PHARMACOLOGICAL TREATMENT FOR ADDICTION:

Does sex & gender matter?

Yale University School of Medicine

Sherry McKee PhD, Professor of Psychiatry

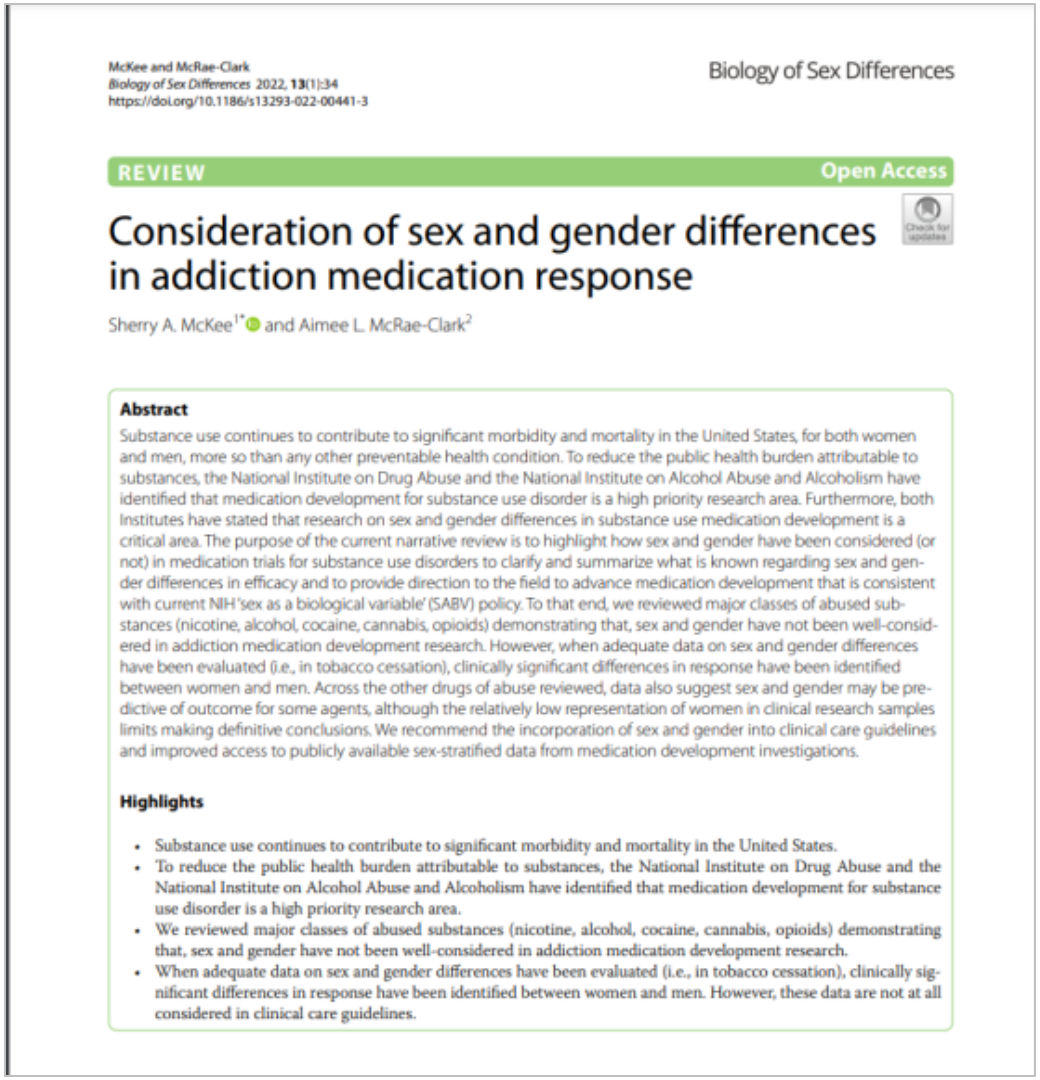
Disclosures

- Disclosures: Lumme, Pfizer, Cerecor, Embera
- Off-label use of medication

Outline

- FDA-approved medications for substance use
- Novel targets for substance use
- Conclusions & recommendations
- New Direction: Targeting stress for medication development

Medications for Substance Use Sex differences?



McKee and McRae-Clark
Biology of Sex Differences 2022, **13**(1):34
https://doi.org/10.1186/s13293-022-00441-3

Biology of Sex Differences

REVIEW Open Access

Consideration of sex and gender differences in addiction medication response

Sherry A. McKee[1*] and Aimee L. McRae-Clark[2]

Abstract

Substance use continues to contribute to significant morbidity and mortality in the United States, for both women and men, more so than any other preventable health condition. To reduce the public health burden attributable to substances, the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism have identified that medication development for substance use disorder is a high priority research area. Furthermore, both Institutes have stated that research on sex and gender differences in substance use medication development is a critical area. The purpose of the current narrative review is to highlight how sex and gender have been considered (or not) in medication trials for substance use disorders to clarify and summarize what is known regarding sex and gender differences in efficacy and to provide direction to the field to advance medication development that is consistent with current NIH 'sex as a biological variable' (SABV) policy. To that end, we reviewed major classes of abused substances (nicotine, alcohol, cocaine, cannabis, opioids) demonstrating that, sex and gender have not been well-considered in addiction medication development research. However, when adequate data on sex and gender differences have been evaluated (i.e., in tobacco cessation), clinically significant differences in response have been identified between women and men. Across the other drugs of abuse reviewed, data also suggest sex and gender may be predictive of outcome for some agents, although the relatively low representation of women in clinical research samples limits making definitive conclusions. We recommend the incorporation of sex and gender into clinical care guidelines and improved access to publicly available sex-stratified data from medication development investigations.

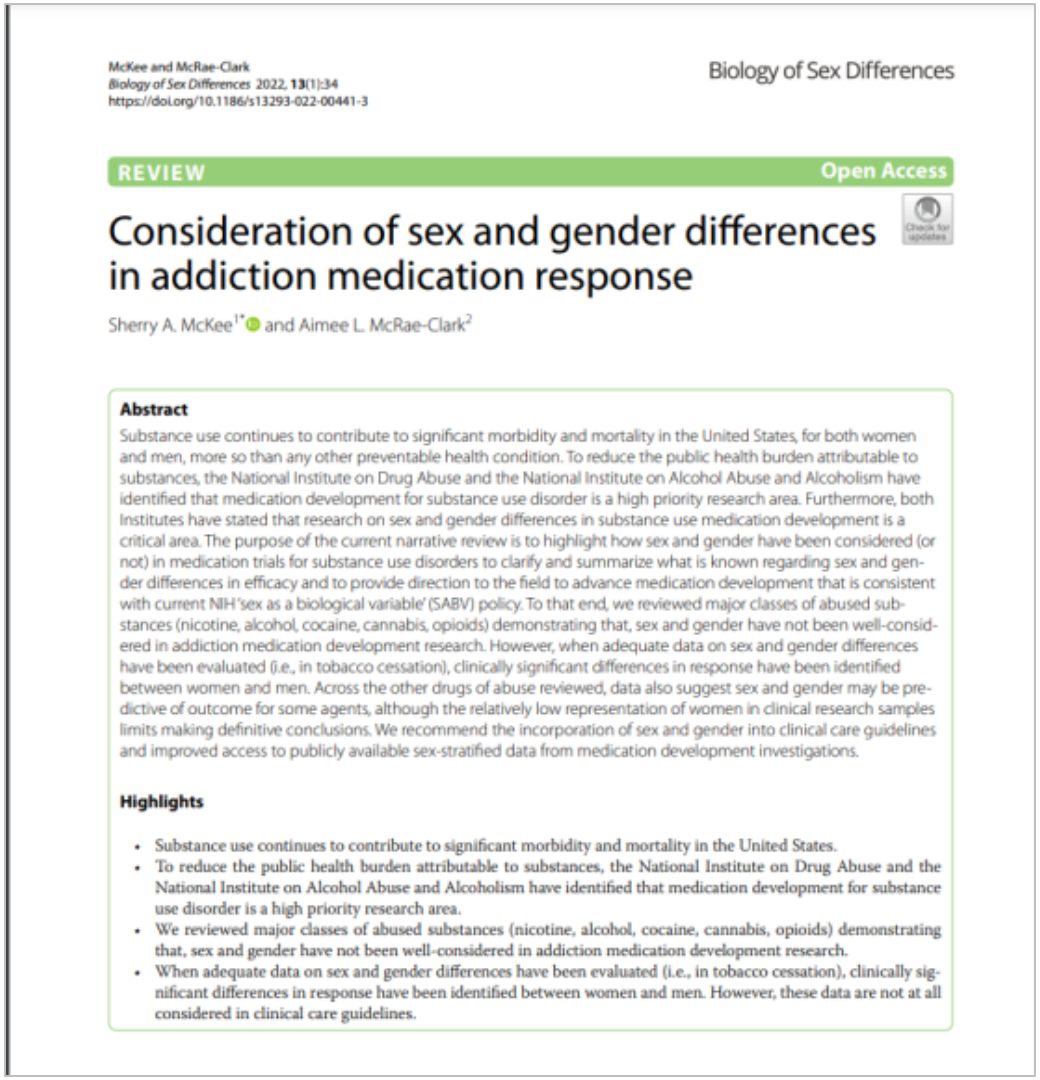
Highlights

- Substance use continues to contribute to significant morbidity and mortality in the United States.
- To reduce the public health burden attributable to substances, the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism have identified that medication development for substance use disorder is a high priority research area.
- We reviewed major classes of abused substances (nicotine, alcohol, cocaine, cannabis, opioids) demonstrating that, sex and gender have not been well-considered in addiction medication development research.
- When adequate data on sex and gender differences have been evaluated (i.e., in tobacco cessation), clinically significant differences in response have been identified between women and men. However, these data are not at all considered in clinical care guidelines.

We reviewed major classes of substances

- Tobacco
- Alcohol
- Opioids
- Cocaine
- Cannabis

Medications for Substance Use: Conclusions



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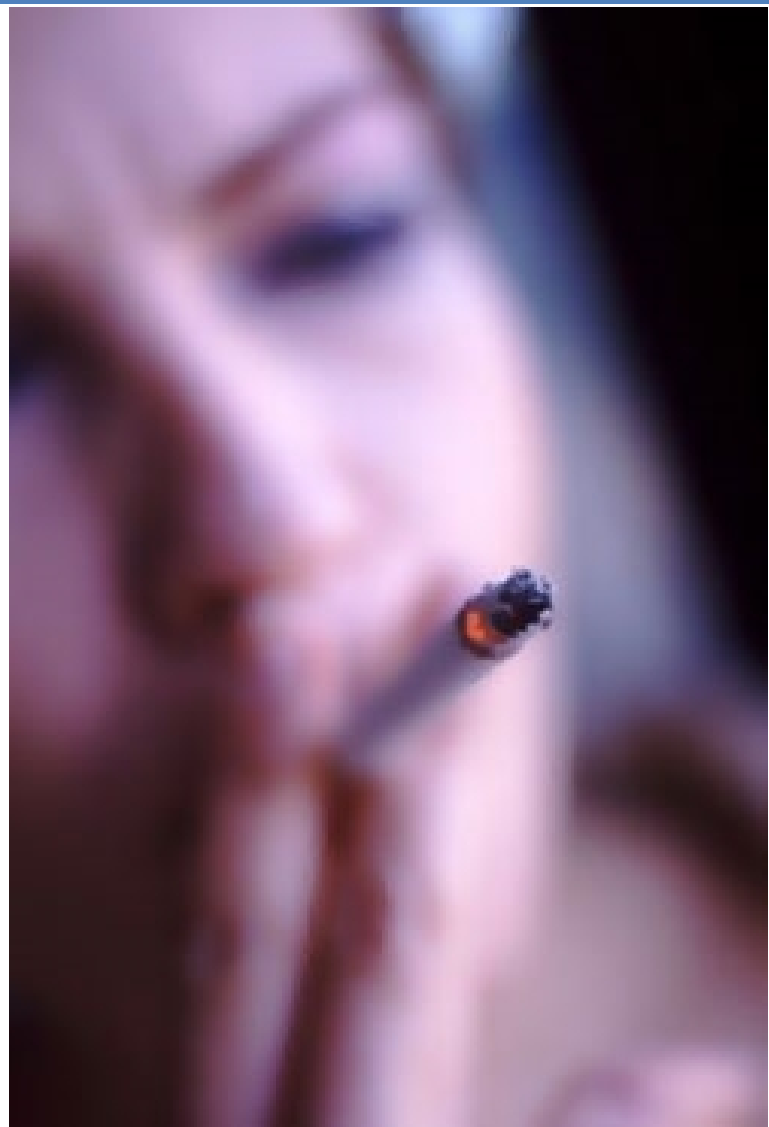
Medications were developed exclusively, or primarily, with samples of men

Existing data is primarily from retrospective studies

Medications for Tobacco: Sex differences?

FDA approved medications for smoking cessation

- Nicotine replacement (various forms)
- Bupropion (Zyban, Wellbutrin)
- Varenicline (Chantix)



Analysis of Nicotine Replacement Efficacy by Sex

Experimental and Clinical Psychopharmacology
2014, Vol. 22, No. 5, 372–393

1064-1297/14/$12.00 http://dx.doi.org/10.1037/a0037692

Consideration of Sex in Clinical Trials of Transdermal Nicotine Patch: A Systematic Review

Andrea H. Weinberger and Philip H. Smith
Yale University School of Medicine

Mira Kaufman
Brown University

Sherry A. McKee
Yale University School of Medicine

Transdermal nicotine patch (TNP) is 1 of the most commonly used smoking cessation treatments; however, the efficacy of TNP by sex is not yet clear. The purpose of the current review was to synthesize how sex has been considered in published clinical trials of TNP for smoking cessation. The specific aims of the study were to examine the inclusion of sex in analyses of cessation outcomes, TNP-related variables (compliance, side effects), and quit- related variables (withdrawal, cravings); to review the consideration of sex-related variables (menstrual cycle phase, pregnancy); and to identify needs for future research. Potential articles published through December 31, 2013 were identified through a MEDLINE search of the terms "clinical trial," "nicotine patch," and "smoking cessation." Forty-two studies used all 3 terms and met the inclusion criteria. Approximately half of the studies reported that they considered sex in smoking cessation outcomes, with 15 studies finding no difference by sex and 7 studies finding better outcomes for men versus women. Only 5 studies reported data on outcomes by sex in their publications. No studies reported analysis of TNP compliance or withdrawal by sex. In the 1 study that examined side effects by sex, more women than men reported discontinuing TNP because of skin irritation. No study examined the association of cessation outcomes with menstrual cycle phase. There is a need to include sex in research on TNP, as well as other pharmacological and behavioral smoking treatments, to clarify the picture of treatment efficacy for women compared with men.

Keywords: clinical trials, review, sex, smoking, transdermal nicotine patch

It is well-known that smoking exerts a negative impact on nearly every organ in the human body, leading to a wide range of negative health consequences and greater mortality (United States Department of Health and Human Services, 2010, 2014). Smoking causes approximately 480,000 deaths in the United States (U.S.) annually (United States Department of Health and Human Services, 2014), whereas across the globe, tobacco accounts for 12% of deaths for adults over the age of 30 with approximately 6 million tobacco-users dying every year (World Health Organization, 2012). Although both male and female smokers experience smoking-related diseases and greater mortality than nonsmokers (United States Department of Health and Human Services, 2010, 2014), women are more likely than men to experience a number of serious health consequences of smoking (e.g., lung cancer, oral cancer, heart disease) (Ceribelli, Pino, & Cecere, 2007; Huxley & Woodward, 2011; Kiyohara & Ohno, 2010; Sarna & Bialous, 2004; United States Department of Health and Human Services, 2001). Further, women experience additional consequences of smoking such as dysmenorrhea and menstrual irregularity, altered ovarian cycle and hormone levels during menstrual cycle phases, infertility, ectopic pregnancy, and spontaneous abortion (Park & Middlekauff, 2009; United States Department of Health and Human Services, 2014; Whitcomb et al., 2010).

This article was published Online First August 18, 2014.

Andrea H. Weinberger, Department of Psychiatry, Yale University School of Medicine Cancer Prevention and Control Research Program, Yale Cancer Center, New Haven, Connecticut; Philip H. Smith, Department of Psychiatry, Yale University School of Medicine; Mira Kaufman, Department of Psychology, Brown University; Sherry A. McKee, Department of Psychiatry, Yale University School of Medicine Cancer Prevention and Control Research Program, Yale Cancer Center.

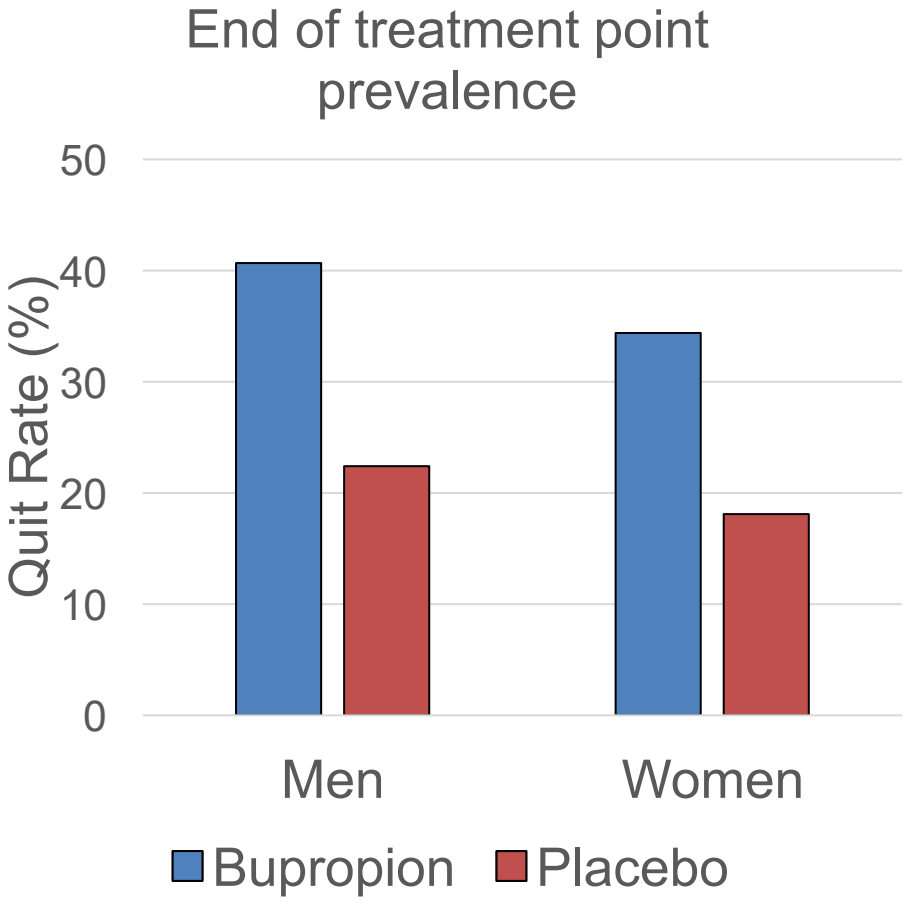
This research was supported by the National Institutes of Health (P50-DA033945 [ORWH, NIDA, & FDA] to Sherry A. McKee); the Grace J.

42 placebo-controlled clinical trials were identified

When men and women differed, women did poorer than men

Virtually no data on differences in compliance, side effects, withdrawal or cravings

Meta-analysis of Bupropion by Sex (n=4,421)



Bupropion increased rates of quitting in women and men

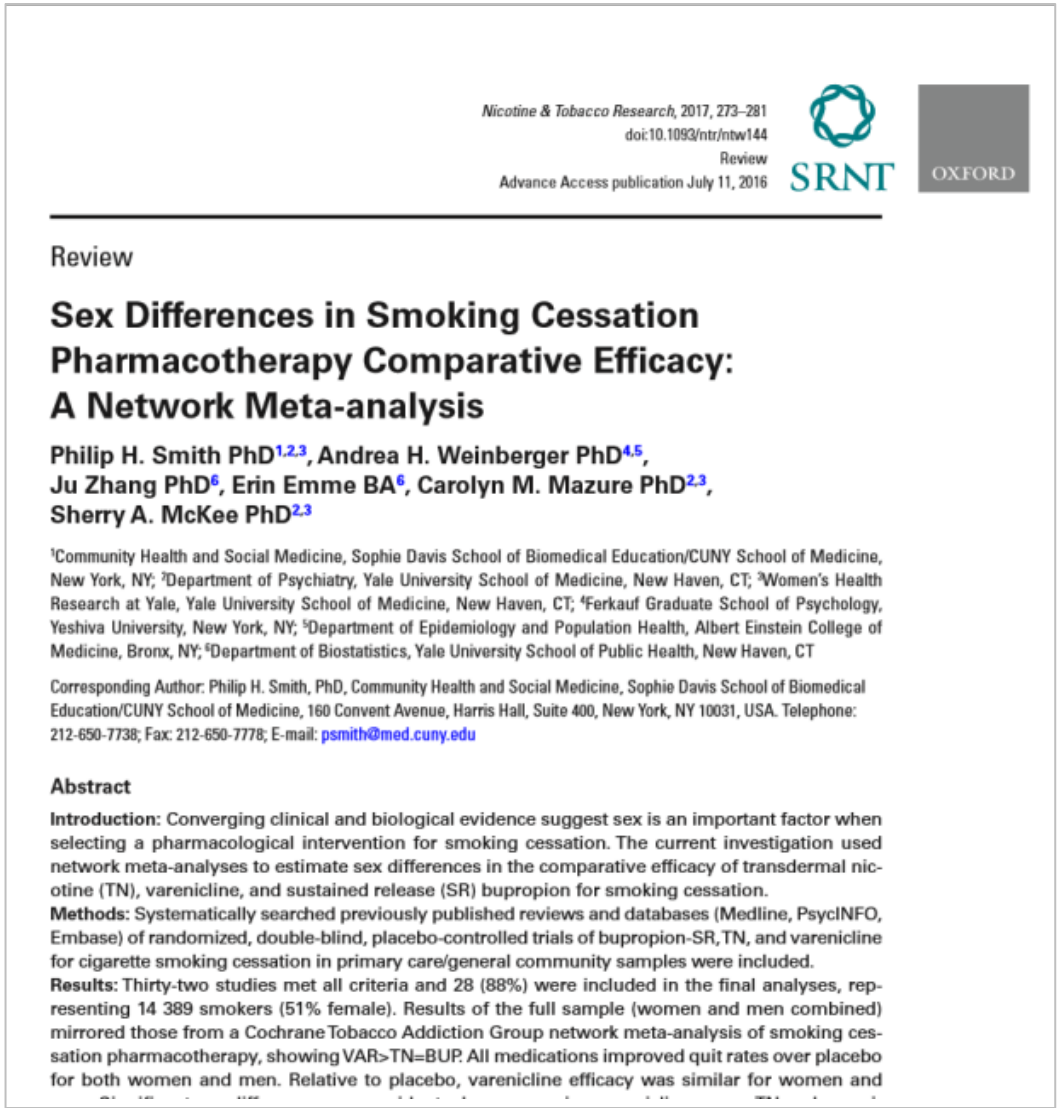
- Men O.R.=2.53
- Women O.R. = 2.47

However, rates of quitting lower in women overall, regardless of treatment condition

- women were 21% less likely to quit

Sharf & Shiffman, 2004, Addiction

Network Analysis of Medication Efficacy by Sex



Nicotine & Tobacco Research, 2017, 273–281
doi:10.1093/ntr/ntw144
Review
Advance Access publication July 11, 2016

SRNT

OXFORD

Review

Sex Differences in Smoking Cessation Pharmacotherapy Comparative Efficacy: A Network Meta-analysis

Philip H. Smith PhD[1,2,3], Andrea H. Weinberger PhD[4,5], Ju Zhang PhD[6], Erin Emme BA[6], Carolyn M. Mazure PhD[2,3], Sherry A. McKee PhD[2,3]

[1]Community Health and Social Medicine, Sophie Davis School of Biomedical Education/CUNY School of Medicine, New York, NY; [2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT; [3]Women's Health Research at Yale, Yale University School of Medicine, New Haven, CT; [4]Ferkauf Graduate School of Psychology, Yeshiva University, New York, NY; [5]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY; [6]Department of Biostatistics, Yale University School of Public Health, New Haven, CT

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Abstract

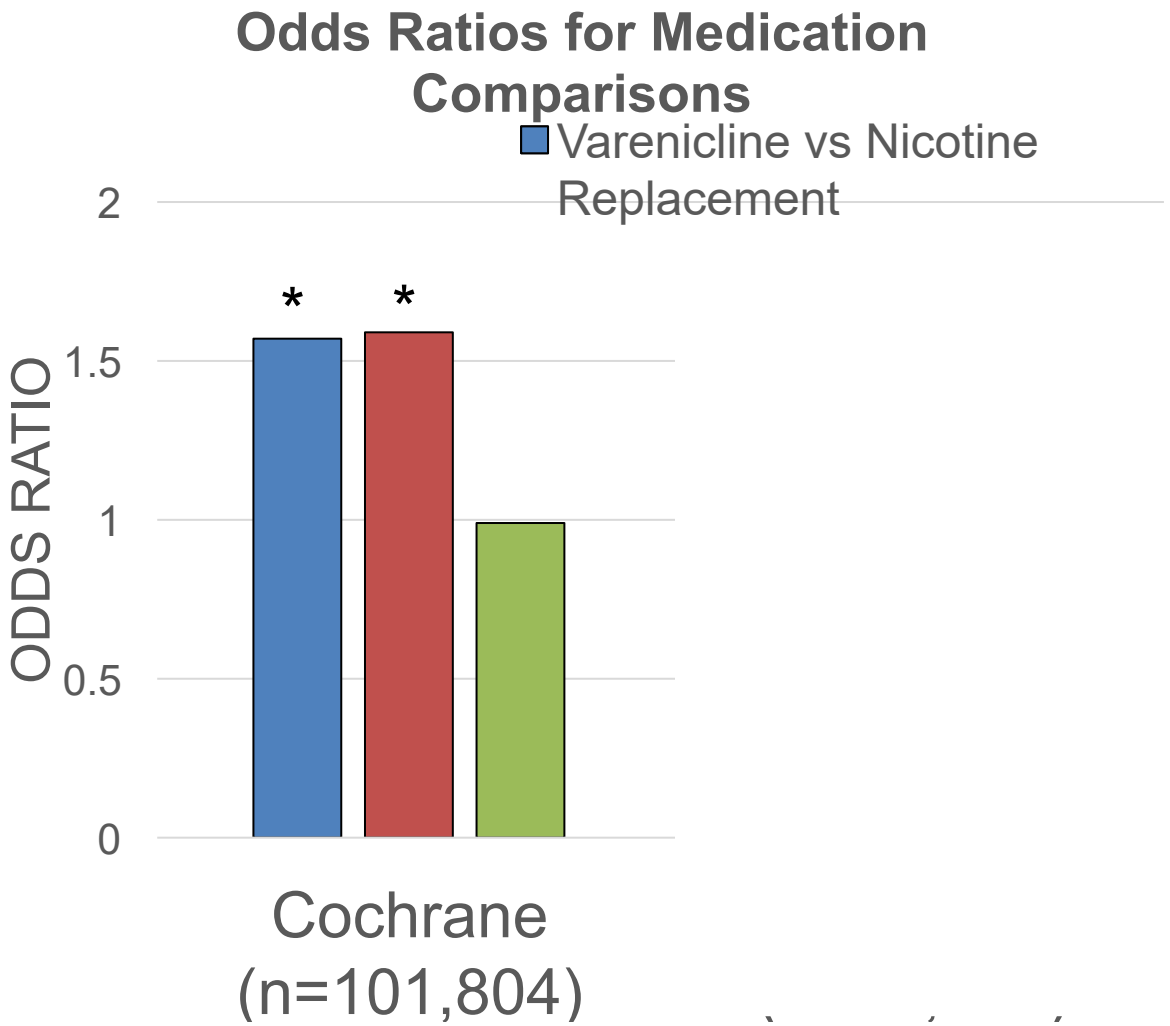
Introduction: Converging clinical and biological evidence suggest sex is an important factor when selecting a pharmacological intervention for smoking cessation. The current investigation used network meta-analyses to estimate sex differences in the comparative efficacy of transdermal nicotine (TN), varenicline, and sustained release (SR) bupropion for smoking cessation.

Methods: Systematically searched previously published reviews and databases (Medline, PsycINFO, Embase) of randomized, double-blind, placebo-controlled trials of bupropion-SR, TN, and varenicline for cigarette smoking cessation in primary care/general community samples were included.

Results: Thirty-two studies met all criteria and 28 (88%) were included in the final analyses, representing 14 389 smokers (51% female). Results of the full sample (women and men combined) mirrored those from a Cochrane Tobacco Addiction Group network meta-analysis of smoking cessation pharmacotherapy, showing VAR>TN=BUP. All medications improved quit rates over placebo for both women and men. Relative to placebo, varenicline efficacy was similar for women and

- Head-to-head comparison of nicotine patch, bupropion, varenicline by sex
- N=14,389

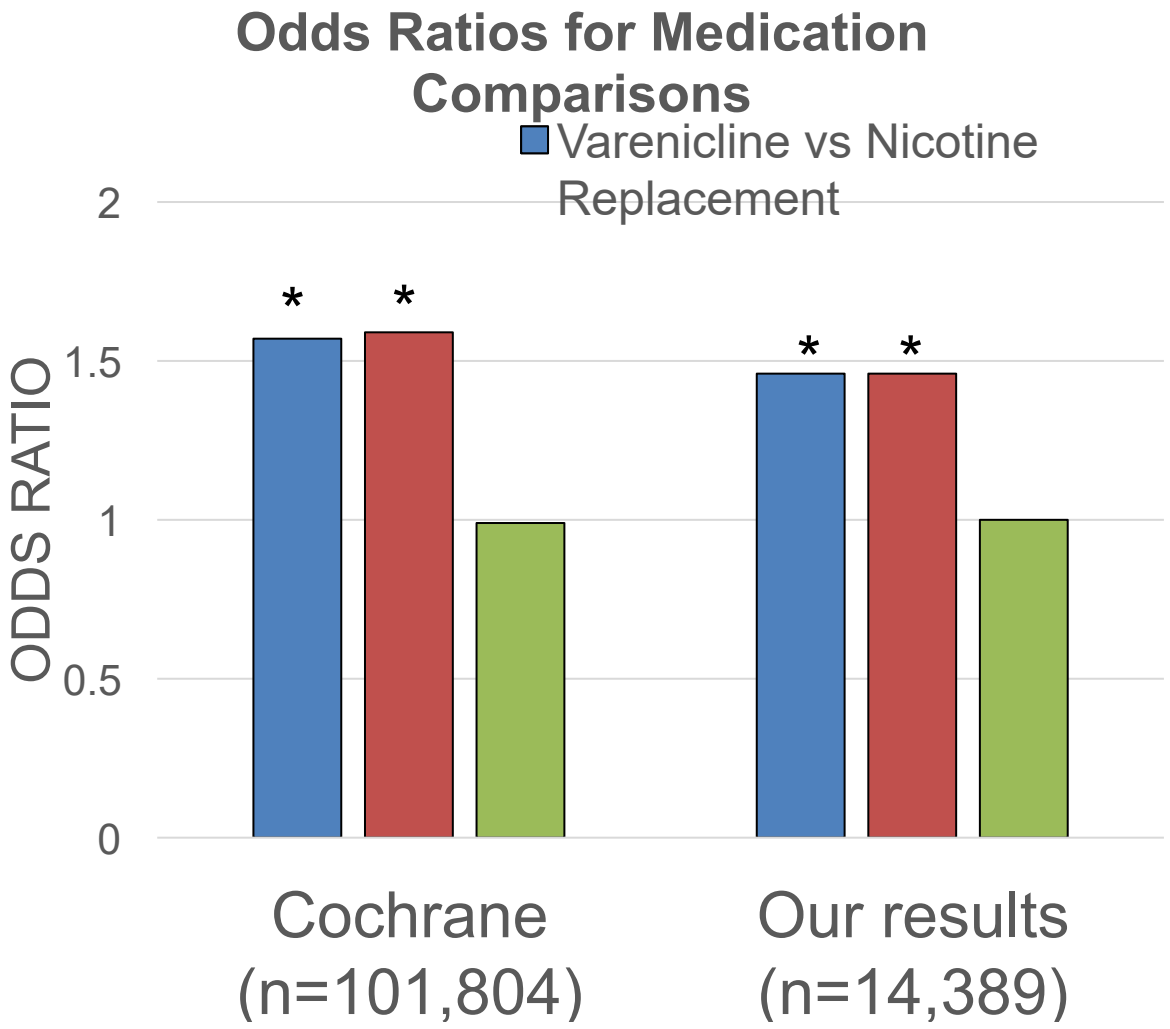
Network Analysis of Medication Efficacy by Sex



- Head-to-head comparison of nicotine patch, bupropion, varenicline
- Cochrane results (VAR>BUP=PATCH)

Cahill et al., Cochrane, 2013; Smith….McKee, NTR, 2017

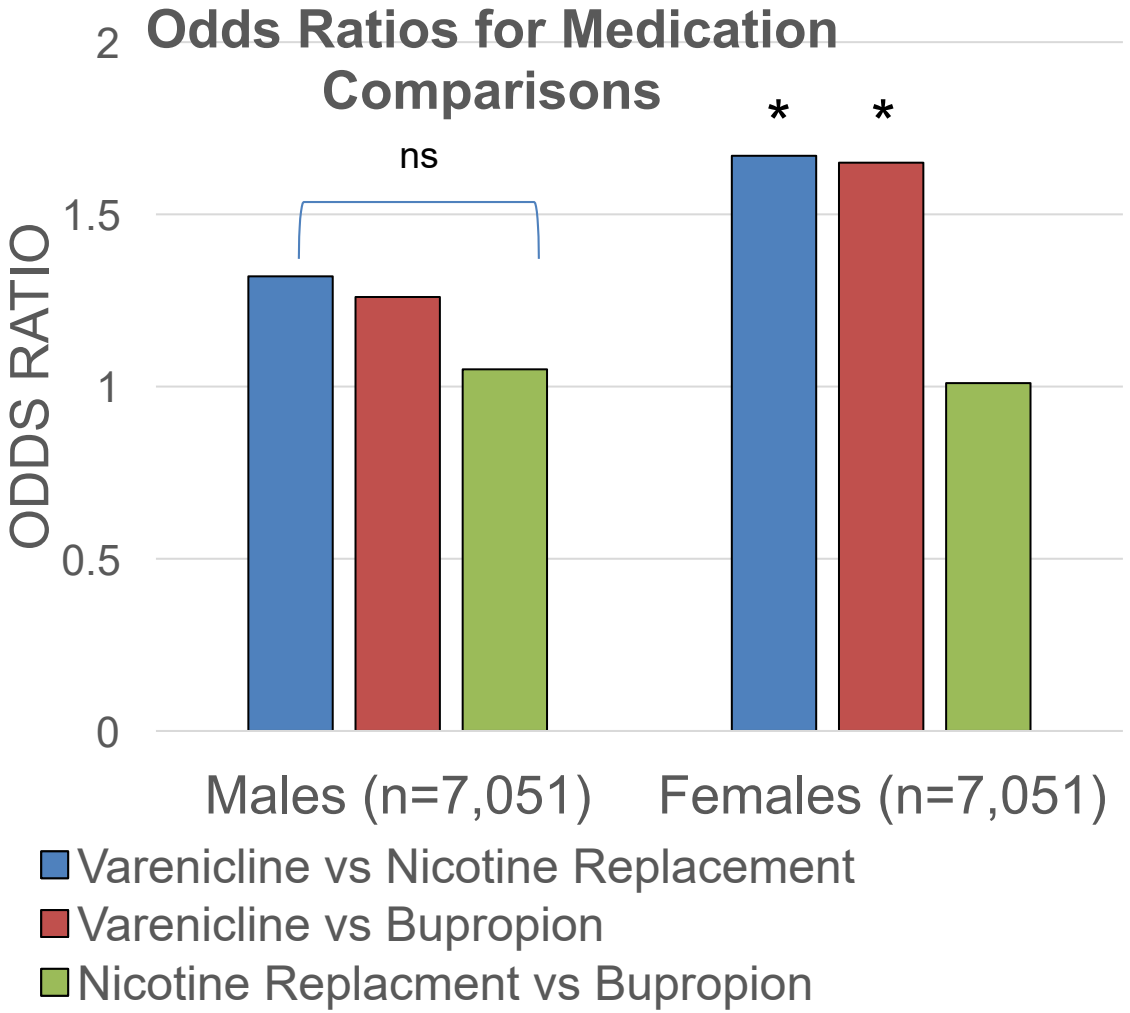
Network Analysis of Medication Efficacy by Sex



- Head-to-head comparison of nicotine patch, bupropion, varenicline
- Cochrane results (VAR>BUP=PATCH)
- Our results (VAR>BUP=PATCH)

Cahill et al., Cochrane, 2013; Smith…McKee, NTR, 2017

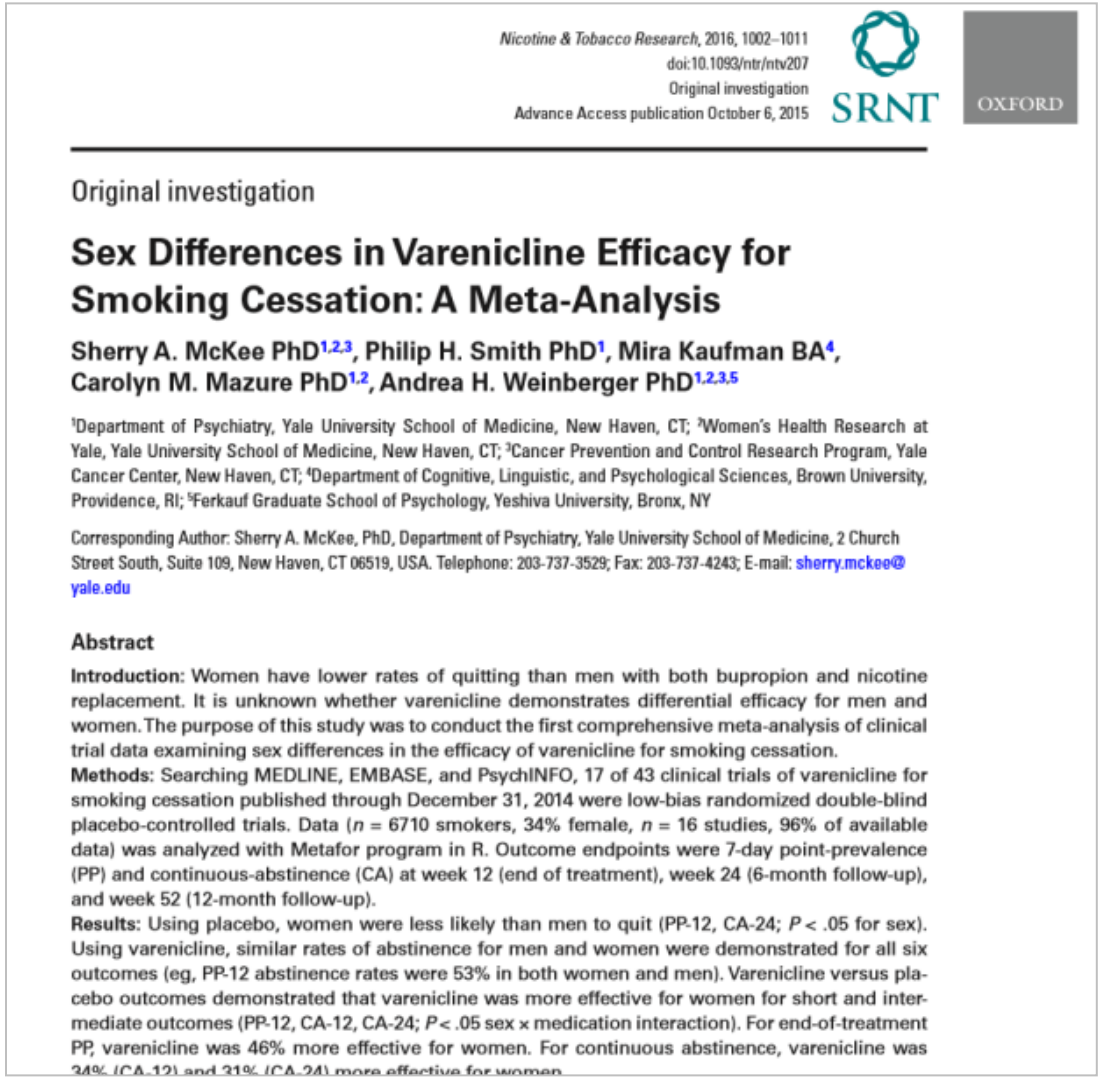
Network Analysis of Medication Efficacy by Sex



- Head-to-head comparisons of medication by sex
- Men (VAR=BUP=PATCH)
- Women (VAR>BUP=PATCH)

Smith….McKee, NTR, 2017

Meta-analysis of Varenicline by Sex



Nicotine & Tobacco Research, 2016, 1002–1011
doi:10.1093/ntr/ntv207
Original investigation
Advance Access publication October 6, 2015

SRNT

OXFORD

Original investigation

Sex Differences in Varenicline Efficacy for Smoking Cessation: A Meta-Analysis

Sherry A. McKee PhD[1,2,3], Philip H. Smith PhD[1], Mira Kaufman BA[4], Carolyn M. Mazure PhD[1,2], Andrea H. Weinberger PhD[1,2,3,5]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT; [2]Women's Health Research at Yale, Yale University School of Medicine, New Haven, CT; [3]Cancer Prevention and Control Research Program, Yale Cancer Center, New Haven, CT; [4]Department of Cognitive, Linguistic, and Psychological Sciences, Brown University, Providence, RI; [5]Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY

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Abstract

Introduction: Women have lower rates of quitting than men with both bupropion and nicotine replacement. It is unknown whether varenicline demonstrates differential efficacy for men and women. The purpose of this study was to conduct the first comprehensive meta-analysis of clinical trial data examining sex differences in the efficacy of varenicline for smoking cessation.

Methods: Searching MEDLINE, EMBASE, and PsychINFO, 17 of 43 clinical trials of varenicline for smoking cessation published through December 31, 2014 were low-bias randomized double-blind placebo-controlled trials. Data (n = 6710 smokers, 34% female, n = 16 studies, 96% of available data) was analyzed with Metafor program in R. Outcome endpoints were 7-day point-prevalence (PP) and continuous-abstinence (CA) at week 12 (end of treatment), week 24 (6-month follow-up), and week 52 (12-month follow-up).

Results: Using placebo, women were less likely than men to quit (PP-12, CA-24; $P < .05$ for sex). Using varenicline, similar rates of abstinence for men and women were demonstrated for all six outcomes (eg, PP-12 abstinence rates were 53% in both women and men). Varenicline versus placebo outcomes demonstrated that varenicline was more effective for women for short and intermediate outcomes (PP-12, CA-12, CA-24; $P < .05$ sex × medication interaction). For end-of-treatment PP, varenicline was 46% more effective for women. For continuous abstinence, varenicline was 34% (CA-12) and 31% (CA-24) more effective for women.

We conducted meta-analysis pooling data from 10,641 adults who smoke, representing 98% of all Phase II & III data

- Data obtained from Pfizer & academic investigators

Women had greater odds for quitting vs men (VAR vs PLA: W>M)

Phase 4 Meta-analysis of Varenicline by Sex

Drug and Alcohol Dependence 178 (2017) 485–491

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Gender differences in the real-world effectiveness of smoking cessation medications: Findings from the 2010–2011 Tobacco Use Supplement to the Current Population Survey

Philip H. Smith[a,*], Ju Zhang[b], Andrea H. Weinberger[c,d], Carolyn M. Mazure[e,f], Sherry A. McKee[e]

[a] Community Health and Social Medicine, CUNY School of Medicine, United States
[b] Yale University School of Public Health, United States
[c] Epidemiology and Population Health, Albert Einstein College of Medicine, United States
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ARTICLE INFO

Keywords:
Gender
Smoking
Cessation
Varenicline
Patch
Effectiveness

ABSTRACT

Background: Meta-analyses of clinical trial data have identified clinically relevant gender differences in the efficacy of smoking cessation pharmacotherapy. It is unclear whether these findings are generalizable to smokers quitting in real-world contexts.

Methods: Using Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2010–2011 cross-sectional data, we generated propensity score matched samples of smokers who quit either unassisted by medication, using only varenicline, or using only transdermal nicotine patch (TNP). We used generalized estimating equations to estimate gender differences in the comparative effectiveness of these cessation options for achieving 30-days of abstinence, adjusting for potential confounders.

Results: When stratified by gender, TNP was significantly more effective than unassisted quit attempts for men

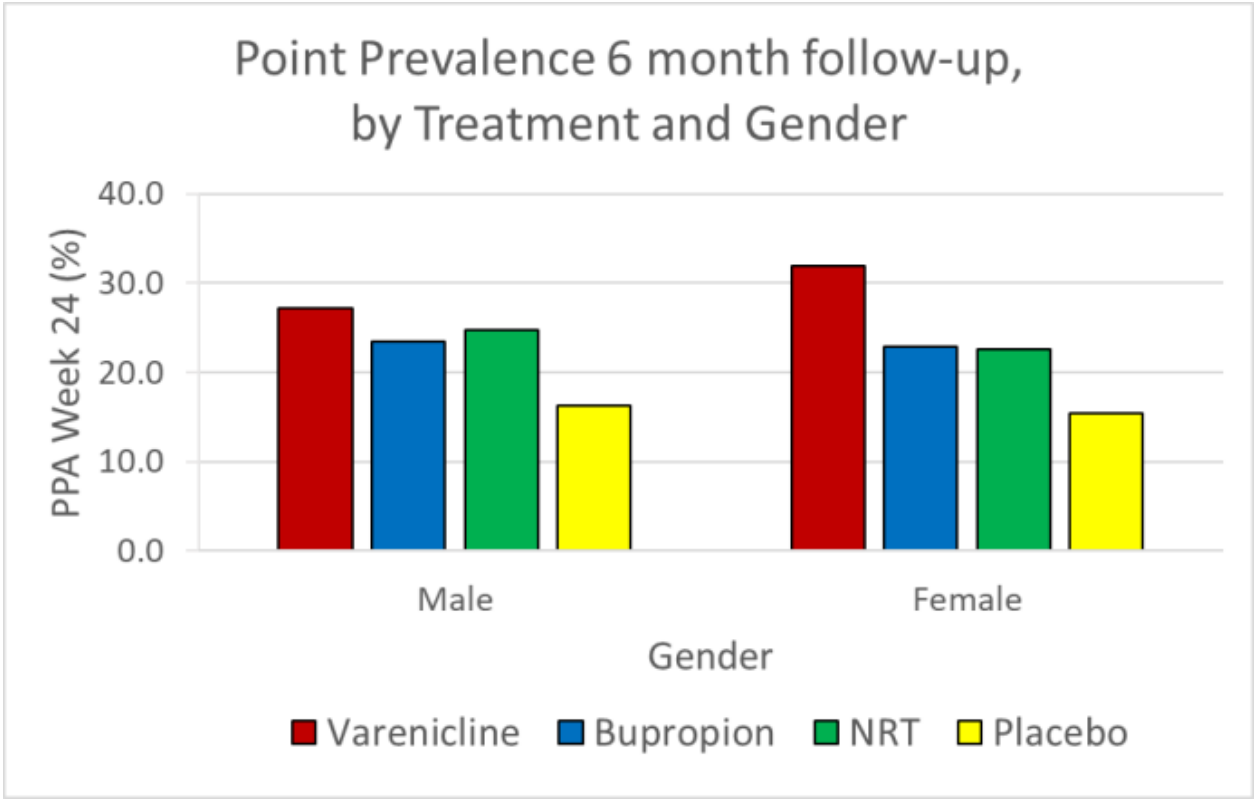
Real-world quitting

Current Population Survey n=7,906 had quit attempt

Women: VAR > PATCH

Men: VAR = PATCH

RCT Pfizer EAGLES study: Sex differences



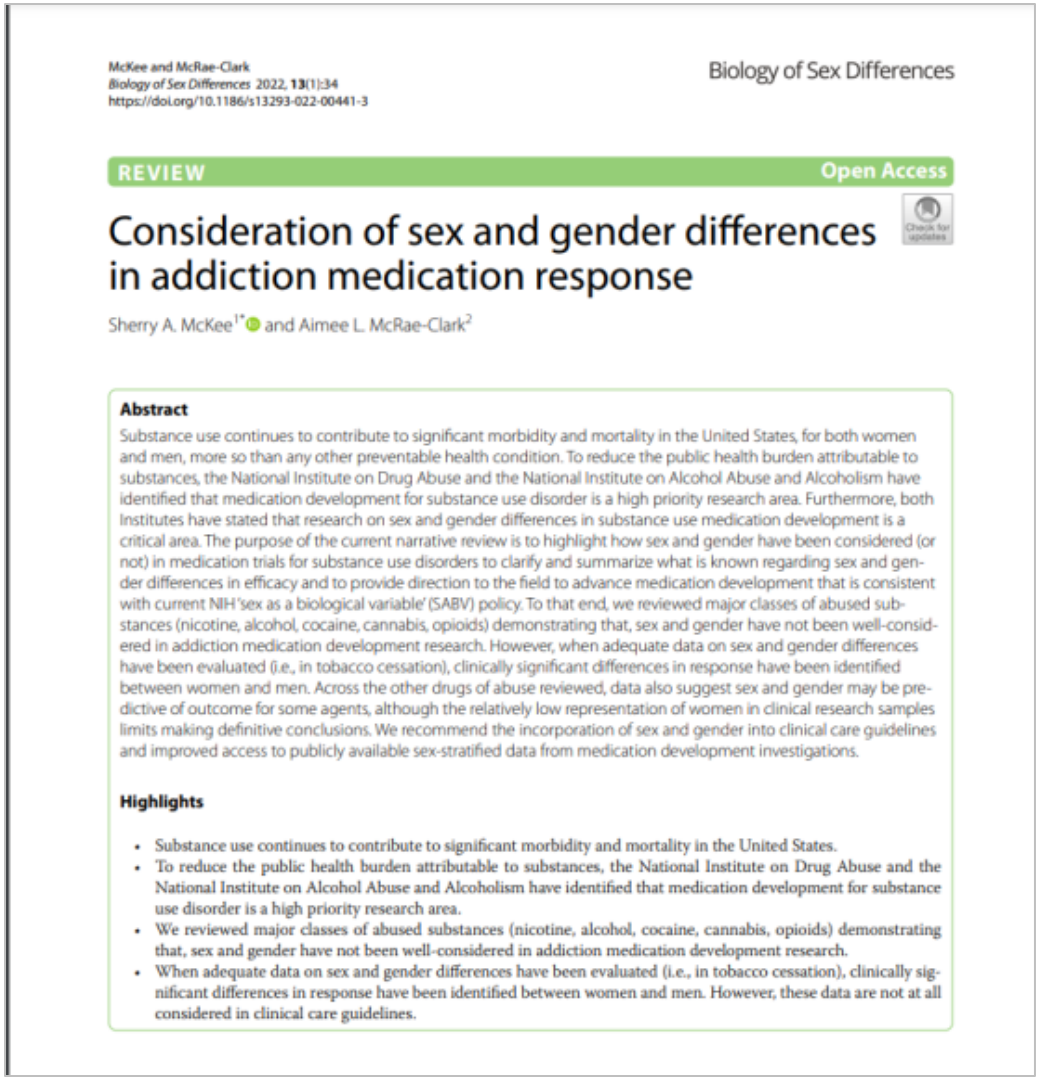
n=8,144 adults who smoke, ~50% with psychiatric conditions

Men (VAR=BUP=PATCH)

Women (VAR>BUP=PATCH)

McKee, Lawrence, Saccone, McRae, Anthenelli, submitted

Medications for Substance Use: Recommendations



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Where there is sufficient data, sex-based data needs to be incorporated into clinical practice guidelines

>41,000 adults who smoke

Men (VAR=BUP=PATCH)

Women (VAR>BUP=PATCH)

Clinical Practice Guidelines: Tobacco Use Disorder

Is gender a consideration in selecting a medication?	There is evidence that NRT can be effective with both sexes; however, evidence is mixed as to whether NRT is less effective in women than men. This may encourage the clinician to consider use of another type of medication with women, such as bupropion SR or varenicline.

Based on current evidence

- Nicotine replacement and bupropion may be less effective for women vs. men
- Should varenicline be recommended as first choice option for women (based on n>41,000 adults who smoke)?

https://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/TreatingTobaccoUseandDependence-2008Update.pdf

FDA-approved Medications for AUD: Sex differences?

Medication	SABV in study design	SABV incorporated into any analysis	Sex differences in efficacy	Sex differences in adverse events
Naltrexone	No	Post-hoc	W=M	W>M
Acamprosate	No	Post-hoc	W=M	W=M
Disulfiram	No	No	????	???

SABV: Sex as a biological variable

McKee & McRae-Clark, BSD, 2022

Novel Medications for AUD

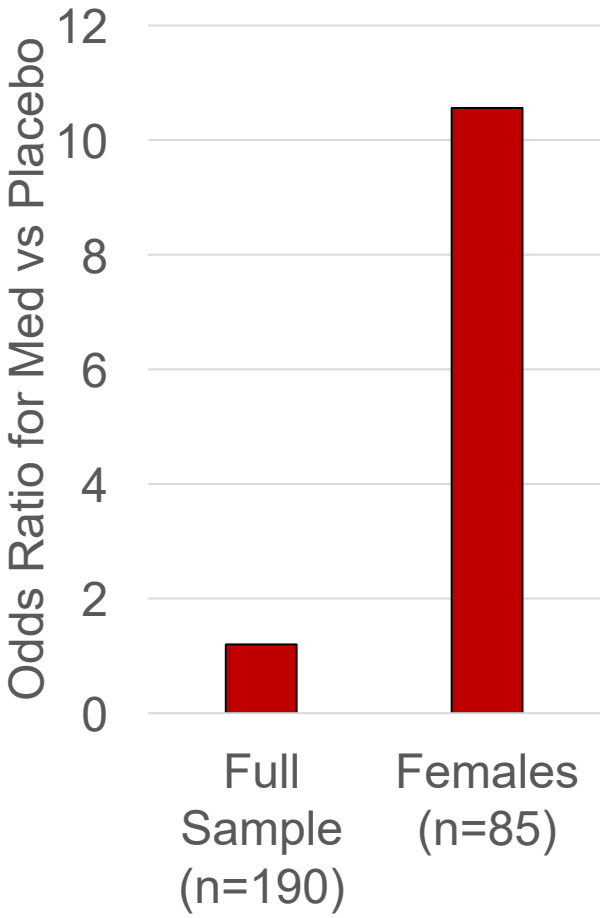
Other medication targets which have shown promise for AUD

Medication Target	SABV in study design	SABV incorporated into any analysis	Sex differences in efficacy	Sex differences in adverse events
Cholinergic	No	2 studies	W<M	???
Noradrenergic	No	1 study	W=M	???
GABA	No	2 studies	W>M	???
Serotonin	No	1 study	W>M	???
Anti-epileptics	No	No	???	???

SABV: Sex as a biological variable

McKee & McRae-Clark, BSD, 2022

Medications for AUD: Sex differences?

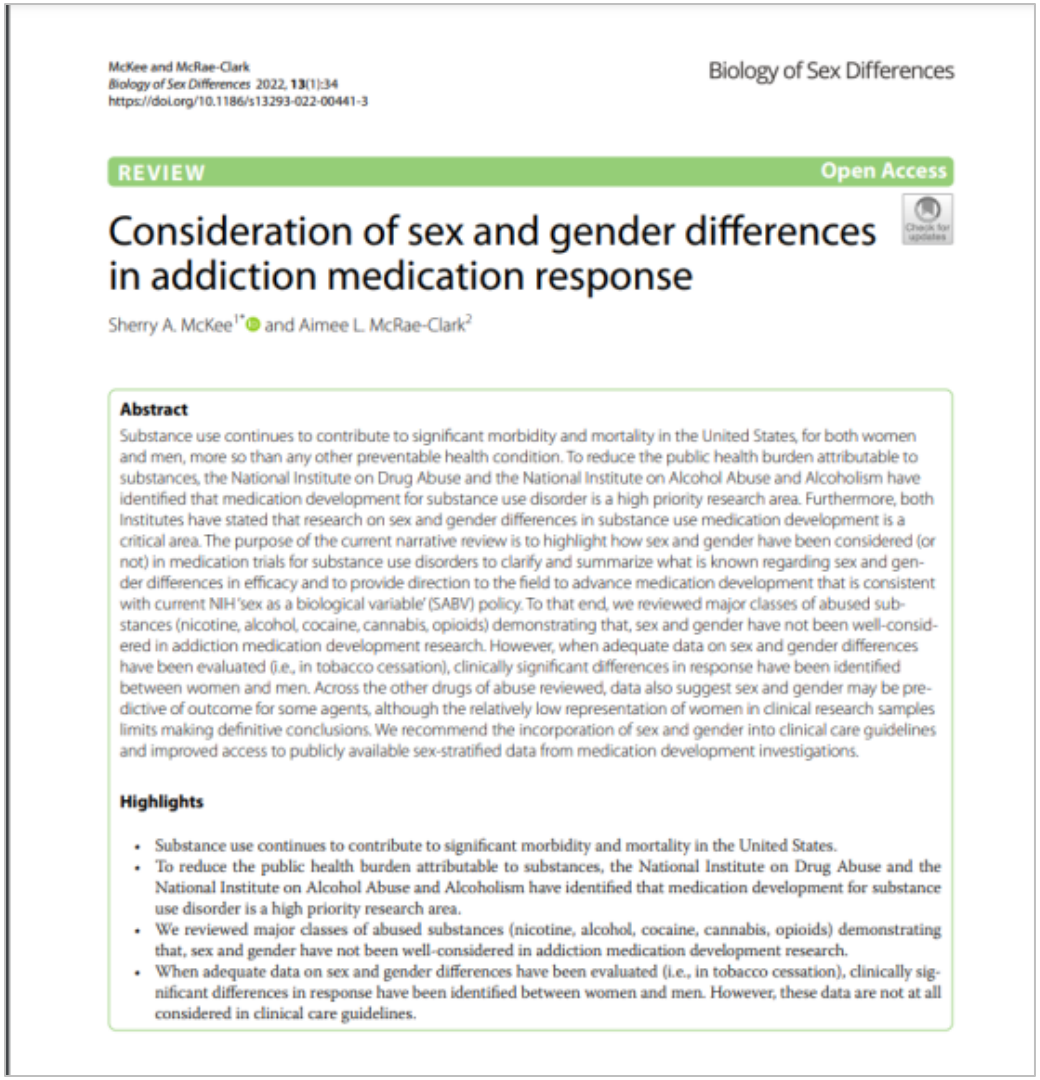


RCT of baclofen (GABA agonist)

Significant sex differences found but not discussed in paper

Reynaud et al., 2017, Alcohol & Alcoholism

Medications for Substance Use: Recommendations



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Recommend improved access to publicly available sex-stratified data from medication development investigations

- NDA information
- Clinicaltrials.gov

Targeting Stress for Treatment Development

- If treatment is going to be effective for women, then treatments need to target factors that underlie substance use in women.

- Targeting stress-

What Drives Use in Women vs Men?

Curr Addict Rep (2016) 3:314–322
DOI 10.1007/s40429-016-0115-x

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Targeting the Brain St of Tobacco/Nicotine De and Clinical Findings

Terril L. Verplaetse[1] · Sherry A. McKe

Published online: 8 July 2016

Abstract
Purpose of review Tobacco use is the lea ventable mortality in the USA, and Administration (FDA) approved medicatic long-term abstinence for the majority of s
Recent findings One of the principal mec with the initiation, maintenance of, and rel stress. Targeting the brain stress systems a ment strategy for tobacco dependence ma benefit.
Summary This review explores brain stress use and dependence. The corticotropin-rele system, the hypothalamic-pituitary-adrenal noradrenergic system are discussed in relat Preclinical and clinical investigations tar systems as treatment strategies for stres use are also discussed. Overall, nicotine- of the CRF system and subsequent activati and noradrenergic system may be relate

Neurobiology of Stress 10 (2019) 100149

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

Sex differences in stress-related alcohol use

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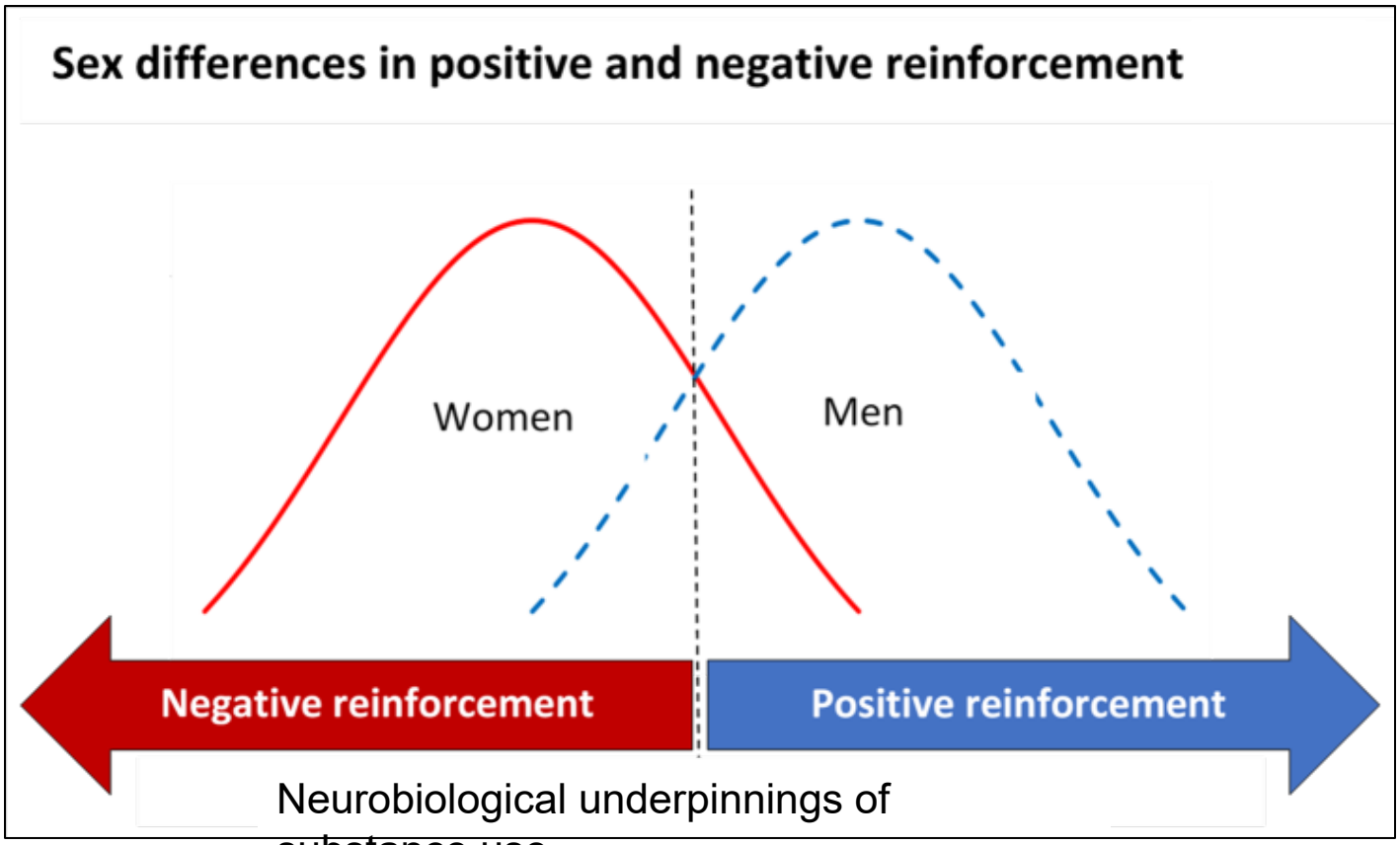
ARTICLE INFO

Keywords:
Alcohol use disorder
Stress
Sex differences
Female
Brain stress systems

ABSTRACT

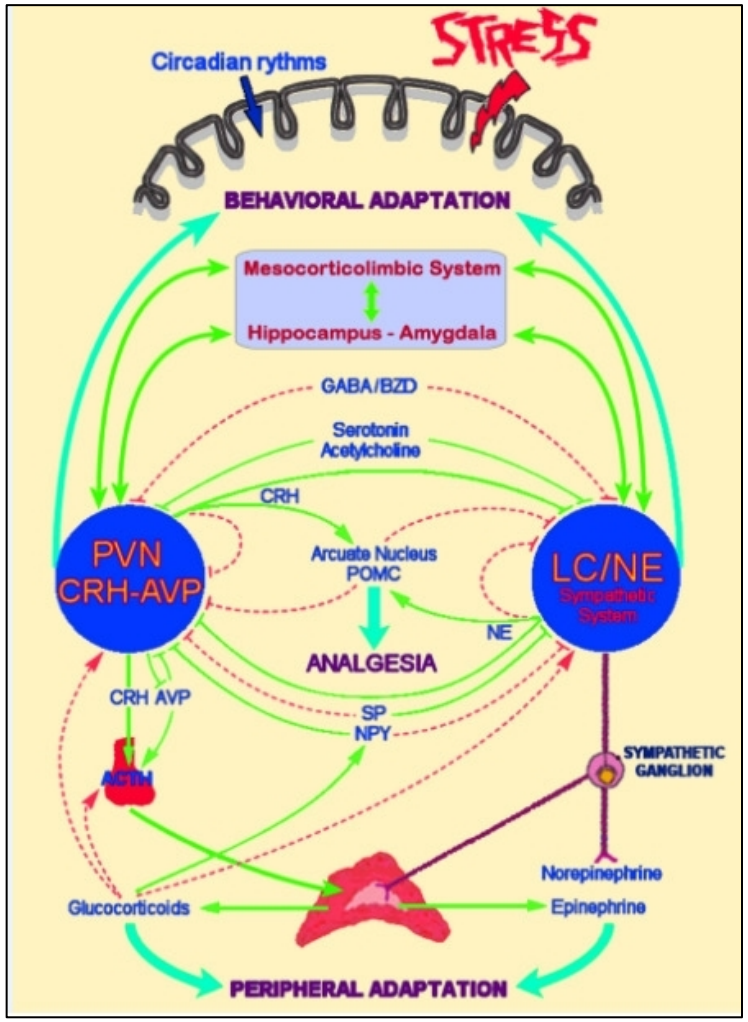
Rates of alcohol use disorder (AUD) have increased in women by 84% over the past ten years relative to a 35% increase in men. This substantive increase in female drinking is alarming given that women experience greater alcohol-related health consequences compared to men. Stress is strongly associated with all phases of alcohol addiction, including drinking initiation, maintenance, and relapse for both women and men, but plays an especially critical role for women. The purpose of the present narrative review is to highlight what is known about sex differences in the relationship between stress and drinking. The critical role stress reactivity and negative affect play in initiating and maintaining alcohol use in women is addressed, and the available evidence for sex differences in drinking for negative reinforcement as it relates to brain stress systems is presented. This review discusses the critical structures and neurotransmitters that may underlie sex differences in stress-related alcohol use (e.g., prefrontal cortex, amygdala, norepinephrine, corticotropin releasing factor, and dynorphin), the involvement of sex and stress in alcohol-induced neurodegeneration, and the role of ovarian hormones in stress-related drinking. Finally, the potential avenues for the development of sex-appropriate pharmacological and behavioral treatments for AUD are identified. Overall, women are generally more likely to drink to regulate negative affect and stress reactivity. Sex differences in the onset and maintenance of alcohol use begin to develop during adolescence, coinciding with exposure to early life stress. These factors continue to affect alcohol use into adulthood, when reduced responsivity to stress, increased affect-related psychiatric comorbidities and alcohol-

What Maintains Use in Women vs Men?



Neurobiological underpinnings of substance use

Potential Systems to Target Stress



Brain stress systems

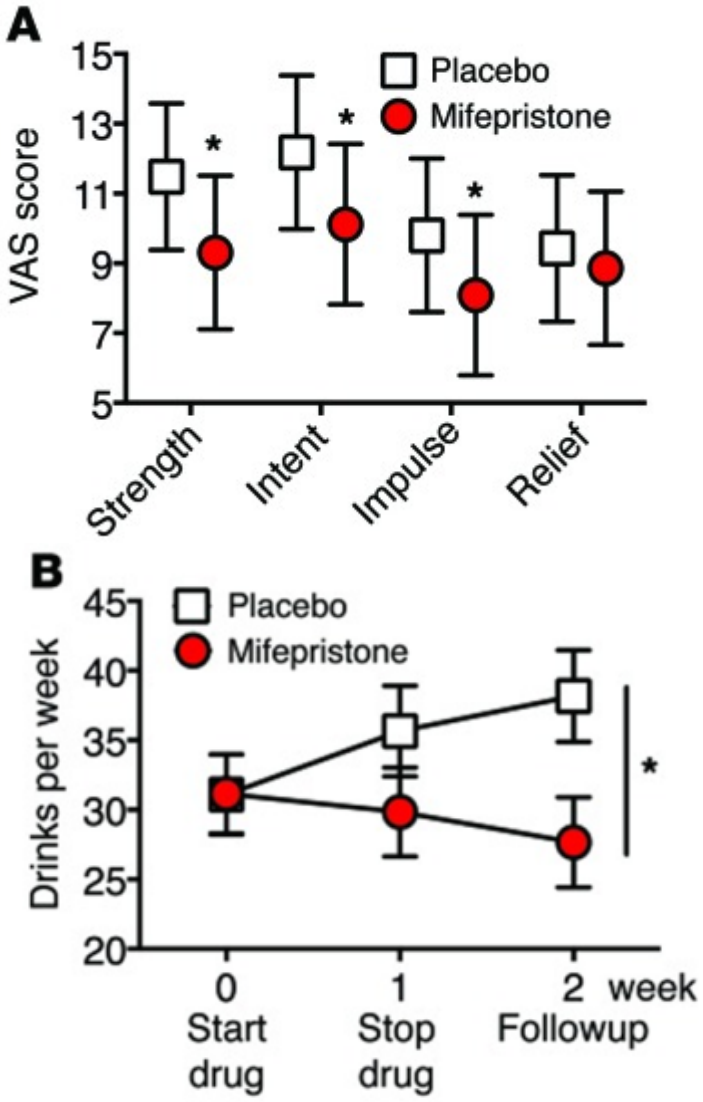
CRF
Dynorphin
Glucocorticoid
Hypocretin
Norepinephrine
Vasopressin

Anti-stress systems

Endocannabinoid
Neuropeptide Y
Nociceptin
Oxytocin

Mason, 2017, Neuropharm

Targeting Stress-Reactivity for Medication Development

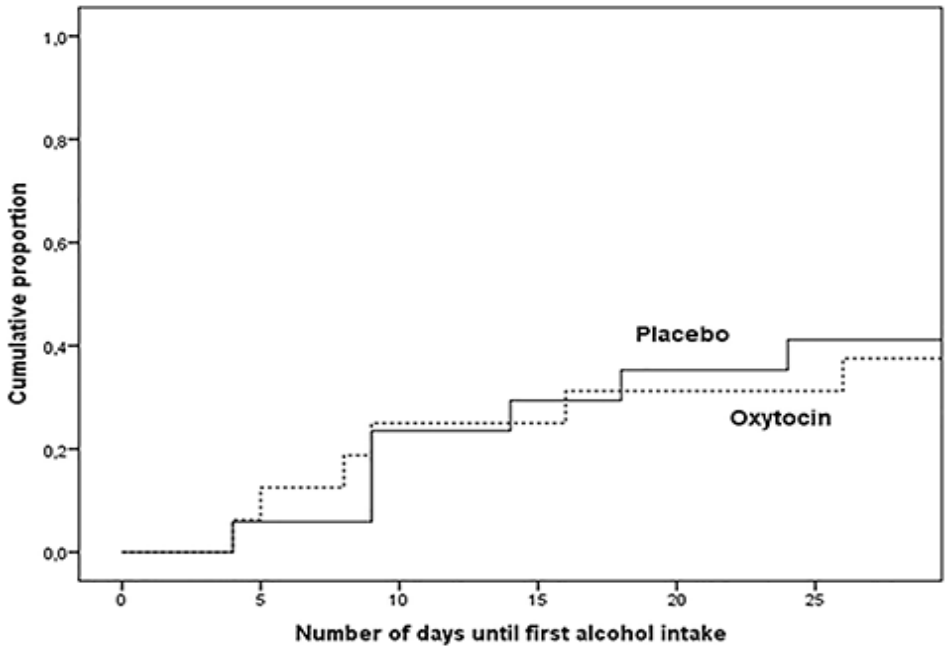


Glucocorticoid receptor antagonist, mifepristone reduced alcohol-cued craving in the laboratory, and naturalistic drinking.

Vendruscolo…Mason, 2015, J Clin Inv

Targeting Stress-Reactivity for Medication Development

Number of days until first alcohol intake in the oxytocin (n = 16) and the placebo (n = 17) groups

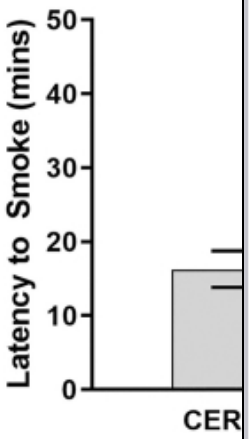


Oxytocin did not increase days to first alcohol use – but sample was 71% male and gender differences not examined.

Melby et al., Alc & Alcohol, 2020

Targetin
Develop

A randomized, d
human laboratory



A kappa
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Addiction Biology, Volume: 25,

Developmental Psychobiology

Melissa Morales
Rachel I. Anderson
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Effects of the Kappa Opioid Receptor Antagonist, Nor-Binaltorphimine, on Ethanol Intake: Impact of Age and Sex

ABSTRACT: *The kappa opioid receptor (KOR) antagonist, nor-binaltorphimine (nor-BNI), was used to investigate the role of the KOR system in mediating ethanol intake. On P25 (adolescent) or P67 (adult) male and female rats were individually housed and given ad libitum access to food and water. The experimental procedure was initiated on P28 or P70: animals were given 30 min/day access to a 10% ethanol/supersaccharin solution every other day (3 baseline exposures). On the day after the final baseline test, rats were injected with nor-BNI (0, 2.5, 5, 10 mg/kg), with testing initiated 24 hr later (30-min access every other day, 3 test exposures). Nor-BNI (10 mg/kg) increased ethanol intake in adult males, whereas the same dose decreased intake in adult females, suggesting pronounced sex differences in KOR-associated mediation of ethanol intake in adulthood. There was no impact of nor-BNI in adolescent animals of either sex, suggesting that the KOR may play less of a role in modulating ethanol intake during adolescence. © 2013 Wiley Periodicals, Inc.* Dev Psychobiol 56: 700–712, 2014.

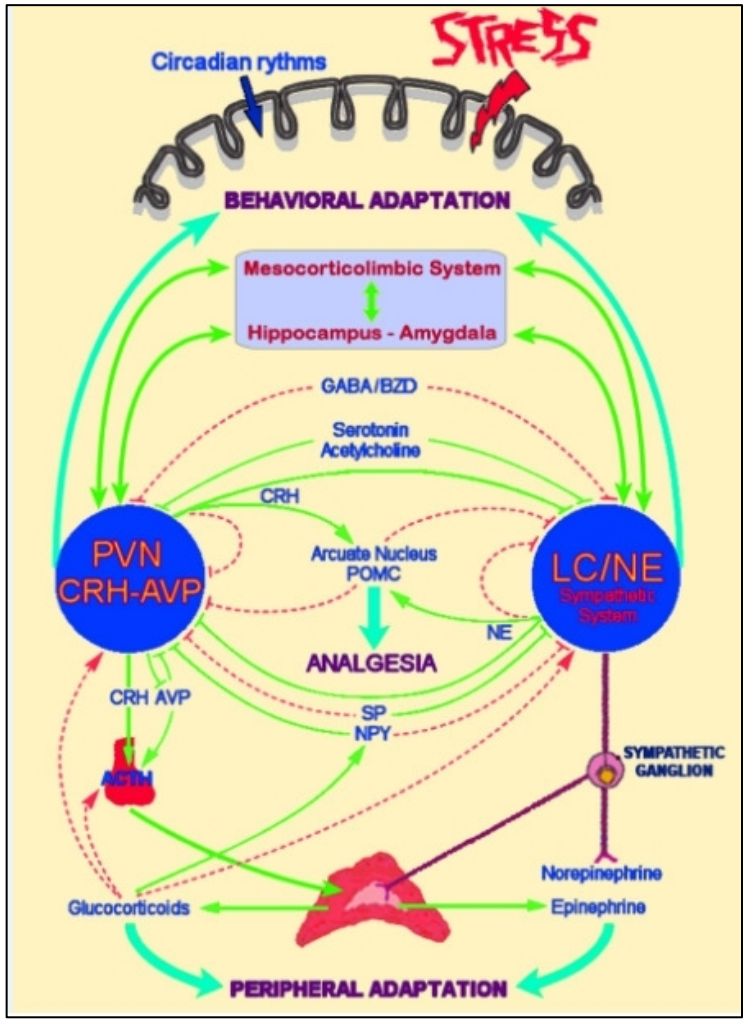
Keywords: *adolescence; ethanol intake; Nor-BNI; sex differences; rat; kappa opioid receptor*

INTRODUCTION

Adolescence is a transitional period from immaturity to maturity associated with hormonal, neural, and behavioral changes that are highly conserved across a variety of mammalian species (Spear, 2000, 2010). It is also a developmental period during which alcohol use is typically initiated in humans (Johnston, O'Malley, Bachman, & Schulenberg, 2013). While adolescents may consume alcohol less frequently than adults do, they drink

enhancement of ethanol intake evident in both humans (Chen & Kandel, 1995) and laboratory rodents, including rats (Doremus, Brunell, Rajendran, & Spear, 2005; Maldonado, Finkbeiner, Alipour, & Kirstein, 2008; Vetter, Doremus-Fitzwater, & Spear, 2007), mice (Tambour, Brown, & Crabbe, 2008) and rodents selectively bred for high alcohol consumption (Dhaher, McConnell, Rodd, McBride, & Bell, 2012). In humans, early initiation of drinking plays a substantial role in alcohol-related problems later in life (Grant & Dawson,

Potential Medications to Target Stress



Noradrenergic targets

- Guanfacine (alpha2a agonist)
- Doxazosin (alpha1 antagonist)
- Carvedilol (combined alpha1 & beta antagonist)

Kappa antagonist

- Cerc-501

Neurosteriods

Targeting the Noradrenergic System

Noradrenergic pathways

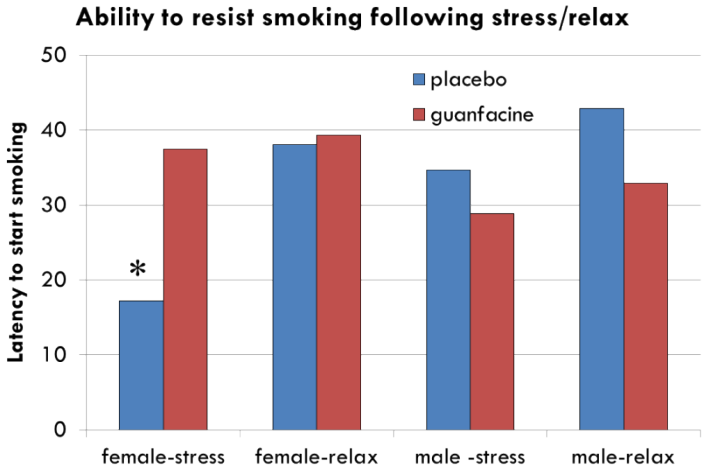
- are involved in stress-induced relapse to drugs, including alcohol and nicotine
- mediate substance-provoked dopamine release in the nucleus accumbens
- are involved in stress-induced decrements in prefrontal functioning

Targeting the Noradrenergic System

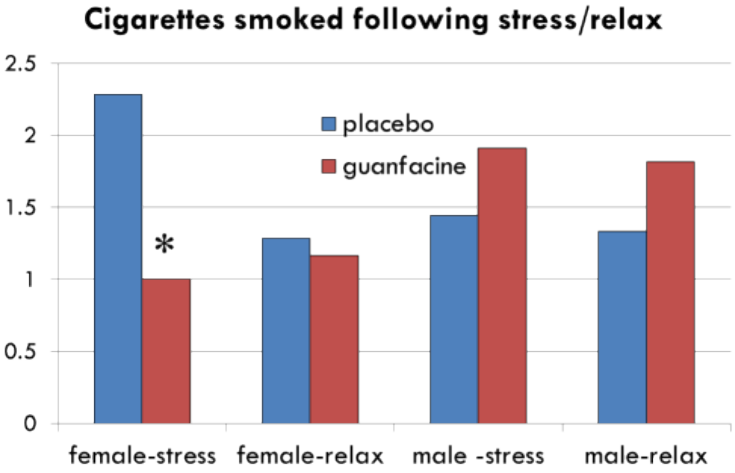
Guanfacine

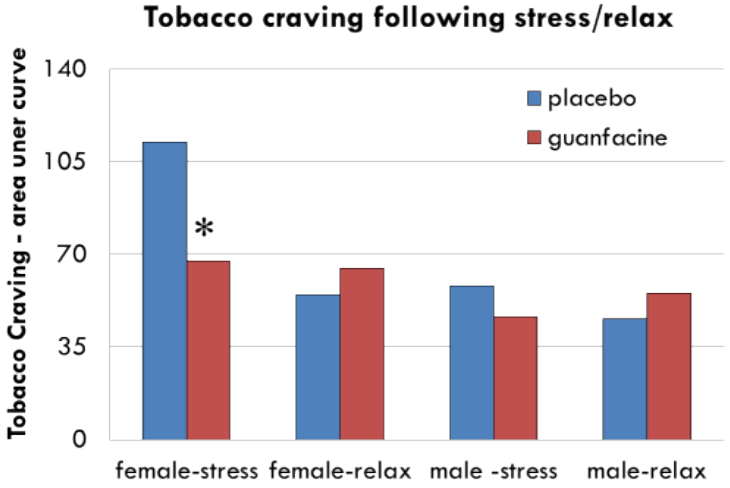
- Alpha2a noradrenergic agoni
- Immediate-release formulatic
  - Tenex (hypertension)
- Extended-release formulatior
  - Intuniv (ADHD)

Targeting the Noradrenergic System

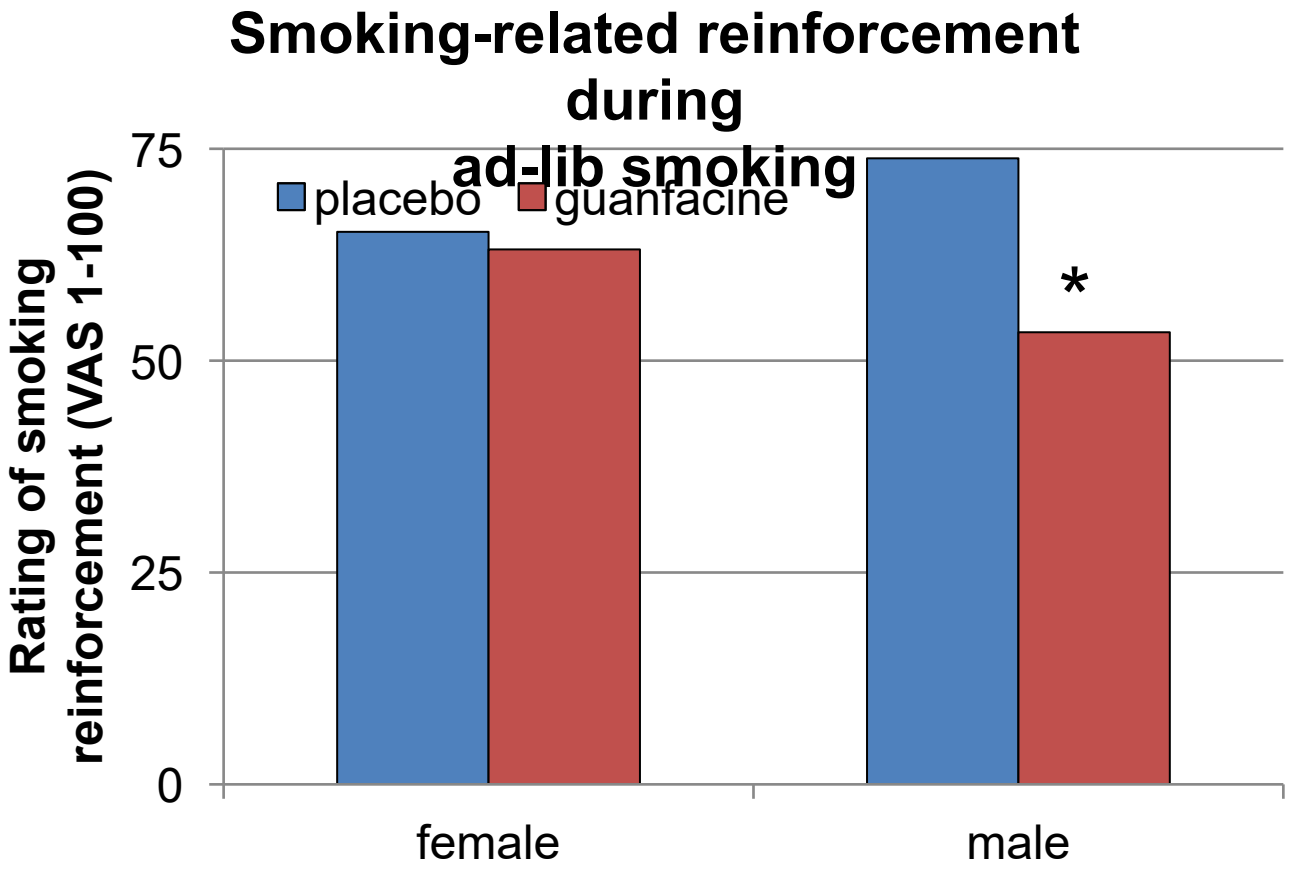


Guanfacine increased the ability to resist smoking, reduced cigarettes smoked, and reduced tobacco craving following stress, in women but not men





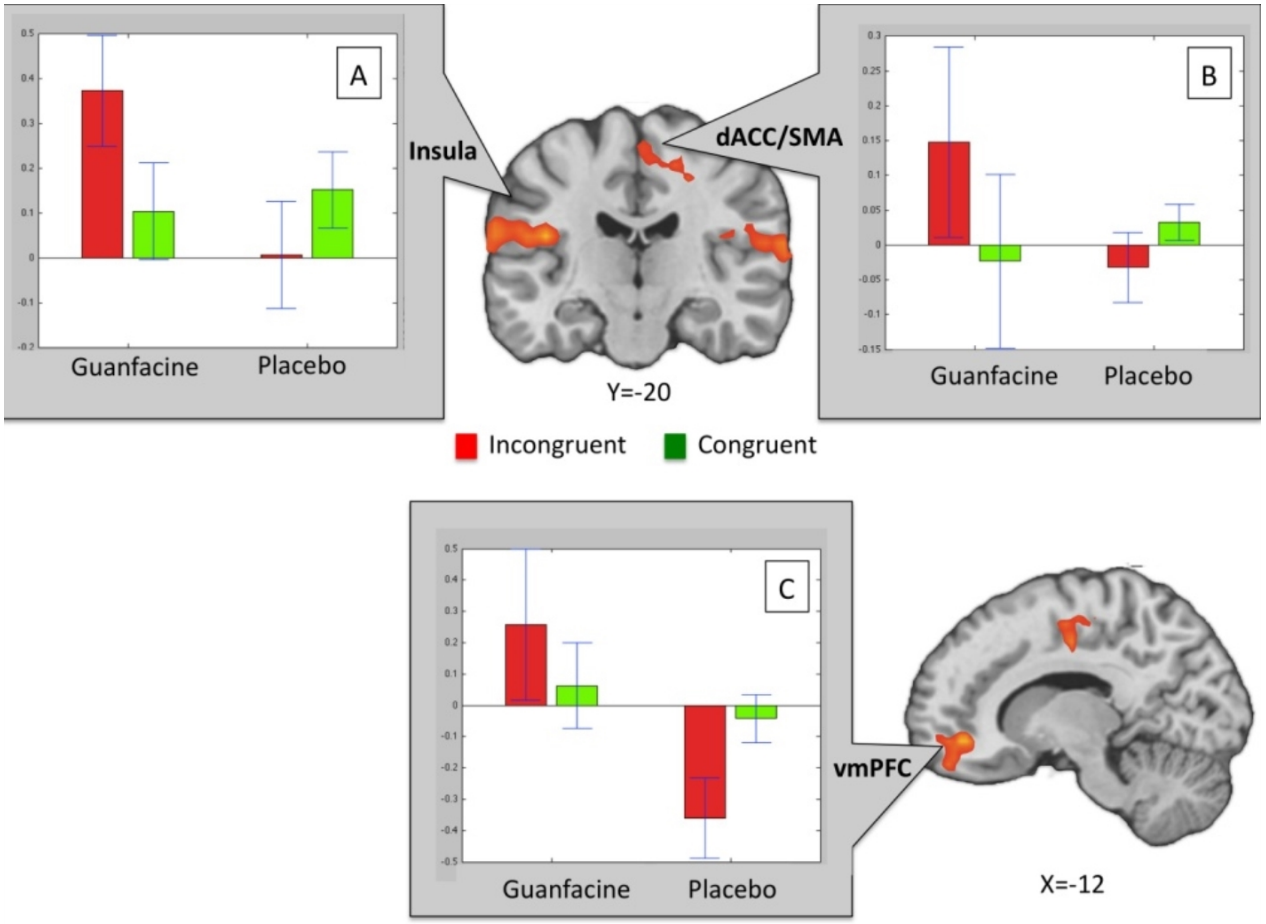
Targeting the Noradrenergic System



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=-

Targeting the Noradrenergic System

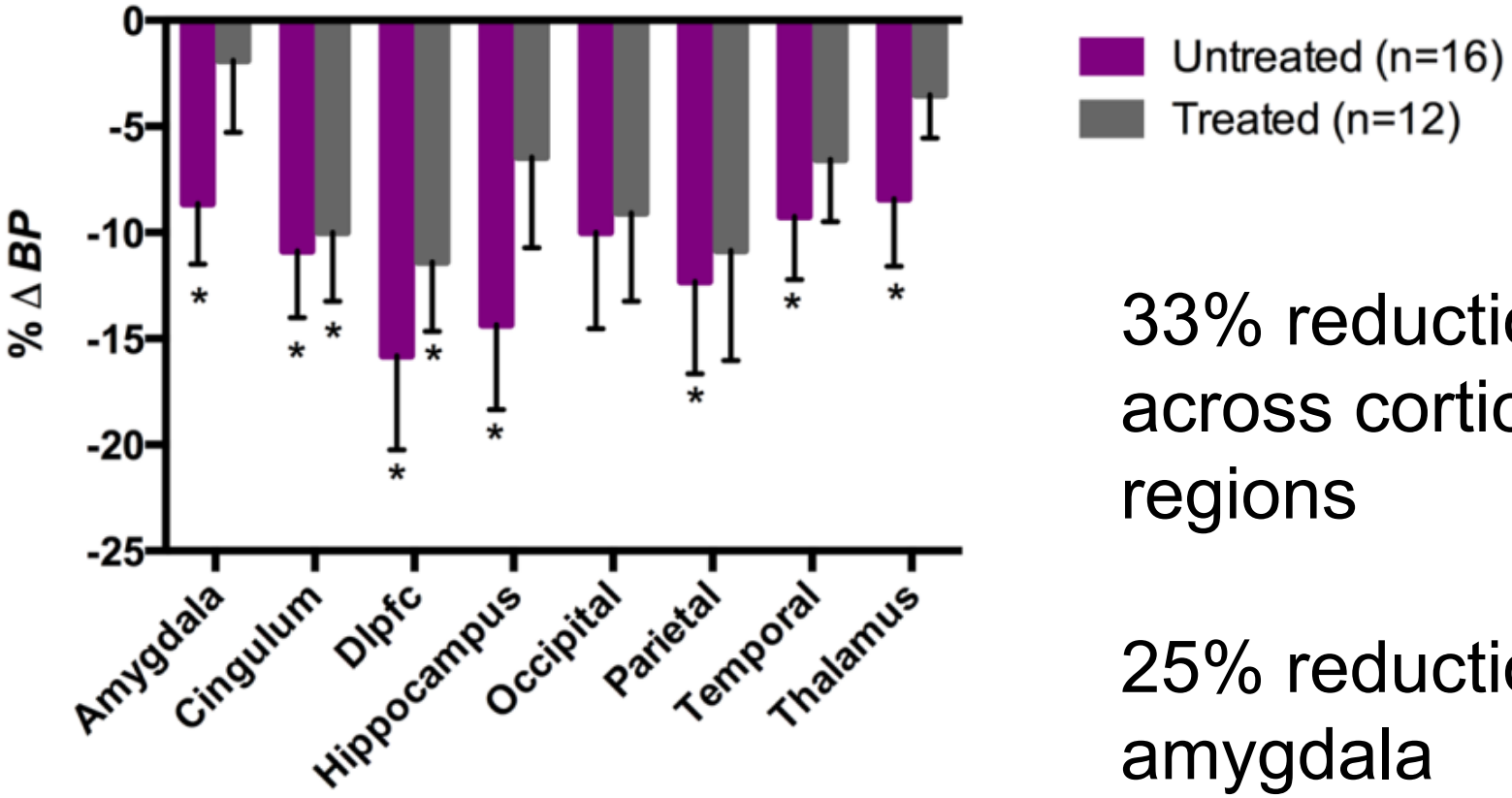


Guanfacine relative to placebo increased activation in the anterior cingulate, ventro-medial prefrontal cortex, and bilateral insula during the incongruent versus the congruent stimuli

Collaboration with Marc Potenza

McKee et al, 2015.

Guanfacine attenuates dopamine response in extrastriatal regions, including cortex

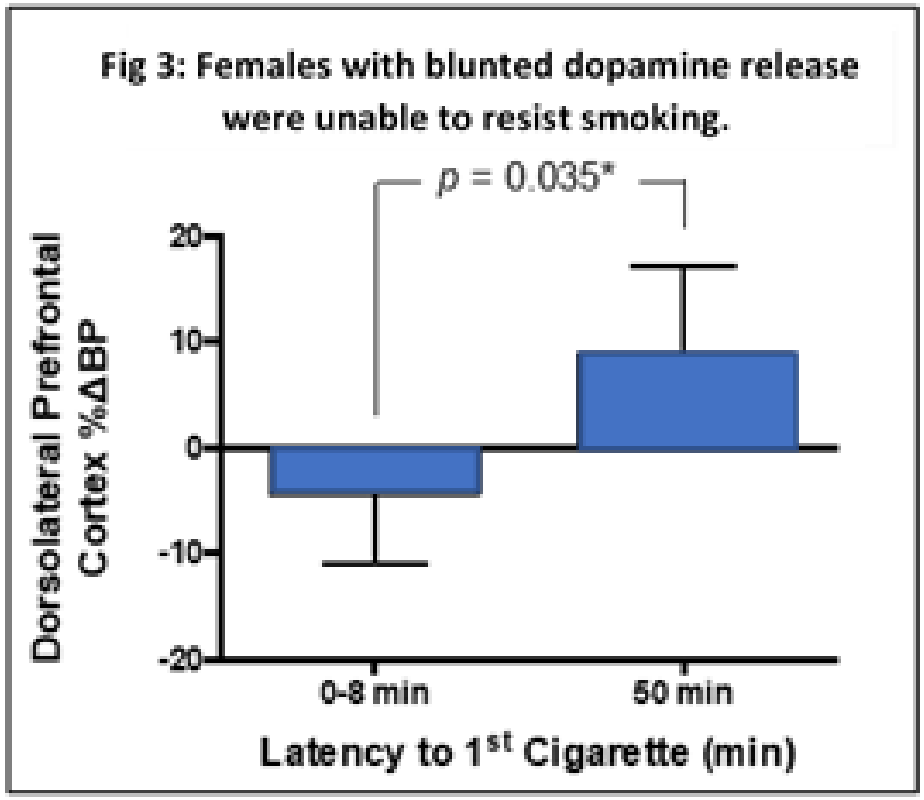


33% reduction across cortical regions

25% reduction in amygdala

Sandiego et al., 2018,

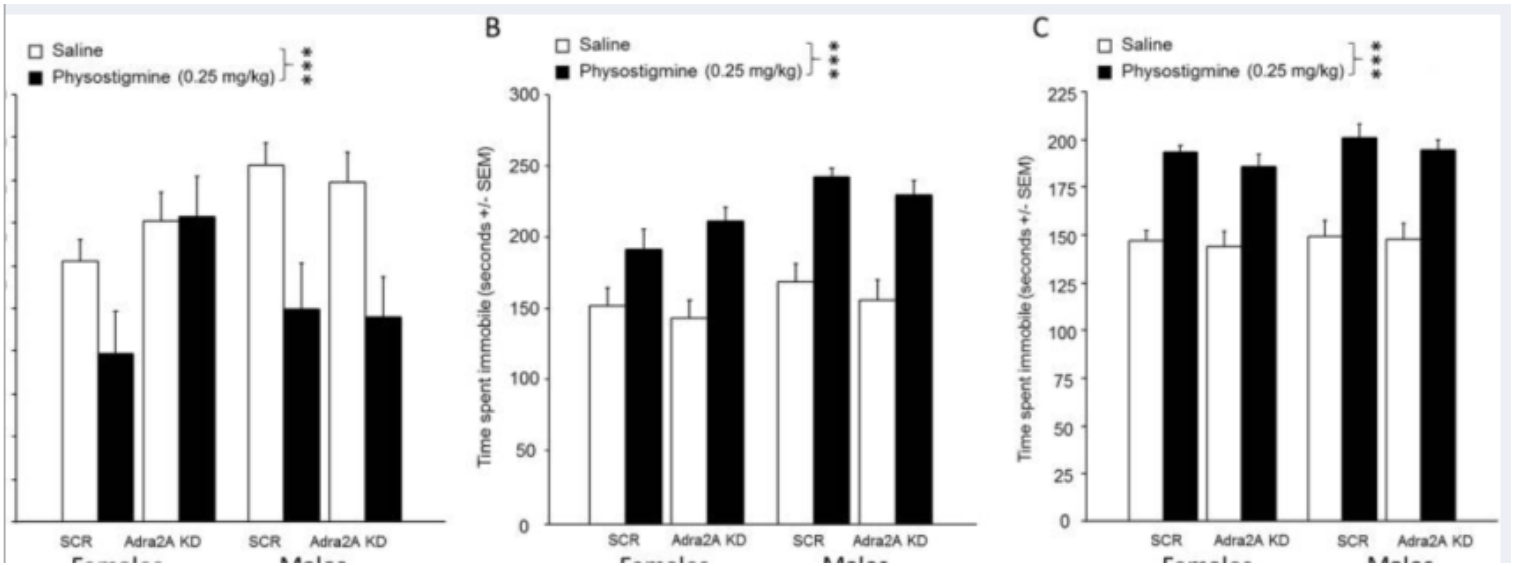
Targeting the Noradrenergic System



Females with greater dampening of dopamine release in the amygdala had greater ability to resist smoking following stress and smoked less cigarettes following guanfacine treatment.

Sandiego et al., 2018,

Alpha2a knockdown in amygdala + guanfacine
Light/dark box

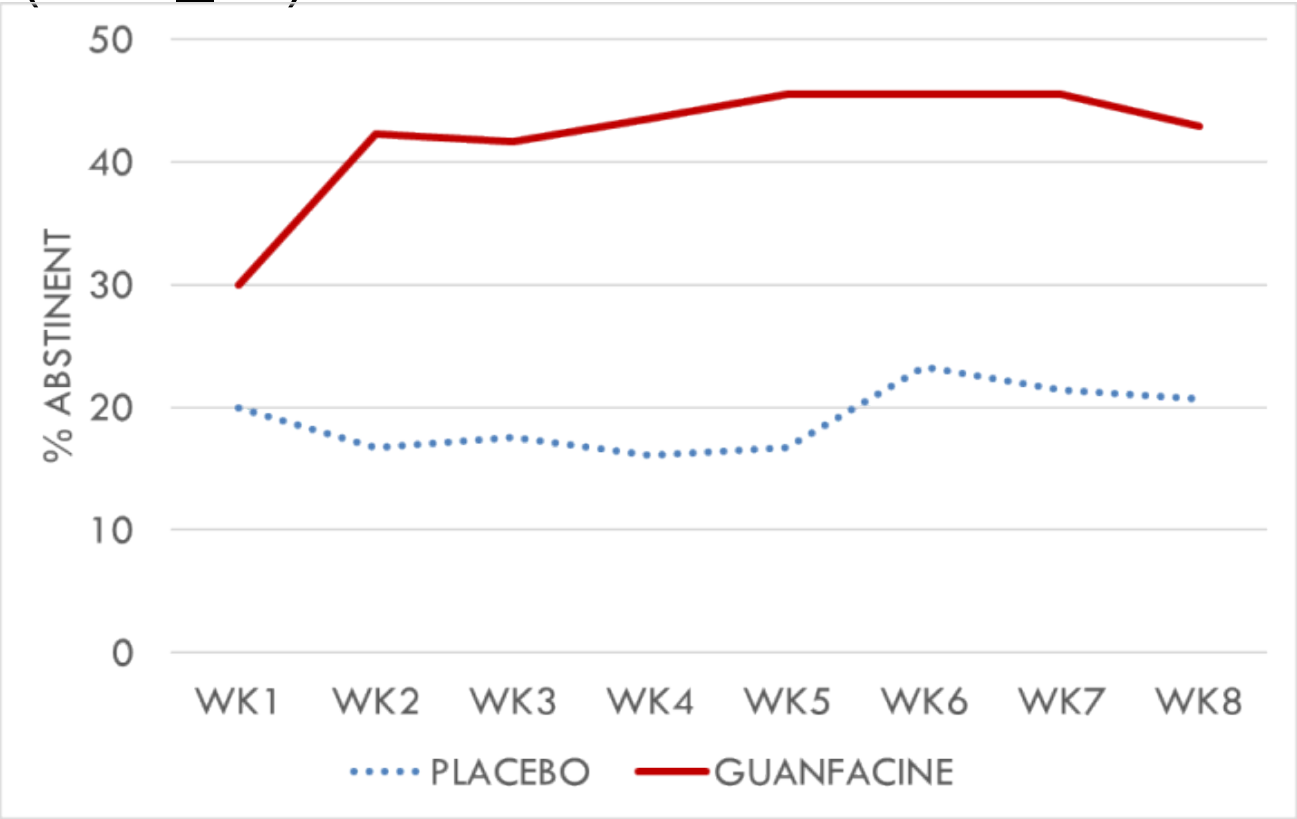


The effect of guanfacine in the amygdala is dependent on α2A receptor. This effect is similar for female and male mice.

Mineur et al, NeuroPsychopharm, 2018

Phase 2 Smoking Cessation RCT

Point prevalence outcomes during treatment (CPD≥10)



Guanfacine 6mg/day ER increased rates of smoking cessation

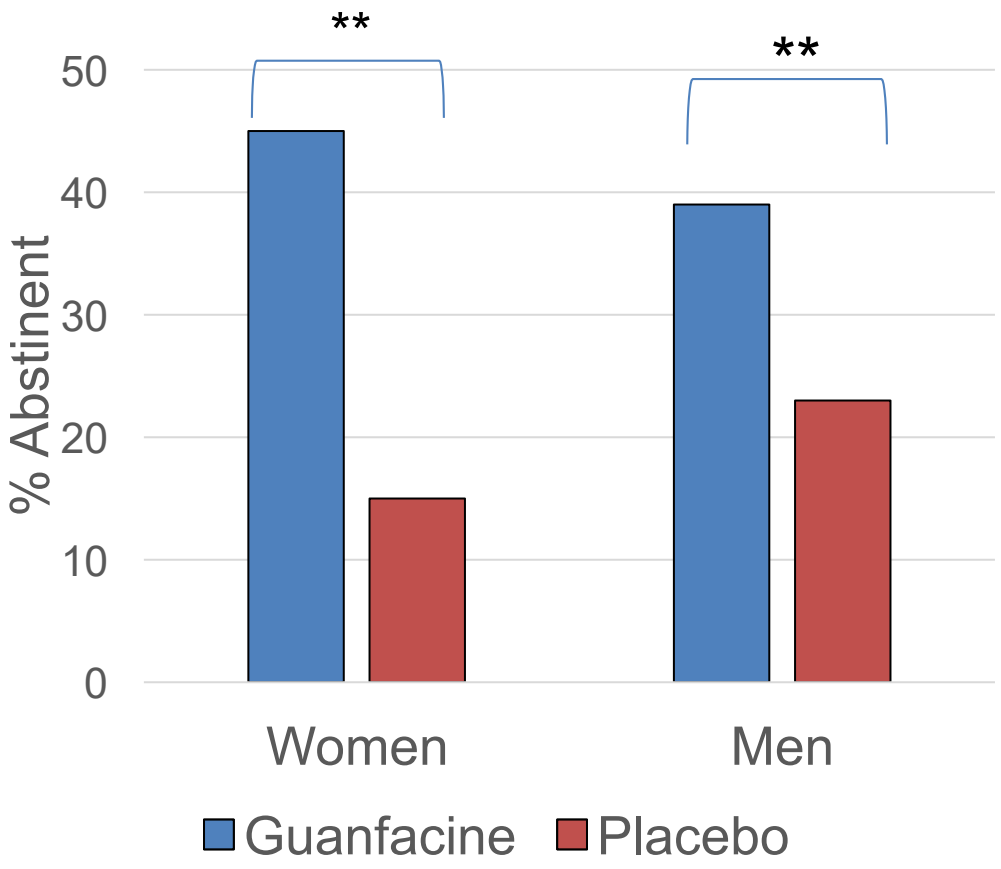
42% vs 19%

p<.05

McKee, R01DA035001

Phase 2 Smoking Cessation RCT

Point prevalence outcomes summarized over treatment



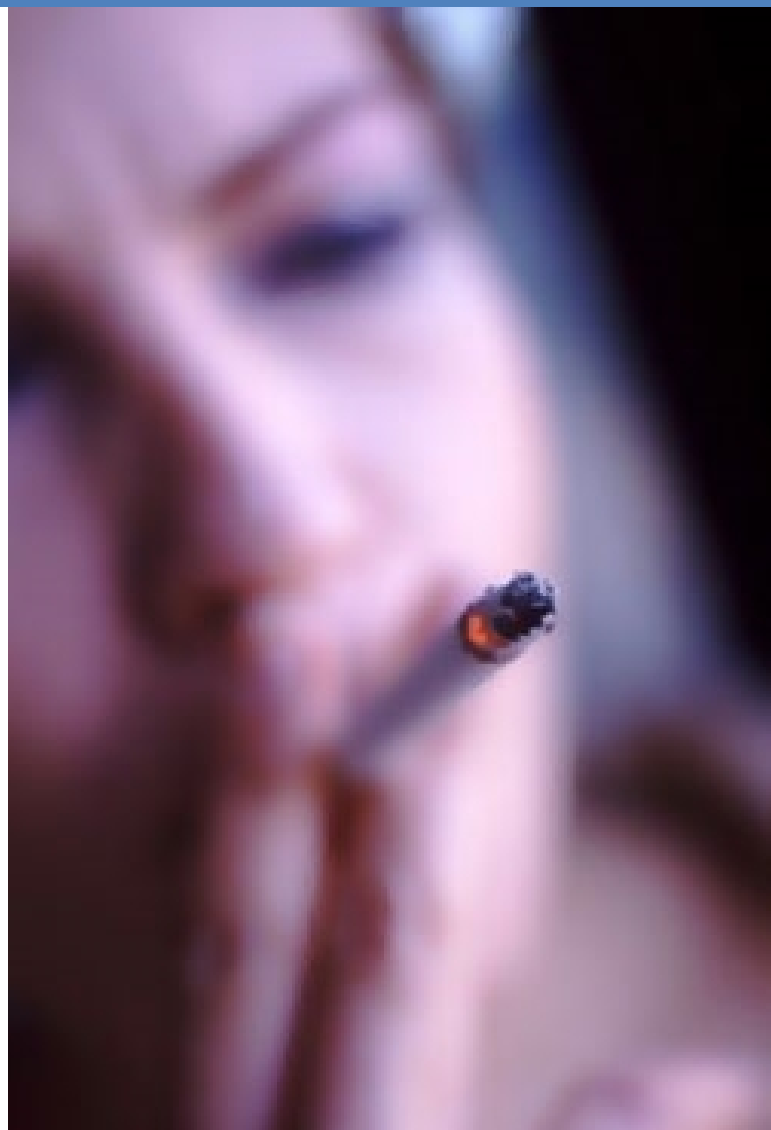
Guanfacine was efficacious for women and men, with larger effects in women

McKee, R01DA035001

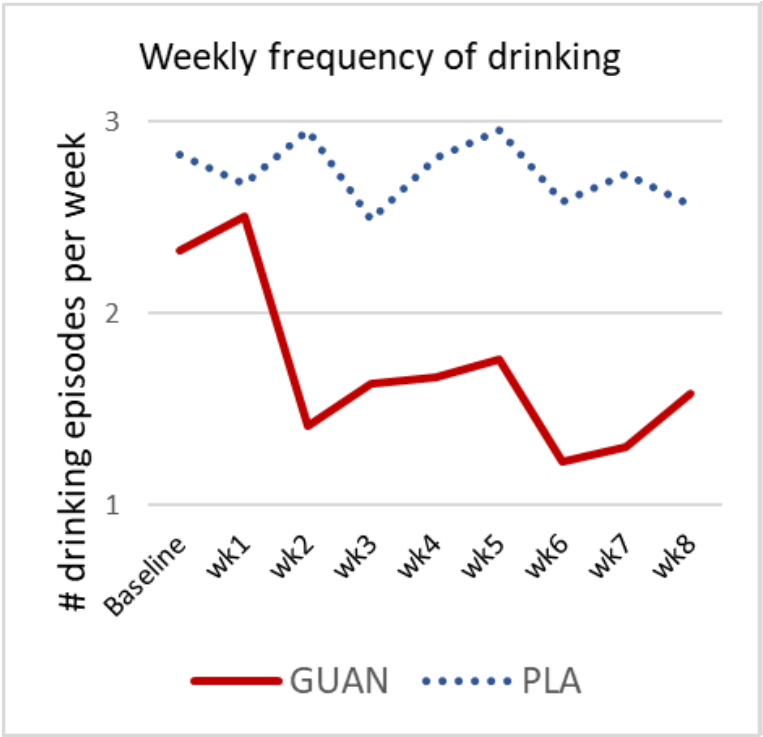
Summary of Smoking Findings

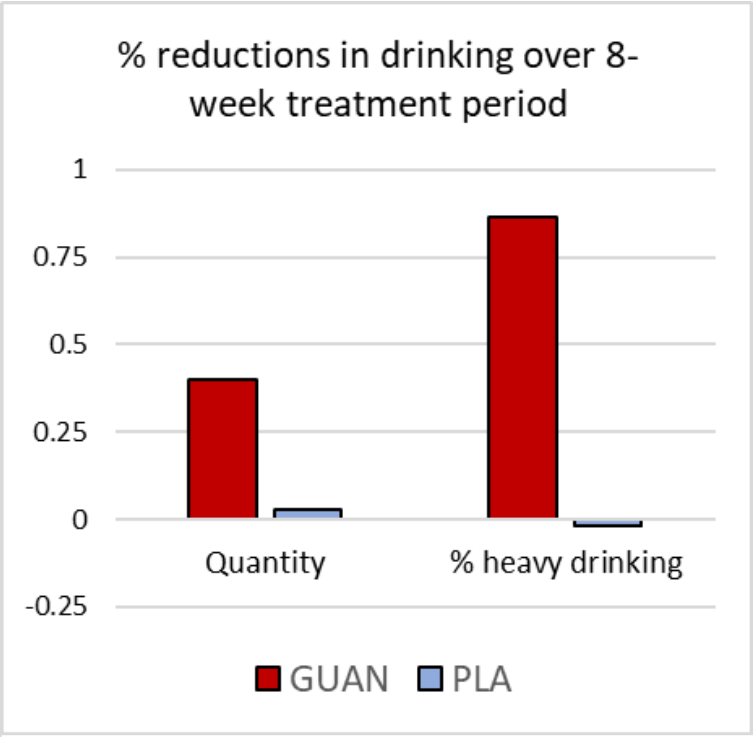
Guanfacine

- Targets stress for women
- Targets smoking-related reinforcement for men
- Mechanisms centralized in the amygdala
- RCT demonstrated reduced smoking with larger effects for women



Smoking Cessation RCT: Alcohol outcomes

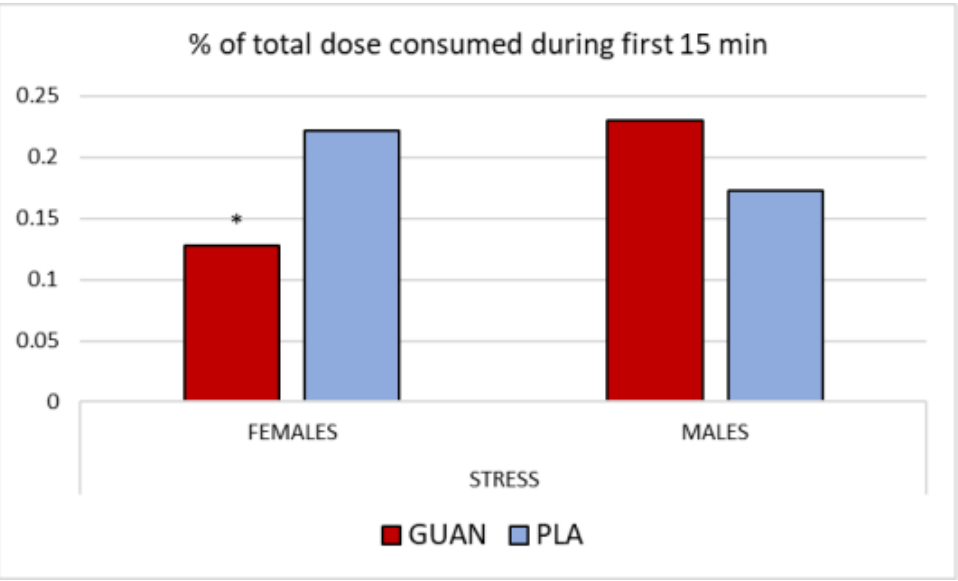


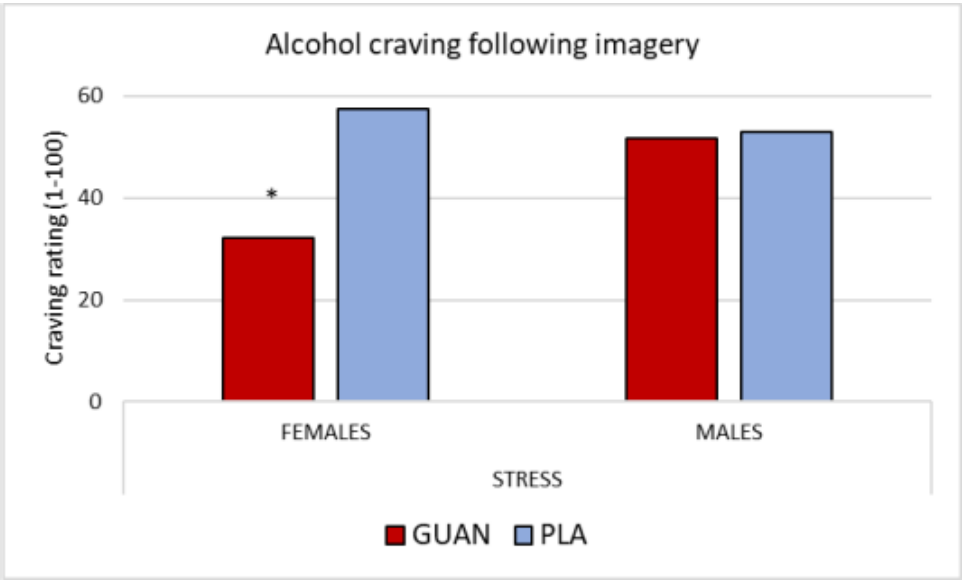


Guanfacine reduced drinking and these reductions were associated with plasma medication levels (-0.44 to -0.81)

McKee, R01DA035001

Phase 2 Study: Stress-precipitated Drinking

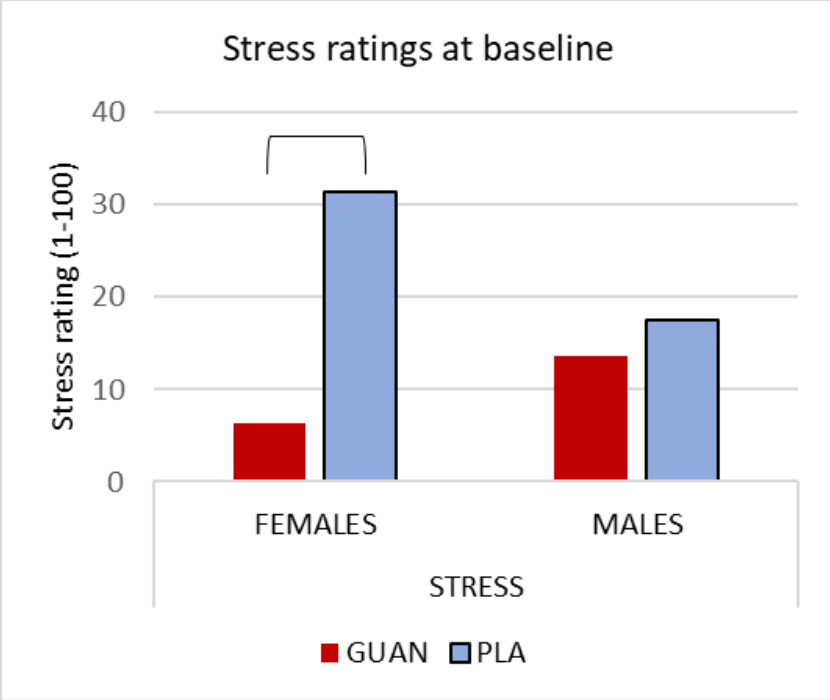


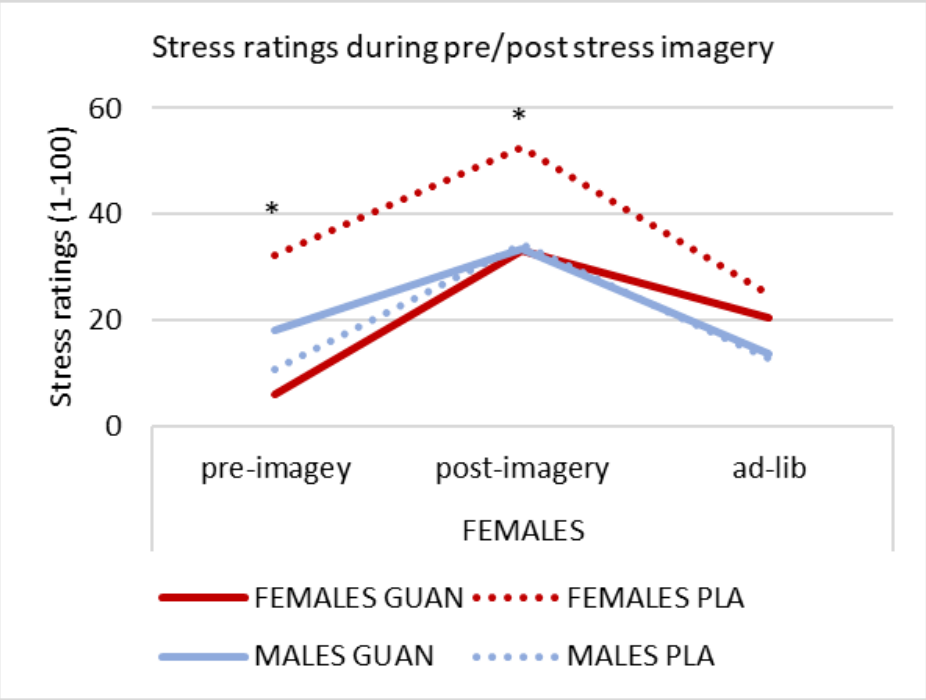


Guanfacine is attenuating stress-precipitated drinking and alcohol craving in women but not in men

In men, guanfacine attenuated ratings of ‘want more alcohol’ (36% men vs 5% women).

Phase 2 Study: Stress-precipitated Drinking



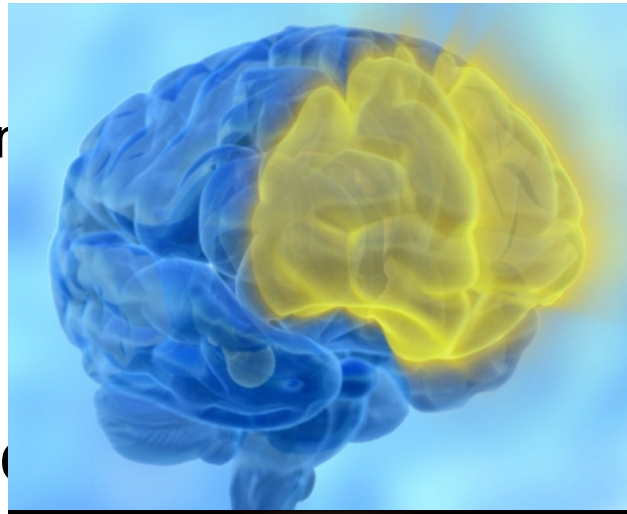


Guanfacine appears to be targeting tonic ratings of stress in women.

Targeting the Noradrenergic System

Different brain systems modulated by noradrenergic activity are activated by substance use in women and men

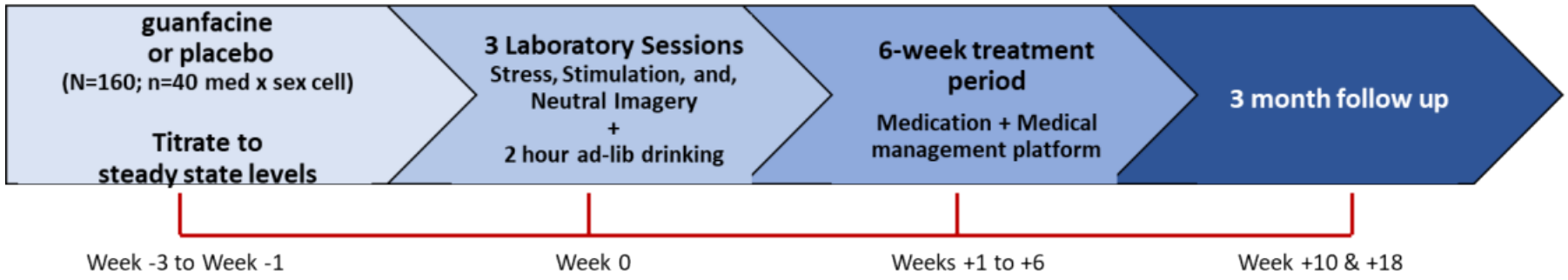
- prefrontal cortex-amygdala axis in women
- mesolimbic dopamine system in men



Guanfacine (an alpha2a noradrenergic agonist) can target these gender-sensitive systems to improve treatment outcomes

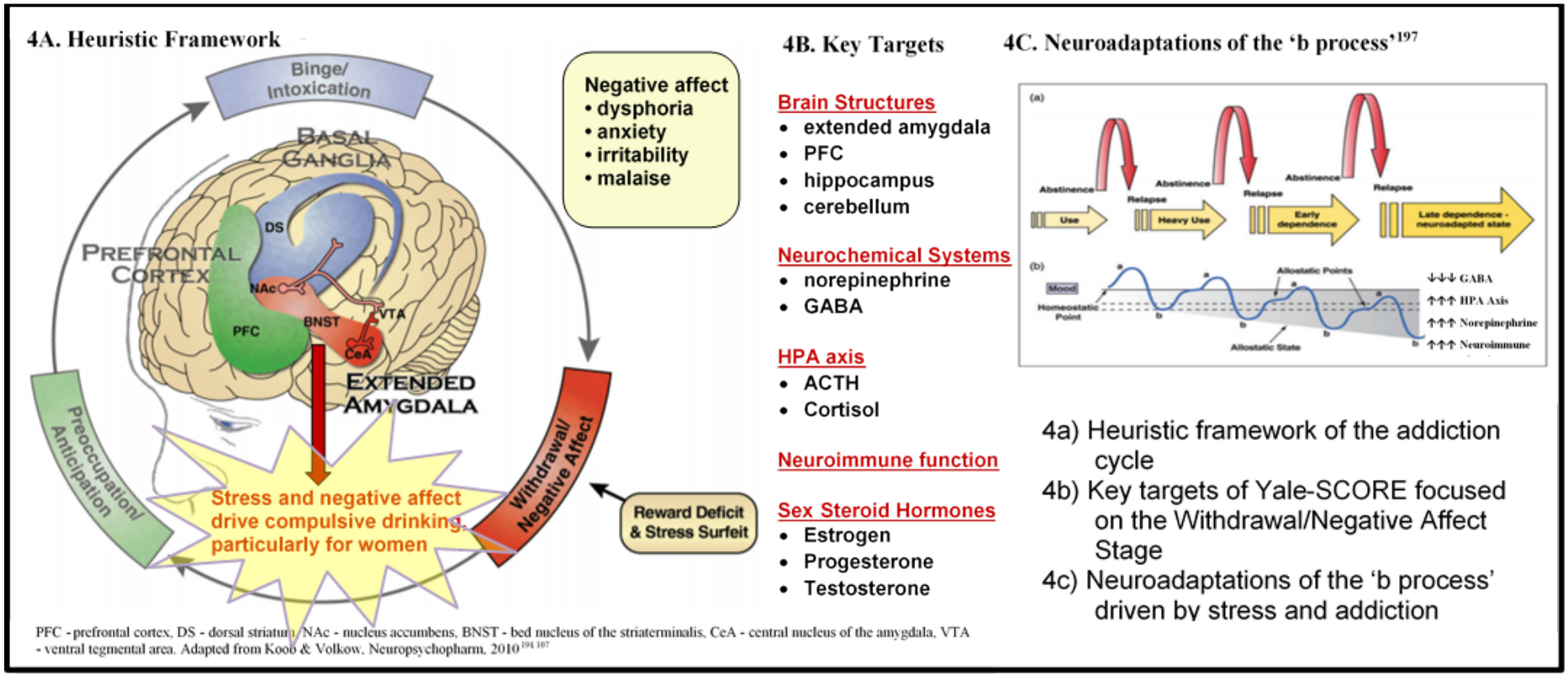
Targeting the Noradrenergic System

- Phase 2 hybrid laboratory/clinical trial design to examine efficacy of guanfacine (6mg/day) for heavy drinking, and sex-dependent mechanisms



YALE-SCORE U54AA027989

Targeting the dark side of addiction for AUD medication development



Summary & Conclusions

- Medication trials for substance use have not considered SABV
- SABV needs to be incorporated into the design, power, analysis and reporting of findings
- Targeting stress for treatment development for women is promising
- Noradrenergic targets hold promise to target gender-sensitive systems involved in substance use

Acknowledgements

Collaborators

Meaghan Lavery
Sabrina Coppola
Paula Cunningham
Andrew Bessette
Kathryn Smith PhD
Walter Roberts PhD
Terril Verplaetse PhD
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Funding:

U54AA027989 (McKee)
P50DA033945 (McKee)
R01AA022285 (McKee)
R01DA035001 (McKee)
CTSA-UL1RR024139