The Route to Utilization of Trend in Trend

16 May, 2019

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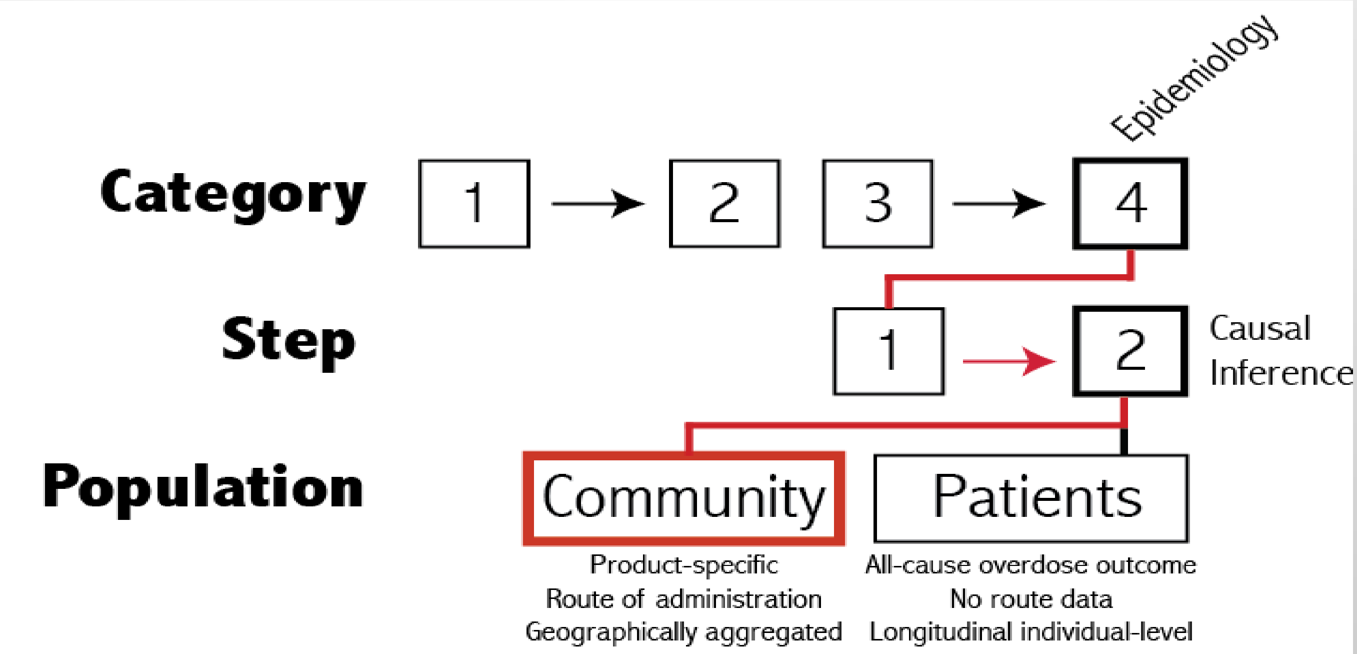
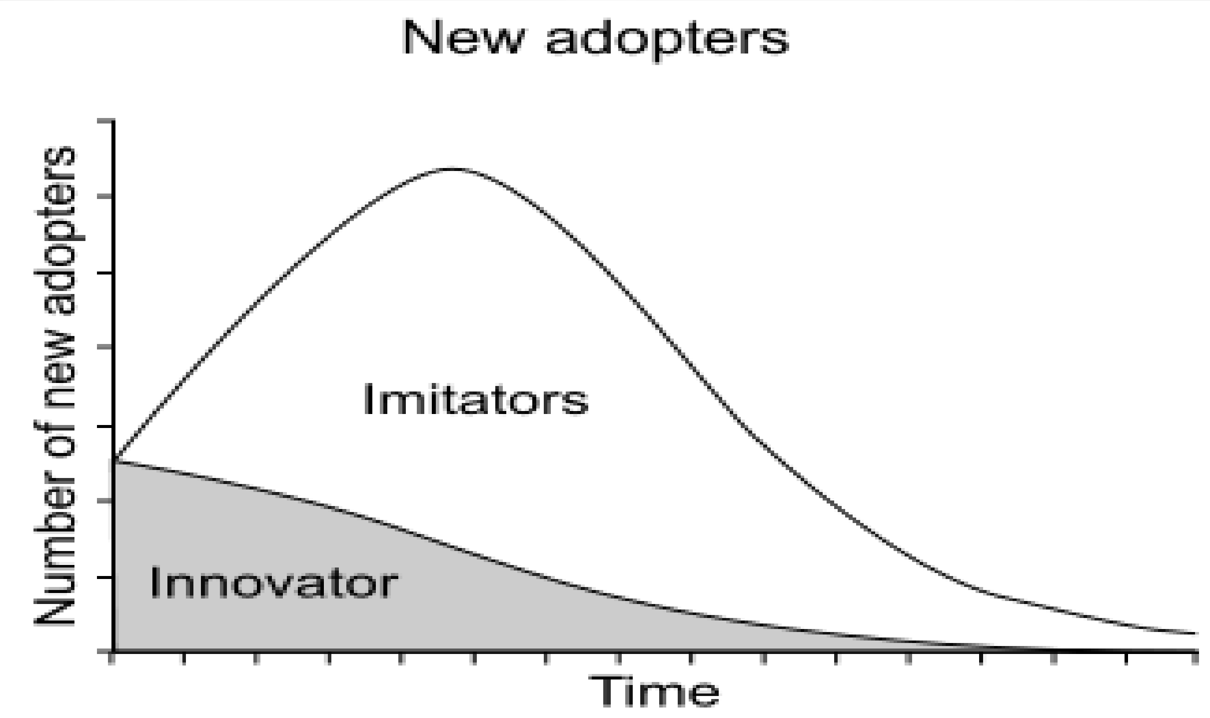
New approaches are needed for epidemiologic studies that will allow causal inference.



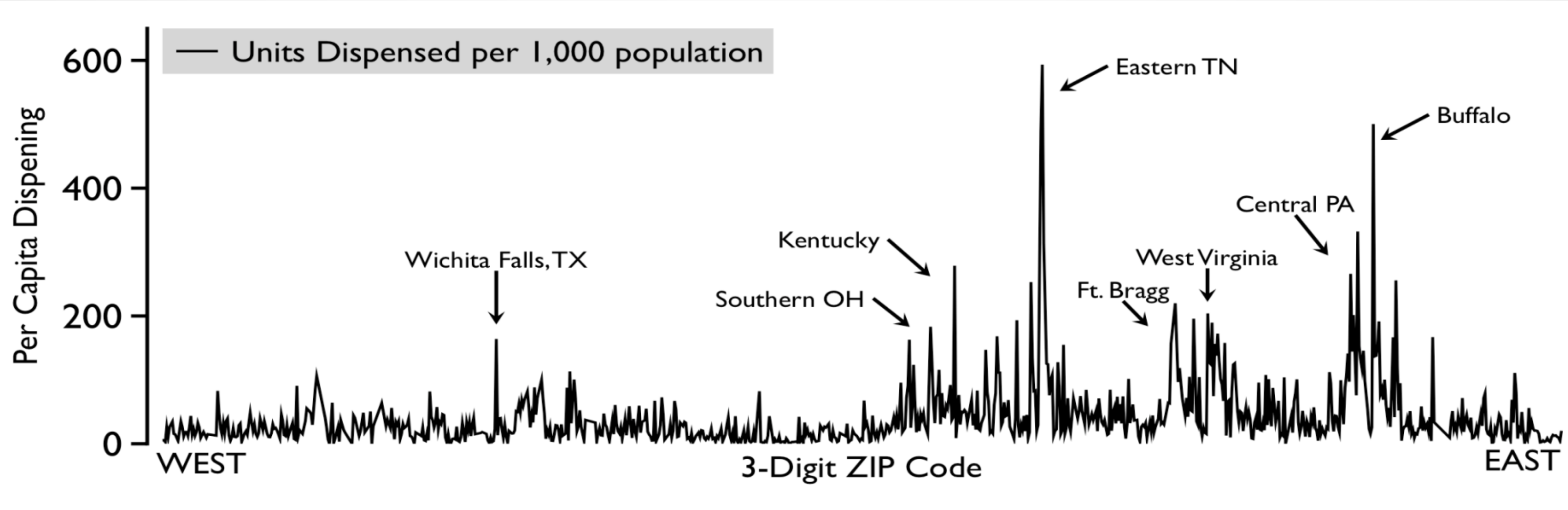
Bass-Krishnan-Jain Diffusion Model for New Consumer Goods



Source: Wikipedia

Observation 1: Geographic Heterogeneity

Each drug has a unique geographic spectrum of per capita dispensing.



Drug: Opana ER
Time: 2009q3 – 2016q4
Source: IQVIA
N: 360,432,541 units dispensed
Analysis unit: 3-digit ZIP
Metric: cumulative population-adjusted rate

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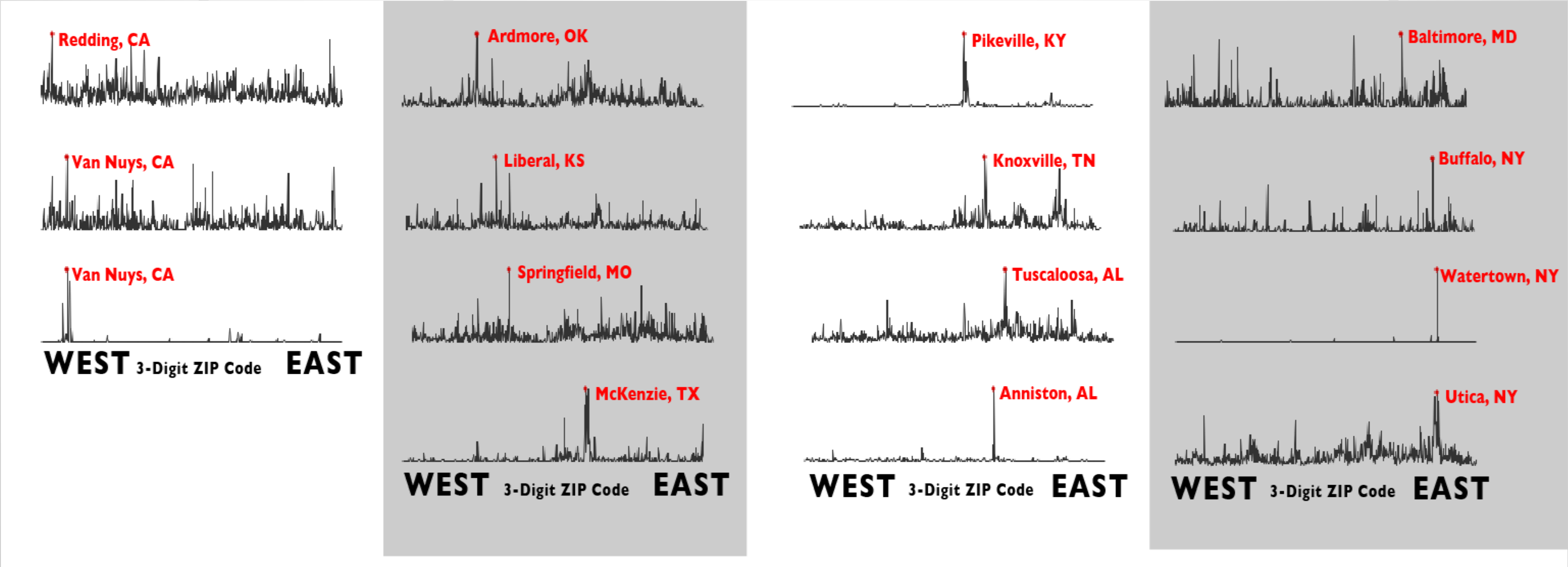
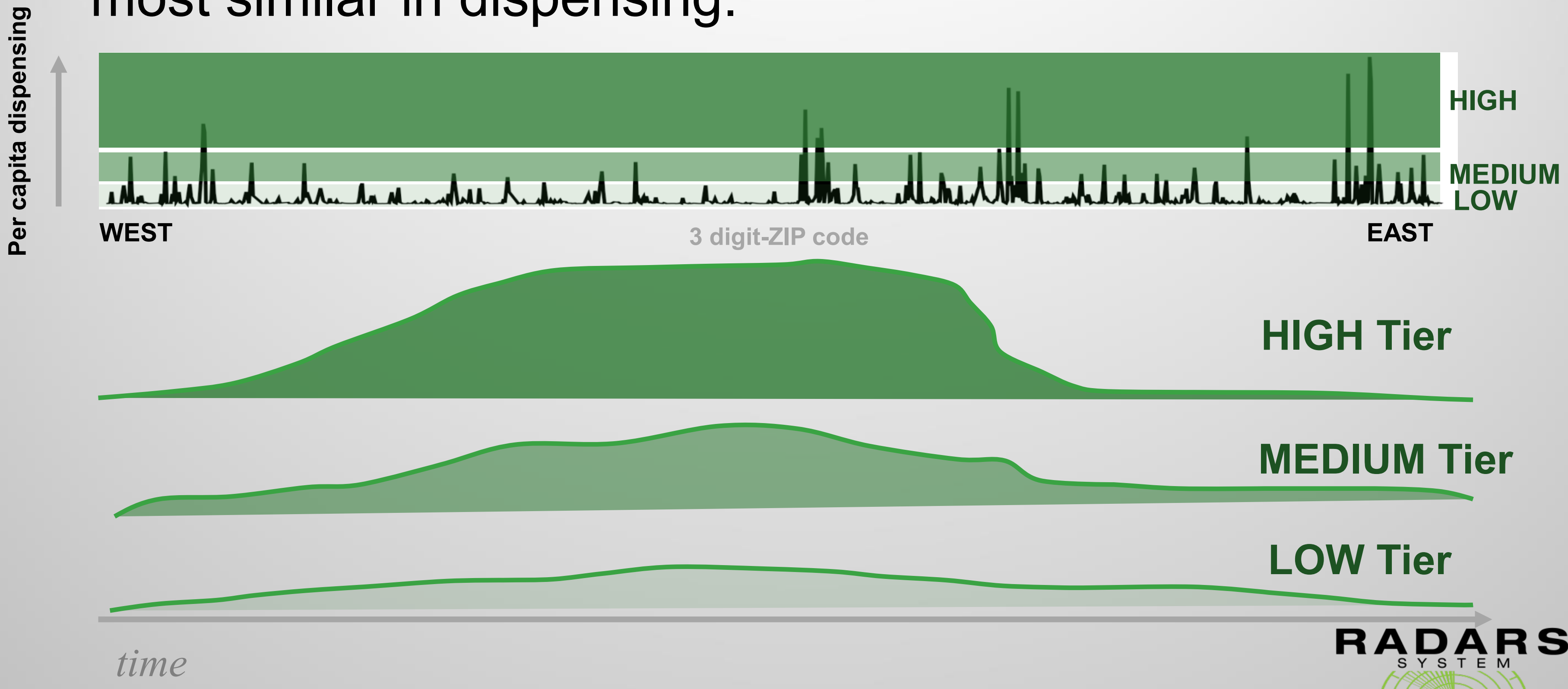
Per Capita Dispensing of 15 Low Volume Opioids



Time: 2009q3 – 2016q4
Visualization: Scaled sparklines
Metric: Units dispensed per 1,000 people
Source: IQVIA
Analysis unit: 3-digit ZIP

Separating by level of dispensing, we can account for the time trend in each tier, grouping together places most similar in dispensing.



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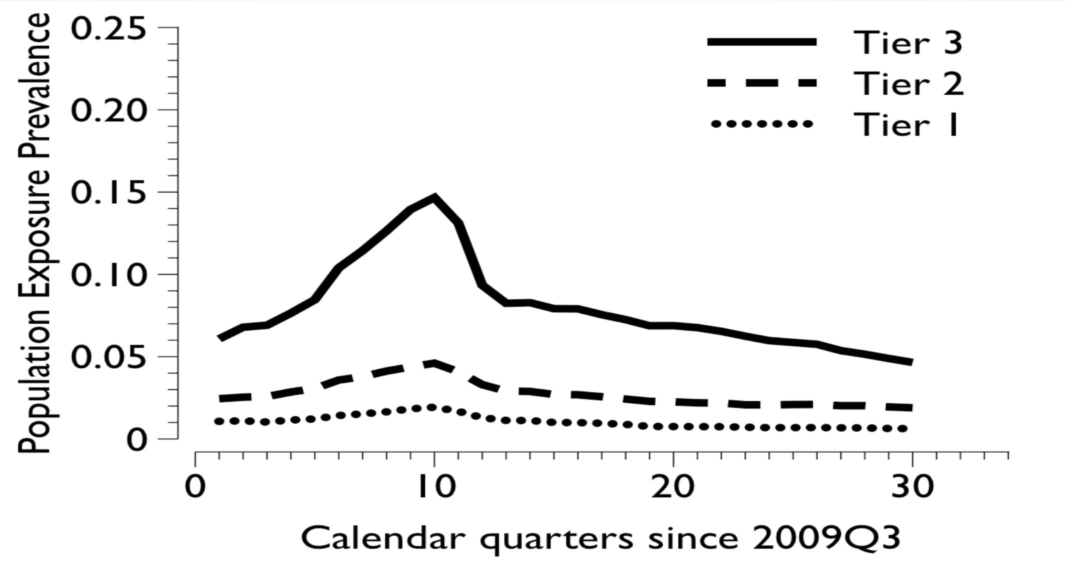
Observation 2: Dispensing Tiers Over Time

High, medium and low tier dispensing locations for a given drug have different shaped trajectories over time.



Drug: Opana ER
Time: 2009q3 – 2016q4
Sources: IQVIA
N: 25,401 ZIP-quarters
Analysis unit: 3-digit ZIP
Stratification: Cumulative exposure tertile

Source: Ji et al. 2017, *Epidemiology*, 10.1097/EDE.0000000000000579

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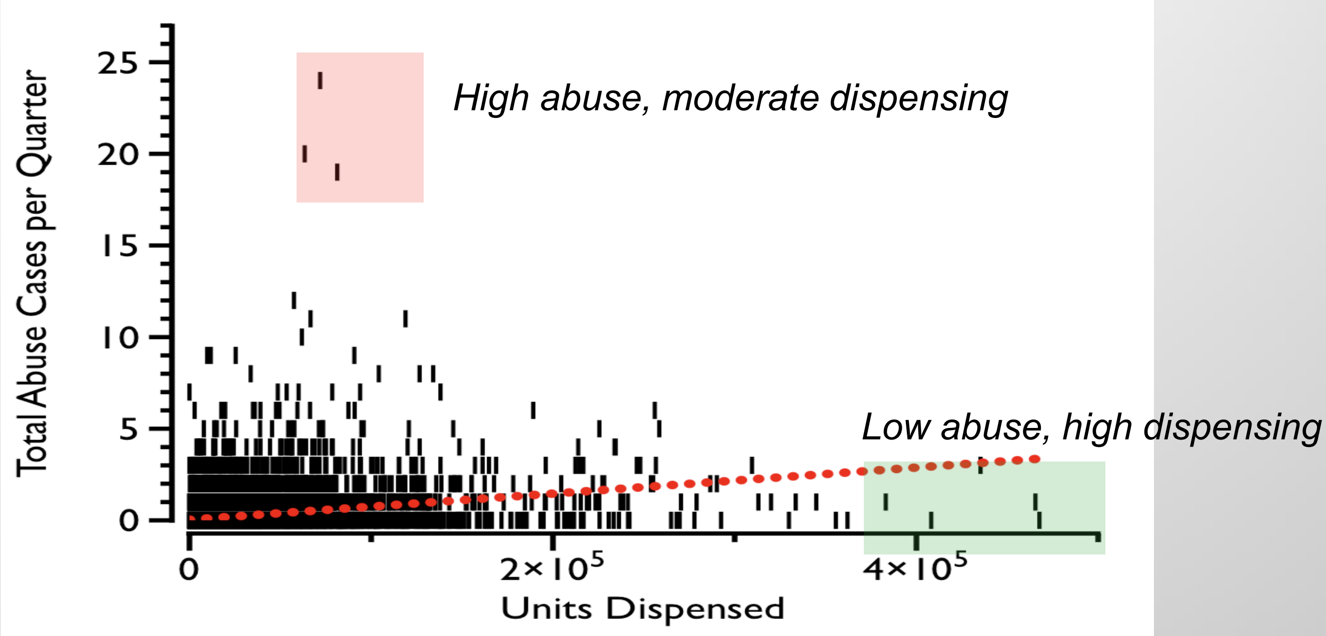
Observation 3: Non-linearity

There is a Non-Linear Association Between Dispensing and Abuse



Drug: Opana ER
Time: 2009q3 – 2016q4
Exposure Source: IQVIA
Outcome Sources: PC + SKIP + OTP
N: 25,401 ZIP-quarters

Linear $R^2 = 0.085$ = no linear association

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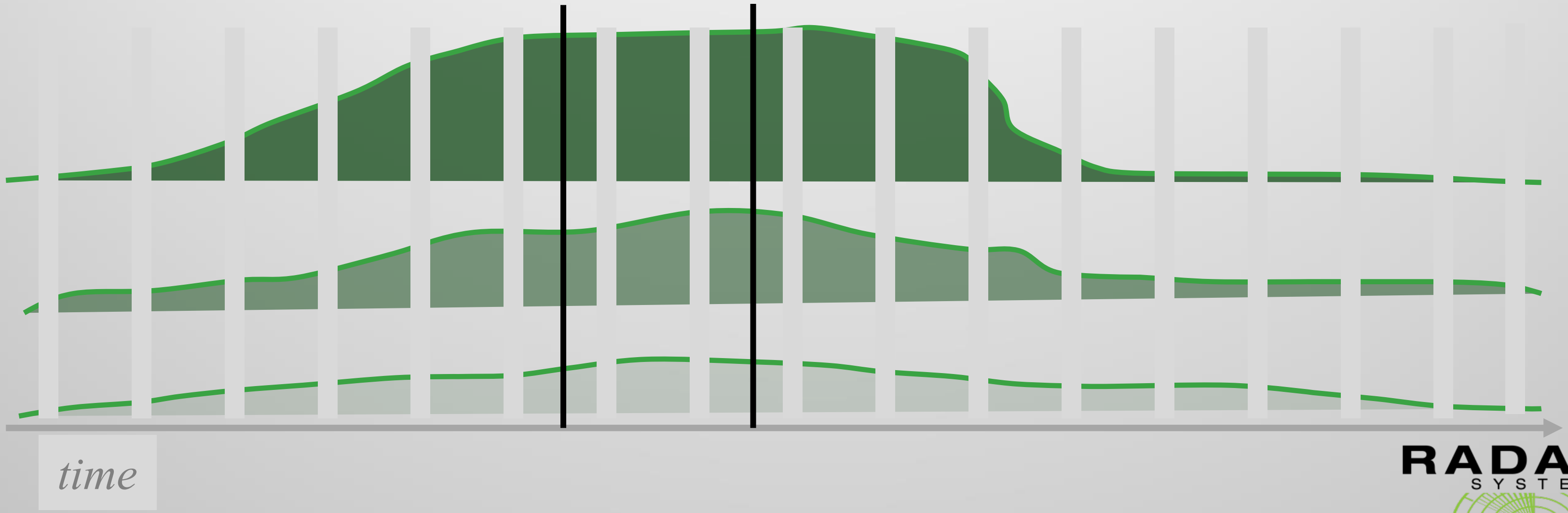
A new method, Trend-in-Trend, is robust to confounding from competing interventions by looking at trends in smaller time units, while simultaneously accounting for dispensing tiers.



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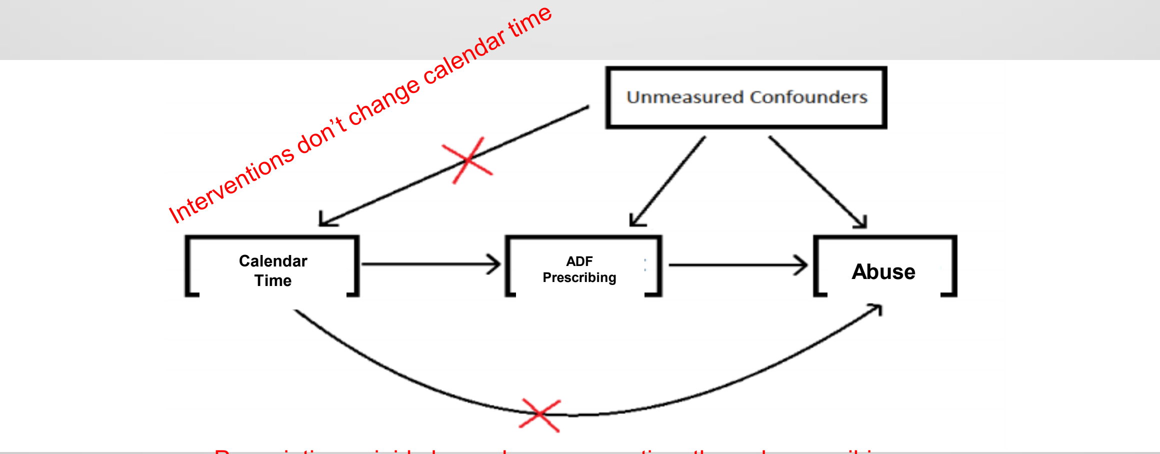
Seeing the Unseen

Borrowing a well-established concept from economics (instrumental variables [IV]), we can calculate how much effect competing interventions might have on opioid abuse, even if we can't directly quantify the interventions themselves.

This is different from "adjusting" for known interventions in a model, which would explain away the observed variation. Instead, we are saying that competing interventions over time are important, and quantifying the influence they might be asserting.



Prescription opioid abuse changes over time through prescribing.

Ertefaie A et al. A tutorial on the use of instrumental variables in pharmacoepidemiology. *PDS*, 2017. doi:10.1002/pds.4158

Extension to the linear model

Expanding to the linear model framework, we have our marginal mean μ_i defined below conditional on Z_i (exposure), G (group/tier), and X_i which represents our unmeasured confounding at time t

$$\mu_i^t = E\left(Y_i^t | Z_i^t, G, X_i^t\right)$$

h() is the logit link function so we can evaluate the model as

$$h(\mu_i^t) = \beta_0 + Z_i^t \beta_1 + t\beta_2 + X_i^t \gamma,$$

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Dasgupta, N, Schwarz, J, Hennessy, S, Ertefaie, A, Dart, RC. Causal inference for evaluating prescription opioid abuse using trend-in-trend design. *Pharmacoepidemiol Drug Saf*. 2019; 1– 10.

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ORIGINAL REPORT

WILEY

Causal inference for evaluating prescription opioid abuse using trend-in-trend design

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Abstract

Purpose: One response to the opioid crisis in the United States has been the development of opioid analgesics with properties intended to reduce non-oral use. Previous evaluations of abuse in the community have relied on population averaged interrupted time series Poisson models with utilization offsets. However, competing interventions and secular trends complicate interpretation of time-series analyses. An alternative research design, trend-in-trend, accounts for heterogeneity in per capita opioid dispensing and unmeasured time-varying confounding, which provides a causal evaluation, provided that underlying assumptions are met.

Methods: Trend-in-trend can be modeled using a logistic regression framework. In logistic regression, exposure was any product-specific outpatient dispensing by three-digit ZIP code and calendar quarter, for 22 opioids. The outcome was any product-specific abuse case ascertained from poison centers and drug treatment programs, covering 94% of the US population, between July 2009 and December 2016. Product-specific odds ratios compared places without dispensing with places with any dispensing; the causal contrast represents the odds of product-specific abuse in the community given exposure.

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