Li	VAL
White Blood Cell Count	↑	(↓)
Autoimmune Disease (Graves, MG)	↑	N
Platelets	N	↓
Pulse	↓	N
Cardiac Arrhythmia Risk	↑	N
Liver Dysfunction	N	↑
Renal Dysfunction	↑	N
Thyroid Dysfunction	↑	N
Parathyroid Dysfunction	↑	N
Neurogenesis	↑	?
Secondary Messengers	Y	Y

# NonSuicide Mortality

- Older Trial literature (metanalysis):

OR= 0.42 (0.27-0.81)

- Randomized, but some placebo-controlled & likely w/o attention controls
  - Only 2 deaths (lithium) vs. 3 deaths (comparators) in active comparator trials
- Older nonrandomized literature consistent with lower mortality risks on than off lithium treatment
  - **Implementation/Safety Need:** Need to rule out substantial changes in Nonsuicide mortality perhaps exceeding any Suicide Prevention benefit!

# hdPS Addresses NonSuicide Mortality Risk

- Charlson Comorbidity Score & Specific Categories
- Elixhauser Comorbidity Categories
- Inpatient Admissions in last 2 years by Speciality (e.g. ICU, Cardiology, Thoracic Surgery, etc.) & Latest Admission
- Specialty Visits, Surgery Visits, ER Visits
  - Even Pacemaker Clinic
- Meds: AntiHTN, Anticoags, Statins, Antibiotics, etc.
- Diagnostic Tests :Angiogram, CT/MRI, Echo, EKG etc.
- Unusual Covariates (PT/OT, Chaplain Visits, etc.)
- ALL BALANCED after match to w/in STD DIFF <0.018

# Core Results

## Risk of Suicide Death (Hazard Ratios)

	ITT	As-Treated	Former User
0-90d	<b>0.67<sup>a</sup></b> <b>(0.51-0.87)</b>	<b>0.59<sup>d</sup></b> <b>(0.42-0.84)</b>	0.88 (0.45-1.74)
0-180d	0.97 <sup>b</sup> (0.82-1.15)	<b>0.59<sup>e</sup></b> <b>(0.42-0.82)</b>	<b>1.54<sup>g</sup></b> <b>(1.01-2.37)</b>
0-365d	0.92 <sup>a</sup> (0.82-1.04)	<b>0.62<sup>f</sup></b> <b>(0.45-0.84)</b>	1.02 (0.79-1.32)

<sup>a</sup> 48 deaths (Li), 72 Deaths (Val); p = 0.003

<sup>b</sup> 128 deaths (Li), 132 deaths (Val); p = 0.73

<sup>c</sup> 274 deaths (Li), 296 deaths (Val); p = 0.17

<sup>d</sup> p = 0.004; <sup>e</sup> p = 0.002; <sup>f</sup> p = 0.002

<sup>g</sup> p=0.045

# Findings

- Strong, large ITT association over 1<sup>st</sup> 90d
  - When Med Persistence is Highest but Confounding also Greatest too...
  - Matches Strong As-Treated Association
- Over Time, ITT association greatly weakens
  - Former User Risk Significant over 180d
  - Counter to Direction of Likely Confounding!
  - Unmatched ITT (365d) 0.74 → 0.92 Matched
  - Suggests Patients Initiating VAL sicker (by measured factors – unmeasured too?) – Would lead to UNDERESTIMATE of Li Risks...

# Back to the Start

- This significant NONSUICIDE mortality risk at 180 days among patients stopping Lithium (HR=1.54) – in a direction COUNTER to likely confounding -- matching the elevated risk observed for suicide death at 180 days in the overall cohort (OR=2.72) and among individuals with bipolar disorder (OR=6.10) is the final, and perhaps most conclusive piece of evidence suggesting some genuine suicide and nonsuicide mortality risks associated with Lithium discontinuation

# Wrap Up of Nonsuicide Study

- Raises question of whether Discontinuation-Associated Risks for NonSuicide Mortality as well
  - Generally, would NOT expect Confounding to Reverse
  - Mechanism?
- Hard To Estimate whether benefit/harm over 1<sup>st</sup> year predominates
  - Due to statistical uncertainty
  - Due to potential influence of even small residual confounding biasing towards Li (central estimate HR=0.92)

# Limitations

- Inpatient prescriptions not available
- Non-VHA prescriptions, system use (e.g. hospitalizations) not available
- Serum Blood Levels of medication not available
- Unable to determine if individuals prescribed meds actually took it
- E.g., “Hidden Discontinuation” in patients classified as receiving treatment (15 day gap tolerated) may lead to underestimate of benefits during active treatment (over and above effect of confounding)...

# Limitations (cont.)

- As discussed,
  - Little information on suicidal ideation, none on plan, intent, access to means, preparatory actions, MH symptoms, or stressors
  - Possibility of Confounding Amplification
- No Nonfatal Suicidal Behavior outcomes
- No correction for multiple comparisons

# Limitations (cont.)

- No Marginal Structural Model reweighting to address changes/confounding during treatment
  - Would be particularly important to address changes in non Li/VAL medications during 365-day followup
    - Although extreme balance in current and recent meds
- But important to recognize that, absent a genuine effect of treatment, significant ITT risks in cohort with bipolar disorder CANNOT be explained by selection during treatment alone...
  - A big reason to favor ITT estimates even in Nonrandomized Studies...

# Limitations - Generalizability

- Generalizability limited to 1<sup>st</sup> Year of Treatment
  - Are at least 3 nonrandomized studies suggesting longer treatment may be necessary
- Generalizability limited to predominantly male sample, Veteran status, broad psychiatric diagnoses and a high burden of comorbid illness
- Generalizability for ITT results limited to cohorts with similar treatment discontinuation rates...

# 3 Core Conclusions

- Discontinuing Lithium within the 1<sup>st</sup> 180 days of treatment appears to pose a risk of increased suicide mortality
- Particular effort should be made to maintain Lithium treatment once initiated, even compared to other medications, as well as educate & monitor patients
- To the extent Lithium has any suicide prevention effects, these appear likely to be more strongly observed in patients without bipolar disorder than with bipolar disorder

# Methods Conclusions

- EXAMINE ITT FINDINGS, either as primary or secondary analysis
- EXPECT UNMEASURED CONFOUNDING and think of ways to even partially examine it (don't be passive!)
  - EXAMINE FORMER USER RISKS and think about what that likely means
  - Use an EXTERNAL MEASURE
  - STRATIFY your analyses (by time, by diagnosis, etc.) to improve inferences
  - (Assess likely DIRECTION OF CONFOUNDING: Unmatched → Matched comparison and/or compare more and less nonselective propensity scores)



# Time to do some (simple) math...

- What if I told you an item was twice as expensive in a “bricks-and-mortar” box store as it was on Amazon.com?
- And what if I told you the price was \$20 in the box store...
- What would be the price at Amazon?...

# Question

- What would be the price on Amazon?
- 1) \$10
- 2) Any other answer

A principle THAT SIMPLE MAY underlie  
a method to get beyond the  
limitations of nonrandomized trials...

- Intentionally create Confounding Amplification to make Inferences about the Size and Direction of Underlying Confounding...
- Need to correct for the effect of the variable(s) you are adding to create Confounding Amplification....

F1000 Research  
METHOD ARTICLE

**The ACCE method: an approach for obtaining quantitative or qualitative estimates of residual confounding that include unmeasured confounding**  
**[v2; ref status: indexed, <http://f1000r.es/3yd>]**

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## ABSTRACT

**Method:** A method is presented that exploits the recently-identified phenomenon of “confounding amplification” to produce, in principle, a quantitative estimate of total residual confounding resulting from both measured and unmeasured factors. Two nested propensity score models are constructed that differ only in the deliberate introduction of an additional variable(s) that substantially predicts treatment exposure. Residual confounding is then estimated by dividing the change in treatment effect estimate between models by the degree of confounding amplification estimated to occur, adjusting for any association between the additional variable(s) and outcome.

# Needs Checks and Validation

- Need checks to be carried out, and may under or overestimate residual confounding in some cases
  - **But key test is** – are the estimates improved over not applying the method at all?
- Entirely theoretical at this point – needs even the most basic validation in simulation and real-world data!
- But, MAY have unusual applicability and value as a method to improve large database research

# Possible Broad Applicability?

- The method MAY permit
  - The use of Variables to generate Confounding Amplification which have associations with Outcome – Broadens Likely Applicability
  - The use of a set of variables to generate Confounding Amplification, rather than just one – Broadens Likely Applicability
  - May Permit Estimate of Unmeasured Confounding AFTER Treatment Initiation, as well as AT BASELINE...
    - Not sure if any current technique does this well...

Stay Tuned...

# THANKS!

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# And Finally...

- My Family!!!
- And Thanks to You for Your Attention...

# Stay Tuned...

To Learn more:

- Suicide Mortality Study: Smith E et al., BMC Psychiatry, 2014 [also has detailed online Appendices]
- NonSuicide Mortality Study: Smith E et al., BJP, 2015 [also has detailed online Appendices]
- ACCE Method: Smith E, f1000Research, 2014 (but you want v2, 2015 – which website will direct you to....)