MOVING BEYOND ‘MICE & MEN’
INNOVATIONS IN TRANSLATIONAL GENDER-SENSITIVE TOBACCO RESEARCH

Yale-SCOR: Sherry McKee PhD
Yale-SCOR Mission:

To inform and expedite the development of gender-sensitive therapeutics for smoking cessation.

Train the next generation of interdisciplinary and translational researchers

Be a national resource to invigorate and galvanize the study of sex and gender differences in relation to smoking.
Some facts about tobacco use

- Tobacco use a leading cause of preventable morbidity and mortality
  - 440,000 deaths annually in the US
  - ~6 million deaths annually worldwide

*Surgeon General's Report*

Figure 13.4  Trends in prevalence (%) of current cigarette smoking among adults, 18 years of age and older, by gender; National Health Interview Survey (NHIS) 1965–2012; United States

*Source: 1965–2012 NHIS, National Center for Health Statistics, public use data tapes.*
Some facts about tobacco use

- Smoking annual deaths: 400,000
- Second hand smoke annual deaths: 100,000
- Population of Atlanta: 750,000
- US World War II deaths: 405,000
- US Vietnam War deaths: 500,000
- Annual auto accident deaths: 150,000
- Annual AIDS deaths: 30,000
- Annual murders: 15,000
- Annual alcohol deaths: 50,000
- Annual illicit drug deaths: 20,000
Women smokers face critical health disparities

- Female smokers vs. male smokers
  - are more likely to develop lung cancer and oral cancers
  - are more susceptible to tobacco carcinogens
  - have increased risk of coronary heart disease
  - experience significant sex-specific health risks, primarily associated with their reproductive health

A recent meta-analysis examining the impact of smoking on coronary heart disease by gender in 76 cohorts from 1966-2010 (2.4 million participants) showed that, after controlling for other cardiovascular risk factors, female smokers demonstrated a 25% greater risk of coronary heart disease than male smokers (Huxley et al., 2011).
Women smokers have more difficulty quitting

**Sex difference in quit ratio (%)**

NHIS, 1965-2012

- Despite being more likely to engage in quit attempts, female smokers vs. male smokers are less successful at quitting smoking.

“for a long time males had a substantially higher quit ratio than females. By 2005, the difference between the genders was trivial.”

p 716
Women smokers have more difficulty quitting

Women have greater relapse (n=33,309)

Women have greater difficulty quitting (n=4,959)

Women less likely to achieve abstinence (n=1,986)

Similar findings in quit behavior across large population based studies, pooled clinical trial findings, and international samples of naturalistic quitting

Weinberger...McKee, 2014; Smith...McKee, in press, McKee et al., under review
Women smokers have more difficulty quitting

- The quit ratio is subject to influences other than actual quitting behavior.
- Can lead to inaccuracies and misinterpretation of population trends and group differences.
Current Population Survey Tobacco Use Supplement (TUS-CPS, n~225,000 per year).

New measure of ‘quit index’ based on past 12 months, highlights significant gender differences in quitting (p<.001).

The gender difference seen here is primarily driven by women have higher rates of relapse.

Results of quit ratio mirror Surgeon General’s findings.
Rates of nicotine dependence are not declining in women

Using national cohort data (NSDUH) from 2002-2011 (n=120,268 smokers)

Rates of nicotine dependence are declining in men but are not changing in women

Smith...McKee., in press
Why do women have more difficulty quitting smoking?

- Factors underlying poor treatment response in women
  - medication response
  - reproductive status & hormones
  - psychiatric co-morbidities
  - weight management
  - stress & negative affect
Medication Response

- Nicotine replacement
  - Most commonly used smoking cessation medication
  - 20% of smokers who try to quit, use nicotine replacement
  - 3.5 million people in the U.S. use nicotine patch each year

......which may be less effective for women

Nicotine replacement 6-m quit rates

- Gum
- Patch
- Spray

Female
Male

West, 2001
Analysis of nicotine replacement efficacy by gender

- Systematic review of nicotine replacement by gender
  - 42 clinical trial studies (from 1993 to 2013)
  - 54% of samples were female
  - 21 studies analyzed outcomes by gender
    - 14 studies found no differences in smoking cessation outcomes
    - 7 studies found better smoking cessation outcomes for men vs women
    - 5 studies provided data by gender
    - 1 study examined side effects by gender

Weinberger..McKee, in press
Why might women smokers have poorer response to NRT?

$\beta_2^*\text{-nAChR}$ availability was significantly higher in male smokers compared to male nonsmokers in striatum, cortex and cerebellum, but female smokers did not have higher $\beta_2^*$-nAChR availability than female nonsmokers in any region.

Cosgrove et al., 2011, Arch of Gen Psych
Medication use attenuates gender disparity in quitting

- Collaboration with Roswell Park and MUSC-SCOR
- Longitudinal data from US, Canada, UK, Australia (n=7,825)
- Use of smoking cessation medications attenuates the gender disparity in quitting behavior

SCM = smoking cessation medication
Reproductive status & hormones

- Systematic review & meta-analysis of menstrual cycle and ovarian hormone effects on smoking
  - ad-lib smoking, cessation, relapse, withdrawal, and craving

- Collaboration with Minnesota & MUSC SCORs

- 36 studies identified

Weinberger...McKee, under review
Women reported greater withdrawal and craving during the luteal phase compared to the follicular phase.
Psychiatric co-morbidities

Smoking and mental illness

Philip H Smith,1 Carolyn M McDermott-Gray,2 John P Catalano3

ABSTRACT

Objectives: Those with any psychiatric diagnoses had substantially greater rates of smoking and lower quit smoking rates than those with no diagnosis of mental illness. Using two rounds of nationally representative data, we sought to estimate smoking rates and longitudinal changes in specific psychiatric diagnoses and mental health service use.


Main outcome measures: We examined lifetime, past year, and past year heavy alcohol and tobacco use rates among those with any lifetime psychiatric diagnosis (DSM-IV), and among those with tobacco use disorders in the past year.

Results: Those with any current psychiatric diagnosis were more likely to smoke (odds ratio, 2.32; 95% CI 3.11 to 3.35) and less likely to quit smoking than those without a diagnosis. Those with an anxiety disorder of any type were also more likely to have a current or past-year diagnosis of tobacco use disorder (odds ratio, 2.32; 95% CI 3.11 to 3.35).

Conclusions: These findings suggest that smoking and mental illness are co-morbid conditions. Smoking may contribute to mental illness, and mental illness may contribute to smoking. This provides an opportunity for research and intervention.

INTRODUCTION

Limitation of both Lasser et al2 and the CDC report

REFERENCES


Odds ratios of daily smoking status by depression diagnosis by gender, n=43,093

*Husky et al., 2008, DAD*

**Women vs men**
- Women are 2x more likely to present with current MDD (16% vs. 7.9%)
- Have stronger associations between smoking and MDD
- Depression is associated with decreased ability to quit and increased likelihood of relapse

**Odds ratios of transitions in smoking status by depression diagnosis, n=34,653**

*Weinberger et al., 2012, Addiction*
Gender not considered in treatment research for depressed smokers

- 68 clinical trials were identified
- 55% of the samples were female
- 13 studies (19%) controlled for gender
- Only 7 studies (10%) examined interactions between gender and smoking cessation outcomes
- 5 of these 7 studies found that depression status has a greater negative impact on treatment outcomes for women
Negative affect & stress

Negative mood reduces latency (seconds) to smoke in females

Across several laboratory studies, smoking in women vs men more likely to be negatively influenced by stress and negative affect

Weinberger & McKee, 2011; Weinberger & McKee, 2012
Negative affect & stress

- Epidemiological investigations examining life event stress (n=783, American Changing Lives)
  - Financial events increase odds of
    - failure to quit smoking in women (O.R. = 4.79)
    - relapse in smoking in women (O.R. = 15.01)
  - Health events increase odds of quitting in men (O.R. = 5.12)

McKee et al., (2003), Addiction
**Negative affect & stress**

**Effect of life event stress on smoking cessation NESARC (n=7,906)**

<table>
<thead>
<tr>
<th>LIFE EVENT STRESS</th>
<th>WOMEN (ODDS RATIO)</th>
<th>MEN (ODDS RATIO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moved/someone come live with you</td>
<td>0.85</td>
<td>0.86</td>
</tr>
<tr>
<td>Financial difficulty</td>
<td>0.49*</td>
<td>0.62</td>
</tr>
<tr>
<td>Interpersonal loss</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>Interpersonal violence/crime victimization</td>
<td>0.63</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Interaction with gender

*Smith....McKee, under review*
Negative affect & stress

Odds of quitting smoking

Moved/had someone come live with you
Interpersonal loss
Financial difficulty
interpersonal violence/crime victimization

women | men | women | men | women | men | women | men

0.9 | 1  | 0.9 | 1  | 1   | 1  | 1   | 1  |

*  |

Childhood adversity - no
Childhood adversity - yes

Smith...McKee, under review
Gender-informed approaches to smoking cessation

- To improve smoking cessation rates for women, effective strategies need to address factors that contribute to difficulty in quitting

- Targeting stress-reactivity
Targeting the noradrenergic system

- Noradrenergic pathways
  - are involved in stress-induced relapse to drugs, including nicotine
  - mediate nicotine-provoked dopamine release in the nucleus accumbens
  - are involved in stress-induced decrements in prefrontal functioning
To probe the noradrenergic system’s effects on stress-reactivity and nicotine reinforcement - hypothesizing that

- different brain systems modulated by noradrenergic activity are activated by smoking in women and men
  - prefrontal cortex-amygdala axis in women
  - mesolimbic dopamine system in men

- guanfacine (an alpha2a noradrenergic agonist) can preferentially target these gender-sensitive systems to improve smoking cessation outcomes
Human laboratory project

- Phase II double-blind, placebo-controlled study to examine gender differences in the effect of guanfacine on
  - stress-reactivity and smoking-related reinforcement in the laboratory
  - clinical outcomes during a subsequent brief smoking cessation treatment.

- Examine gender differences in mechanisms
  - craving, mood, cardiovascular reactivity, HPA axis reactivity, catecholamines, cognitive function)

PI: Sherry McKee
Co-I: Mehmet Sofuoglu
Co-I: Andrea Weinberger
Targeting the noradrenergic system

% Reduction in cigarettes per day following a quit attempt

Guanfacine significantly reduced cigarettes per day for both men and women over the 4-week treatment phase.
Guanfacine increased the ability to resist smoking, reduced cigarettes smoked, and reduced tobacco craving following stress, in women but not men.
Targeting the noradrenergic system

Guanfacine reduced smoking-related reinforcement in men but not women.

Reductions in smoking-related reinforcement were associated with an increased ability to resist smoking in men ($r=-0.62$), but not women ($r=-0.18$).
Targeting the noradrenergic system

Guanfacine relative to placebo increased activation in the anterior cingulate, ventro-medial prefrontal cortex, and bilateral insula during the incongruent versus the congruent stimuli.

Collaboration with Marc Potenza, Rajita Sinha, Hedy Kober

McKee et al, under review.
Preclinical project

- Acetylcholine-Norepinephrine interactions and their implications for the effects of nicotine in reinforcement and stress reactivity

- Identify the brain areas important for ACh-NE interactions in male and female mice

- Determine the effects of guanfacine on ACh-NE interactions

PI: Marina Picciotto
Co-I: Yann Mineur
Neuroimaging project

- To determine sex differences in the anatomical locus of DA release in healthy tobacco smokers with PET imaging.
- To determine whether guanfacine differentially alters DA release between male and female tobacco smokers.
- To determine relationships between DA release before and after guanfacine treatment and smoking-related reinforcement, stress reactivity, and important correlates of smoking behavior (e.g., craving, negative affect, inhibitory control) collected in Project III (PI: McKee).

PI: Kelly Cosgrove
Yale-SCOR Pilot project

Produce movies at significant voxels

Model dynamic changes in dopamine release during in-vivo smoking. PI: Evan Morris, Associate Professor, Diagnostic Radiology
### Project 1: ACh-NE interactions in male and female mice

- Phase II clinical trial of guanfacine for smoking cessation
- Meta-analysis of varenicline Phase III data for sex differences in smoking cessation efficacy
- Meta-analysis of nicotine replacement Phase III data for sex differences in smoking cessation efficacy
- Meta-analysis of the impact of ovarian hormones on smoking outcomes
- Systematic review of gender representation in depression/smoking cessation research
- Phase II investigations of behavioral investigations

### Project 2: Sex differences in anatomical locus of DA release in healthy tobacco smokers with PET imaging

- International Phase IV investigation of sex differences in smoking cessation medication efficacy
- Provider and patient-based health service research
- Local and national dissemination of research findings (e.g. themed issue in NTR)

### Project 3: Phase II human laboratory study of an alpha2a agonist

- Interactions of sex and mental health on policy interventions (smoke-free legislation, tobacco taxes)
- Epidemiological based investigations examining predictors of smoking transitions and dependence by gender (e.g., depression, stress, childhood adversity, candidate genes)

### Additional Projects

- PK and human laboratory investigations of additional noradrenergic targets
- Resting state fMRI
- GWAS and candidate gene investigations
- Sex-dependent regulation of synaptic transmission in PFC by chronic exposure to guanfacine (SCOR pilot)
- Imaging stress-induced dopamine release in the cortex and limbic system (SCOR pilot)

### Technology Development

- Smoking-lapse models
- PET imaging of real-time dopamine release during in-vivo smoking (SCOR pilot)

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### Snap-shot of current projects covering T1 to T4 translation

Mentor 18 trainees, within and outside of Yale - from junior faculty to high school students, including 4 BIRCWH fellows
What I’ve learned...

- To conduct good science, studies need to include sex in a comprehensive and meaningful way
  - Studies need equal representation at sufficient numbers to test for sex/gender differences
  - Strategic partnerships – with academic or industry partners to pool data
  - ...and you need to be thoughtful about your data

- Be an advocate for good science
  - To recruit talented scientists to conduct sex-difference research
  - Persuade grant reviewers & journal editors

- Provide resources to support sex-difference research
  - Pilot funds, salary support including training mechanisms, consultation on papers & grants, opportunities to disseminate
RETURN ON INVESTMENT

Our $4.6 million in pilot project grants have generated feasibility data resulting in more than $56 million in new external grants.

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QUESTIONS?