Medicine: Mind the Gap

Time-varying effect modeling to study developmental and dynamic processes

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Outline

1. Background

2. Study I: Nicotine addiction
   o Recovery is dynamic

3. Study II: E-cigarette use
   o A developmental perspective

4. Next steps
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Human behavior as it relates to health is dynamic

Orientation is relevant for understanding

- Behavioral change – across age, time
- Changes in process – across age, time
- Differential intervention effects – across age, time
A motivating example

We know that negative affect and craving to smoke are tightly linked among addicted smokers. What does recovery look like?

TVEM can address questions such as:

*Is negative affect differentially associated with craving at various points in the smoking cessation process?*

*How does a smoking cessation intervention affect that link over time?*
A thought exercise

Suppose an intervention was conducted to reduce alcohol abuse

2-arm RCT

Post-baseline measurement

- One time point
- Two time points
- Multiple time points (moving window)
Effect of intervention: One time

Rate of heavy episodic drinking

Time 1

- Placebo
- Intervention
Effect of intervention: Two times

Rate of heavy episodic drinking

Time 1  Time 2

Placebo  Intervention

0.0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8

0.8  0.7  0.6  0.5  0.4  0.3  0.2  0.1  0.0
Effect of intervention: Multiple times

Rate of heavy episodic drinking

Time 1  Time 2  Time 3  Time 4  Time 5  Time 6  Time 7  Time 8  Time 9  Time 10
Placebo  Intervention

SEND QUESTIONS TO PREVENTION@MAIL.NIH.GOV  USE @NIHPREVENTS & #NIHMTG ON TWITTER
TVEM: Direct extension of regression

P50-DA039838: Center for Complex Data to Knowledge (CD2K) in Drug Abuse and HIV Behavioral Science

Why collect longitudinal data?
◦ capture temporal changes in an outcome and time-varying covariates

Natural to expect that the associations between covariates and outcome may change over time

TVEM is designed to evaluate whether and how associations change over time
TVEM: Direct extension of regression

Regression coefficients express associations between variables

Traditional regression predicting outcome ($Y$) from covariate ($X$)

$$Y = \beta_0 + \beta_1 X + e$$

TVEM allows coefficients to be **dynamic**

$$Y = \beta_0(t) + \beta_1(t)X + e$$
Coefficient functions are estimated

TVEM estimates regression coefficients as flexible function of continuous time
  ◦ Intercept
  ◦ Slopes

Use figure to interpret a “coefficient function”
Brief history of TVEM

1990’s

○ Functional regression analysis introduced in statistical literature (Hastie & Tibshirani, 1993; Hoover et al., 1998)

2010

○ SAS software released (under direction of Runze Li)
Brief history of TVEM

2012
- Demonstration paper – *Prevention Science*
- Pre-conference workshop – Society for Research on Nicotine and Tobacco
- NCI R01 – Smoking cessation dynamics

2013
- Pre-conference workshop – Society for Prevention Research
- NCI, OBSSR funds supplemental issue of *Nicotine and Tobacco Research*
- Application paper – *Drug and Alcohol Dependence*
Brief history of TVEM

2014

◦ Supplemental issue published
  (Lanza, Piper, & Shiffman, Eds.)

◦ Other researchers picking up TVEM

2015

◦ Summer Institute on Innovative Methods
◦ Pre-conference workshop – Society for Ambulatory Assessments
◦ Software extended: random effects
◦ NIDA R01 – Epidemiology of substance use
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Nicotine addiction

Tobacco use is leading cause of preventable death globally.

95% cessation attempts end in relapse; withdrawal symptoms primary reason.

Improved understanding of withdrawal symptoms and how treatments alleviate them could:
  ◦ Lead to new treatments
  ◦ Inform tailored treatments (to people, to time)
Nicotine addiction

Overall goal:

To apply innovative methods to existing data from an RCT to gain knowledge that can inform next generation of smoking interventions

R01-CA168676: Advancing Tobacco Research by Integrating Systems Science and Mixture Models
Wisconsin Smokers’ Health Study

1504 daily smokers enrolled in smoking cessation RCT
  ◦ Funded by P50-CA84724

Placebo group
  ◦ Counseling only

Treatment group
  ◦ Five combinations of Bupropion, lozenge, patch

Real-time assessment of dynamic phenomena (withdrawal symptoms, mood, behavior)
Study design

EMA: 4 assessments per day
- Upon waking
- 2 random times
- At bedtime
Time-varying effects of smoking intervention

**Goal 1:** Study the underlying dynamics of craving during cessation attempt

**Goal 2:** Estimate effect of intervention on decoupling craving from its key drivers (e.g., negative affect)

From Lanza et al. (2014) *Nicotine and Tobacco Research*
Measures

**Outcome:** Craving during first two weeks of quit attempt
- Intensively assessed via EMA

**Predictors:**
- Baseline nicotine dependence (not time-varying, but effect can be!)
- Negative affect (time-varying)

**Moderator:** Intervention group
Specify model

Within each intervention group, what varies with time?

- Mean craving (intercept function)
- Negative affect
- Effect of negative affect (slope function)
- Effect of baseline dependence (slope function)

\[
CRAVING_{it} = \beta_0(t) + \beta_1(t)AFFECT_{it} + \beta_2(t)DEP_i + \epsilon_{it}
\]
Effect on craving: **Negative affect**

Lanza et al. (2014)
Nicotine and Tobacco Research
Effect on craving: Baseline dependence

Lanza et al. (2014)
Nicotine and Tobacco Research
Implications for smoking cessation

Think differently about intervention effects

With time, intervention changes the relationship between baseline dependence and craving

Intervention diffuses role of negative affect—a key driver of craving—early in quit attempt
Broader implications

Effects of static “baseline” variables can change over time

Effect of treatment in standard RCT may be time-varying
  • Model intervention processes we posit

Could inform tailoring of treatment to **individuals** and to **time**
(adaptive intervention designs)
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NIDA R01

Overall goal:

To apply TVEM to existing national data to study etiology of substance use, co-use, comorbidity with mental health problems, and health disparities

R01-DA039854: Age-Varying Effects in the Epidemiology of Drug Abuse
E-cigarette use among adolescents

Developed as “reduced harm product” thus often considered safe alternative to traditional cigarettes *(Cobb et al., 2010)*

Inhalation-activated devices; heat produced which turns solution (nicotine, other additives) into vapor

- Eliminates combustion/smoke, but long-term effects of use inconclusive *(Chapman & Wu, 2014; Cobb et al., 2010; Pepper & Brewer, 2014, Williams & Talbot, 2011)*

Rate of adolescent use rising rapidly

- Lack of FDA regulations
- Gateway to traditional cigarettes?
National Youth Tobacco Study

Cross-sectional data from 2014

CDC to assess “tobacco-related beliefs, attitudes, behaviors, and exposure to pro- and anti-tobacco influences”

22,007 US middle- and high-school students
- ages 11-19 (mean 14.5)
- 49% female
- 29% Hispanic, 48% NH White, 17% NH Black
Etiology of traditional and e-cigarette use

**Goal 1:** Estimate disparities in rates of use across adolescence for sex and race/ethnicity population subgroups

**Goal 2:** Estimate rate of use of both products as continuous function of age

From Lanza et al. (under review)
Measures

**Current traditional cigarette smoking**
- Coded 1 if use in past 30 days, 0 otherwise (6.4% yes)

**Current e-cigarette smoking**
- Coded 1 if use in past 30 days, 0 otherwise (9.2% yes)

**Age** (to nearest year)

**Sex, Race/ethnicity** (moderators)
Specify model (logistic TVEM)

What varies with age?

- Probability of cig use
- Probability of e-cig use
- Effects of sex, race/ethnicity
- Effect of cig on e-cig (age-varying odds ratio)

\[
\ln \left( \frac{p(CIG_i)}{1 - p(CIG_i)} \right) = \beta_0(age) + \beta_1(age)SEX_i
\]

\[
\ln \left( \frac{p(E\_CIG_i)}{1 - p(E\_CIG_i)} \right) = \beta_0(age) + \beta_1(age)CIG_i
\]
E-cigarette and traditional cigarette use: Sex differences (ages 11-19)
E-cigarette and traditional cigarette use: Race/ethnicity differences (ages 11-19)
Use of both products  
(odd ratio, ages 11-19)

Among those age 12, adolescents using e-cigarettes are >40 times as likely to use traditional cigarettes compared to those not using e-cigarettes.
Implications for policy and prevention

Identification of key ages of risk can inform targeted, age-appropriate intervention

Traditional and e-cigarette use go hand in hand, particularly in very early adolescence

Early use of e-cigarettes significantly more likely among Hispanic youth, suggesting greater risk for future nicotine dependence
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New information contained in contemporary data sources

Intensive longitudinal data (ILD)
  ◦ EMA, wearable devices

Electronic medical records (EMR)

Genetic data

Big data, complex data = big opportunity

Adaptive interventions, Mobile interventions, Precision medicine
  ◦ Stress, mood, context, health behaviors
TVEM can unlock new knowledge from existing data

Complex processes unfolding with time
Dynamic effects of interventions
Developmental associations
Associations across historical time
Complex link between age-of-onset and later outcomes
John Dziak
Runze Li
Michael Russell
Sara Vasilenko

KEY TVEM COLLABORATORS
Thank you!
EXTRA SLIDES
Getting started with TVEM
TVEM is freely available

Download SAS macro and user’s guide at methodology.psu.edu
Data requirements for TVEM
Data requirements
(intensive longitudinal data)
Data requirements (cross-sectional and panel studies)

Only one or a few waves, but many ages sampled

Example: The National Longitudinal Study of Adolescent to Adult Health (Add Health)

- Nationally representative sample
- 4 waves of data collected from 1996-2008
- $N \sim 12,000$ (core sample)
- 34,562 person-times (spans ages 12-32)
Add Health: Coverage across age
TVEM to examine change over historical time
Rates of use over time: By race

Lanza et al. (2015)
Journal of Adolescent Health
Rates of co-use over time: Black youth

Lanza et al. (2015)
Journal of Adolescent Health
Rates of co-use over time: White youth

Lanza et al. (2015)
*Journal of Adolescent Health*
TVEM to understand age-of-onset
Rate of dependence as function of age of onset

Estimated Prevalence of Dependence

Age of Onset

Lanza & Vasilenko (2015)
Journal of Adolescent Health
Rate of dependence as function of age of onset: **By sex**

Lanza & Vasilenko (2015)
*Journal of Adolescent Health*