CTS1 BERD Recent Topics in Research Methods Seminar:

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. Conclusions and next steps
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1. **Background**
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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
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
TVEM: Direct extension of regression

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 ($X$)

$$Y = \beta_{\downarrow 0} + \beta_{\downarrow 1} X + e$$

TVEM allows coefficients to be dynamic

$$Y = \beta_{\downarrow 0}(t) + \beta_{\downarrow 1}(t)X + e$$
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, PSU Distinguished Professor of statistics)
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)

\[
\text{CRAVING}_{it} = \beta_{0}(t) + \beta_{1}(t) \text{AFFECT}_{it} + \beta_{2}(t) \text{DEP}_{i} + \epsilon_{it}
\]
Effect on craving: **Negative affect**

![Graph showing the effect of craving over days since quit date with Placebo and Treatment lines.](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)

$$\ln(p(CIG\downarrow_i)/1-p(CIG\downarrow_i)) = \beta_{\downarrow 0} (age) + \beta_{\downarrow 1} (age) \times SEX\downarrow_i$$

$$\ln(p(E_CIG\downarrow_i)/1-p(E_CIG\downarrow_i)) = \beta_{\downarrow 0} (age) + \beta_{\downarrow 1} (age) \times CIG\downarrow_i$$
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 (odds 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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Getting started with TVEM
TVEM is freely available

Download SAS macro and user’s guide at methodology.psu.edu
Other applications of TVEM:

Examining 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
Other applications of TVEM:

Understanding the role of 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
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
EXTRA SLIDES
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~12,000 (core sample)
- 34,562 person-times (spans ages 12-32)
Add Health: Coverage across age