Reducing Cigarette Smoking: Innovations and Challenges

Neal L Benowitz MD
Emeritus Professor of Medicine
University of California
San Francisco

9th Annual VCBH Conference
October 7, 2021
Conflict of Interest Statement

• I am a consultant to Achieve Life Sciences, a company that is developing smoking cessation medications.
• I am not promoting or discussing this company or its products in this presentation.
• I also serve as an expert witness in litigation against tobacco companies.
Why are we still concerned about Smoking and Health?
Major causes of death in U.S. 2016
All are smoking-related

1. Ischemic heart disease
2. Lung cancer
3. Chronic obst lung disease
4. Alzheimer /dementias
5. Colo-rectal cancer
6. Motor vehicle injuries
7. Lower respir tract infections
8. Diabetes
9. Intracerebral hemorrhage
10. Ischemic stroke
Cigarette Smoking in the U.S.

• 14% adults = 34 million smokers
• Smoking more common in people with lower education, lower income, LGBT, mental illness, substance use disorders. Smoking prevalence ZSFG 25-30%
• 480,000 premature deaths annually from smoking
• Lifelong smoking costs 10 years of life
Getting smokers to quit as soon as possible is essential for public health
Projected Global Mortality from Smoking 2000-2050: Cessation reduces mortality much faster than prevention

Henningfield and Slade, FDLI, 1998
Despite interest in quitting, smoking cessation rates have remained low for > 15 years.

Babb et al. MMWR 2017
Topics I will cover

• Innovations in smoking cessation
  – Nicotine neurobiology translation – precision medicine
  – Emerging medications
  – Approaches to pharmacotherapy

• Combusted Tobacco Endgame
  – Thirdhand smoke
  – Nicotine reduction
  – Cigarette harm reduction/Electronic nicotine delivery devices
Innovations in Smoking Cessation
Nicotine Neurobiology Translation
Tobacco Combustion Products Responsible for Most Tobacco-related Disease

Nicotine

Addictive Combusted Tobacco Use

10 Million Deaths Annually
Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to “Nicotinic Cholinergic Receptors”
Structure of Nicotinic ACh Receptors

Acetylcholine

Pore

Ion

Muscle type nicotinic receptor

Neuronal type nicotinic receptors

Picciotto M. Emerging neuronal nicotinic receptor targets. SRNT 9th Annual Meeting; February 2003; New Orleans, La.
NICOTINE

- **DOPAMINE** ➔ Pleasure, Appetite Suppression
- **NOREPINEPHRINE** ➔ Arousal, Appetite Suppression
- **ACETYLCHOLINE** ➔ Arousal, Cognitive Enhancement
- **GLUTAMATE** ➔ Learning, Memory Enhancement
- **SEROTONIN** ➔ Mood Modulation, Appetite Suppression
- **BETA-ENDORPHIN** ➔ Reduction of Anxiety and Tension
- **GABA** ➔ Reduction of Anxiety and Tension
Biology of nicotine and smoking behavior

- TOBACCO PRODUCT
- ENVIRONMENTAL INFLUENCES
  - VULNERABILITY FACTORS
    - Age
    - Gender
    - Genetics
    - Psychiatric Disease
    - Substance Abuse

- SMOKING BEHAVIOR
- NICOTINE IN BODY
  - METABOLISM

- NICOTINIC CHOLINERGIC RECEPTORS
  - NEUROTRANSMITTER RELEASE
    - TOLERANCE
  - REINFORCEMENT
    - Enhanced Performance
    - Mood Modulation
    - Lower Body Weight
    - Reversal of Withdrawal Symptoms
    - Self-Medication
Genetic variation and personalized smoking cessation treatment

**CYP2A6 – Nicotine metabolism**
- More rapid nicotine metabolism associated with more cigarettes per day and higher risk lung cancer
- Nicotine metabolite ratio (3HC/cotinine) surrogate marker, measurable in smokers; Genetic risk score for NMR
- Slow metabolizers respond well to nicotine patch, fast metabolizers do not
- Fast metabolizers need varenicline or other pharmacotherapy regimen

**CHRNA5 – α5 nAChR**
- Rs16969968 allele increases risk of tobacco dependence 30-50%
- Associated with heaviness of smoking and risk of lung cancer and COPD
- α5 nAChR in medial habenula mediates aversive effects of nicotine
- Mice with α5 nAChR KO self-administer more nicotine
- Potential biomarker to signal need for more intense smoking cessation therapy
Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial

Caryn Lerman, Robert A Schnoll, Larry W Hawk Jr, Paul Cinciripini, Tony P George, E Paul Wileyto, Gary E Swan, Neal I Benowitz, Daniel F Heitjan, Rachel F Tyndale. on behalf of the PGRN-PNAT Research Group

Transferrability of Ancestry-Specific and Cross-Ancestry CYP2A6 Activity Genetic Risk Scores in African and European Populations

Ahmed El-Boraie1,2, Meghan J. Chenoweth1,2, Jennie G. Pouget2,3, Neal L. Benowitz4, Koya Fukunaga5, Taisci Mushiroda5, Michiaki Kubo5, Nicole L. Nollen6, Lisa Sanderson Cox6, Caryn Lerman7, Jo Knight8 and Rachel F. Tyndale1,2,3,*

Lancet Respir Med 2015
Clin Pharmacol Therap 2021
Slow metabolizers respond well to nicotine patch; normal metabolizers do not

(Lerman, Lancet Resp Med 2015)
Both NMR and ancestry-specific genetic risk score predict response to medications

El-Boraie CPT 2021
Genetic Variant in CHRNA5 and Response to Varenicline and Combination Nicotine Replacement in a Randomized Placebo-Controlled Trial

Li-Shiun Chen$^{1,2,*}$, Timothy B. Baker$^3$, J. Philip Miller$^1$, Michael Bray$^1$, Nina Smock$^1$, Jingling Chen$^1$, Faith Stoneking$^1$, Robert C. Culverhouse$^{4,5}$, Nancy L. Saccone$^6$, Christopher I. Amos$^{7,8}$, Robert M. Carney$^1$, Douglas E. Jorenby$^3$ and Laura J. Bierut$^{1,2}$

Clin Pharmacol Therap 2020
CHRNA5 risk genotype (GA/AA) predicts poorer cessation with cNRT in African American smokers
Emerging Smoking Cessation Therapies
Effect of Cytisine vs Varenicline on Smoking Cessation
A Randomized Clinical Trial

Ryan J. Courtney, PhD; Hayden McRobbie, PhD; Piotr Tutka, MD; Natasha A. Weaver, PhD; Dennis Petrie, PhD; Colin P. Mendelsohn, MBBS; Anthony Shakeshaft, PhD; Saki Talukder, MPH; Christel Macdonald, BPsych; Dennis Thomas, PhD; Benjamin C. H. Kwan, PhD; Natalie Walker, PhD; Coral Gartner, PhD; Richard P. Mattick, PhD; Christine Paul, PhD; Stuart G. Ferguson, PhD; Nicholas A. Zwar, PhD; Robyn L. Richmond, DSc; Christopher M. Doran, PhD; Veronica C. Boland, PhD; Wayne Hall, PhD; Robert West, PhD; Michael Farrell, MB
Cytisine slightly less effective but fewer side effects compared to VAR

- 1452 Australian smokers, 43 yo, 18 cpd
- 25 day cytisine v 12 week varenicline
- Quit-line behavioral support
- CAR 1-6 mos: cytisine 11.7% v VAR 13.3%
- More frequent AEs with VAR – abnormal dreams and nausea
- Limitation – other cytisine dosing regimens appear to be more effective in ongoing clinical trials; longer dosing may be better
Lorcaserin – Serotonin 5HT2C receptor agonist

- Decreases firing of DA neurons and decreases nicotine self-admin in rats
- Increases proopiomelanocortin secretion and decreases food intake
- Improves glycemic control in diabetics
- Approved for weight loss 2012
Lorcaserin for Smoking Cessation and Associated Weight Gain: A Randomized 12-Week Clinical Trial

William R. Shanahan MD\textsuperscript{1,2}, Jed E. Rose PhD\textsuperscript{3}, Alan Glicklich MD\textsuperscript{1,4}, Scott Stubbe MBA\textsuperscript{1}, Matilde Sanchez-Kam PhD\textsuperscript{1}

NTR 2017
Lorcaserin promotes smoking cessation while preventing weight gain
Psilocybin – Serotonin 5HT2A receptor agonist

- *Psylocybe* genus mushroom
- Ritual use for centuries
- Acts on central 5HT2A and 5HT1A receptors
- Amelioration of negative affect states and stress
- Enhanced cognitive flexibility and reduced compulsivity
- Ongoing trials SUDs, PTSD, anxiety and depressive disorders
Pilot Study of the 5-HT$_{2A}$R Agonist Psilocybin in the Treatment of Tobacco Addiction

Matthew W. Johnson, PhD$^1$, Albert Garcia-Romeu, PhD$^1$, Mary P. Cosimano, MSW$^1$, and Roland R. Griffiths, PhD$^{1,2}$

J Psychopharmacology 2014
Study design

- Open label
- 15 healthy smokers, ages 25-65
- Mean 19 cpd
- 15 weeks therapy
- Psylocibin 20 mg/70kg week 5, 30 mg/70 kg week 7 and 13
- TQD week 5, preceded by 4 weekly preparatory CBT sessions
- Daily phone calls for 2 weeks after 1st dose

- During each session
  - Lying on couch
  - Mask over eyes
  - Music through headphones
  - Instructed to focus on internal experience
  - Interpersonal support for any dysphoric subjective effects
  - Motivational statement prior to and guided imagery after session
Study results

- 80% PPA at 6 mos (67% at 12 m)
- Adverse events: increased BP, HR; dysphoric effects (fear, fear of insanity, feeling trapped); headaches (up to 24 hr)
- Reasons for quitting:
  - Changing orientation toward future
  - Stronger belief is ability to quit
  - Changing life priorities/values
Approaches to Pharmacotherapy
Pre-cessation pharmacotherapy

• Many smokers would like to quit but not prepared to set date
• Starting pharmacotherapy before quitting with the expectation that quitting will be easier at a later date
• Pre-cessation nicotine patch and varenicline reduce cigarette nicotine reward and promote quitting over time
• Can be coupled with gradual CPD reduction – such as 50% at 4 wk, 75% at 8 wk, quit at 12 wk
• Clinicians can approach every patient this way, just as one would treat hypertension or high cholesterol.
Use of varenicline for more than 12 months for smoking cessation in heavy chronic obstructive pulmonary disease smokers unmotivated to quit: a pilot study

Raúl H. Sansores, Alejandra Ramírez-Venegas, Rosario Arellano-Rocha, Valeri Noé-Díaz, Leonor García-Gómez, Oliver Pérez Bautista and Mónica Velázquez Uncal

Ther Adv Resp Dis 2016
Pre-cessation varenicline resulted in 71% CO-verified quit rate at 18 months

- 30 CS with mild-mod COPD seen in pulmonary clinics
- Avg 55 yo, 24 cpd, FTCD 7
- Purchased their own VAR
- Counseling VAR action/expected benefits; no set quit date
- Visits at 1 to 6 week intervals
- Median VAR duration 4 mos (3-24) in quitters; 2 mos (1-8) in non-quitters
Combusted Tobacco Endgame
The Combustible Tobacco Endgame

Strategy to eradicate or reduce to minimal levels the use of (and disease caused by) combustible tobacco products.
Ongoing Tobacco Control Policies are important: MPOWER (WHO FCTC)

- **M (Monitor)** Tobacco use and prevention policies
- **P (protect)** Clean air laws
- **O (offer help)** Cessation support
- **W (warn)** Mass media and package warnings
- **E (enforce)** Enforce ad bans, promotions
- **R (raise)** Raise taxes
Another Protection Opportunity

Thirdhand Smoke: New Evidence, Challenges, and Future Directions

Peyton Jacob, III, Neal L. Benowitz, Hugo Destaillats, Lara Gundel, Bo Hang, Manuela Martins-Green, Georg E. Matt, Penelope J. E. Quintana, Jonathan M. Samet, Suzaynn F. Schick, Prue Talbot, Noel J. Aquilina, Melbourne F. Hovell, Jian-Hua Mao, and Todd P. Whitehead

Chem Res Toxicology 2016
Indoor Surfaces

SHS

THS
What is Thirdhand cigarette smoke?  

**The 3 R’s**

Chemicals in cigarette smoke that:

- **Remain** on surfaces and in dust
- **Re-emit** back into the gas phase
- **React** with other chemicals in the environment to make new chemicals

Animal studies demonstrate systemic absorption of carcinogens, oxidative stress, metabolic abnormalities and genotoxicity
Thirdhand smoke policies could promote the tobacco endgame

- Environments of high risk: housing, workplaces, hotels, rental cars
- Vulnerable populations: children; lower income people in multi-unit housing
- Mandatory disclosure policies, THS contamination standards and remediation requirements provide a strong economic incentive not to smoke
THS Resource Center at thirdhandsmoke.org
funded by the California Tobacco Related Disease Research Program (TRDRP)
Nicotine Pharmacology and Public Policy
Nicotine

Addictive Combusted Tobacco Use

10 Million Deaths Annually

Tobacco Combustion Products Responsible for Most Tobacco-related Disease, but People Smoke for Nicotine
A Nicotine-Focused Framework for Public Health

Scott Gottlieb, M.D., and Mitchell Zeller, J.D.

Despite extraordinary progress in tobacco control and prevention, tobacco use remains the leading cause of preventable disease and death in the United States. Combustible cigarettes cause the overwhelming majority of tobacco-related disease and are responsible for more than 480,000 U.S. deaths each year. Indeed, when used as intended, combustible cigarettes kill half of all long-term users. With the tools provided to the Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act of 2009, the agency has taken consequential steps to prevent sales of tobacco products to children, expand the science base for understanding traditional and newer tobacco products, and conduct public education campaigns. But the agency needs to do more to protect Americans;
Addictiveness/Appeal

Toxicity

Continuum of Risk

non-combustible
nicotine replacements

combustibles
Reducing the Nicotine Content to Make Cigarettes Less Addictive
Establishing a Nicotine Threshold for Addiction

- **Goal:**
  - To prevent nicotine addiction in youth.

- **Threshold for Addiction:**
  - Dose to establish and maintain addiction
    \[ \sim 5 \text{ mg/day}. \]

- **Proposal:**
  - A gradual reduction of nicotine content of cigarettes over 10-15 years.

---

Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy

![Graph showing nicotine availability over years with lines for cigarettes and clean nicotine, intersecting at the addiction threshold.](image)
Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Eric C. Donny, Ph.D., Rachel L. Denlinger, B.S., Jennifer W. Tidey, Ph.D., Joseph S. Koopmeiners, Ph.D., Neal L. Benowitz, M.D., Ryan G. Vandrey, Ph.D., Mustafa al'Absi, Ph.D., Steven G. Carmella, B.A., Paul M. Cinciripini, Ph.D., Sarah S. Dermody, M.S., David J. Drobes, Ph.D., Stephen S. Hecht, Ph.D., Joni Jensen, M.P.H., Tonya Lane, M.Ed., Chap T. Le, Ph.D., F. Joseph McClernon, Ph.D., Ivan D. Montoya, M.D., M.P.H., Sharon E. Murphy, Ph.D., Jason D. Robinson, Ph.D., Maxine L. Stitzer, Ph.D., Andrew A. Strasser, Ph.D., Hilary Tindle, M.D., M.P.H., and Dorothy K. Hatsukami, Ph.D.

Donny et al., NEJM, 2015
Immediate Nicotine Content Reduction Comparing Cigarettes with Different Nicotine Content

Threshold dose to reduce addictiveness is $< 0.4 \text{ mg/g tobacco}$

- 70% reduced nicotine intake
- Reduced # cigarettes smoked
- Reduced dependence and urges
- Increased quit attempts
- Resulted in no compensatory smoking
- Did not lead to greater use of substances of abuse or increase in depressed mood.

Donny et al., NEJM, 2015
Quotes from Reduced Nicotine Content Cigarette Smokers

– “I no longer feel the need to have coffee and cigarettes first thing in the morning.”
– “experiencing less craving”
– “smoking these cigarettes are like quitting and therefore, might as well quit.”
– “smoking is losing its pleasure”.
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
21 CFR Part 1130
[Docket No. FDA–2017–N–6189]
RIN 0910–AH86

Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.
Challenge: Will the FDA Implement a Nicotine Reduction Policy?

- Nicotine reduction appears to be safe and likely to markedly reduce smoking prevalence
- Tobacco company litigation may argue reducing nicotine to non-addicting levels alters the essence of a cigarette
- Others may argue that nicotine reduction violates personal autonomy and represents government over-reach
- Concern about suddenly depriving smokers of nicotine, resulting in severe withdrawal, aggravation of mental illness and other harms
Gaining smokers’ acceptance of nicotine reduction: Adjuncts to manage dependence

• Nicotine replacement medications
• Non-combustible tobacco products
• Electronic nicotine delivery devices
Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game

Neal L. Benowitz, Eric C. Donny, Dorothy K. Hatsukami
C’est une E-cigarette
Heated tobacco products: iQOS
Challenge: Will ENDS become a legitimate component of U.S. tobacco control efforts?
Balancing Consideration of the Risks and Benefits of E-Cigarettes

David J. K. Balfour, DSc, Neal L. Benowitz, MD, Suzanne M. Colby, PhD, Dorothy K. Hatsukami, PhD, Harry A. Lando, PhD, Scott J. Leischow, PhD, Caryn Lerman, PhD, Robin J. Mermelstein, PhD, Raymond Niaura, PhD, Kenneth A. Perkins, PhD, Ovide F. Pomerleau, PhD, Nancy A. Rigotti, MD, Gary E. Swan, PhD, Kenneth E. Warner, PhD, and Robert West, PhD

Amer J Pub Health 2021
Nicotine vaping controversy has divided the tobacco control community

**Opponents**
- Nicotine addiction in youth
- Renormalizing smoking
- Harm to adolescent brain
- Substantial health risks
- Questionable benefit for smoking cessation

**Proponents**
- Promotion of smoking cessation
- Vaping far less risky than smoking
- Smoking among youth declining rapidly
- Important adjunct to cigarette regulation
Evidence that vaping increases smoking cessation

- Randomized trials – 2 RCTs show benefit vs NRT
- Population studies – Studies in US (1) and UK (3) suggest 10-15% increased cessation rate
- Cigarettes sales in US have decreased much more rapidly while vaping sales increased
- Policies restricting vaping (Minnesota e-cigarette tax) increased adult smoking
Why vaping is likely substantially less dangerous than smoking

- >7000 chemicals in cigarette smoke; exceeds number in e-cigarette aerosol by two orders of magnitude
- Among potentially toxic substances in both products, cigarette smoke generally contains substantially larger quantities than e-cigarette aerosol
- Biomarkers reflecting exposure to toxic substances are present at much higher levels in exclusive cigarette smokers than in exclusive vapers
- Toxicant exposures decrease in smokers who switch to e-cigarettes
- Lung and vascular function improve in cigarette smokers who switch to e-cigarettes
- Exclusive users of e-cigarettes (most former smokers) report fewer respiratory symptoms than do cigarette smokers and dual users
Concerns about youth vaping

- Nicotine addiction among those who never have tried smoking
- Increasing the risk of trying smoking, renormalizing smoking
- Harm to the developing adolescent brain
- However, as vaping has become more popular, smoking prevalence among youth has reached record low
National Youth Tobacco Survey

Past 30-Day Product Use by High School Students (9th - 12th Grade)

Prevalence (%)
Social justice and vaping

• To the more privileged members of society, today’s smokers are nearly invisible. Many affluent Americans believe that the problem of smoking is nearly “solved”.
• Yet, one in seven adults Americans remain a smoker
• Smoking accounts for a significant proportion of the large life expectancy difference between affluent and poorer Americans. Vaping might help more of these smokers to quit
Challenge: What is the appropriate role of ENDS in tobacco control?

Medicine vs Consumer Product
Challenge: Is long-term nicotine use without combusting tobacco acceptable in our society?

Benefits vs Risks

Comparisons to alcohol and marijuana
Challenge: FDA regulation of E-cigarettes

Flavor restrictions: youth uptake vs adult harm reduction
Nicotine limits in e-liquids: high nicotine/low power vs low nicotine/high power
Challenge: Is there a role for tobacco companies in tobacco control?

Cigarette sales could end in many countries 'within 10 to 15 years' says tobacco giant Philip Morris
My thoughts 1: nicotine reduction would be the fastest path to the cigarette endgame

- Reducing the nicotine content of cigarettes will reduce the addictiveness of cigarettes.
- The result would be preventing children from becoming addicted smokers and giving people greater freedom to stop smoking when they decide to quit.
- Immediate rather than gradual nicotine reduction probably safest and most feasible.
My thoughts 2: nicotine-based harm reduction will facilitate other endgame approaches

• Electronic cigarettes or other non-combusted tobacco products would provide an attractive alternative to conventional cigarettes and would likely enhance public acceptance of a nicotine reduction policy.
• I am skeptical that ENDS will outcompete cigarettes, but could support harm reduction for many smokers
• Possible long-term adverse health consequences of ENDS use, including gateway to smoking and primary nicotine addiction in youth remain a concern.
Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States

Benjamin J. Apelberg, Ph.D., M.H.S., Shari P. Feirman, Ph.D., Esther Salazar, Ph.D., Catherine G. Corey, M.S.P.H., Bridget K. Ambrose, Ph.D., M.P.H., Antonio Paredes, M.S., Elise Richman, M.P.H., Stephen J. Verzi, Ph.D., Eric D. Vugrin, Ph.D., Nancy S. Brodsky, Ph.D., and Brian L. Rostron, Ph.D., M.P.H.

Apelberg et al., NEJM, 2018
Apelberg Simulation of Effects of Mandatory Nicotine Reduction

• U.S. Population-based simulation model, 2016 to 2100
• Prediction: by year 2100 more than 33 million youth and young adults who would have become regular smokers would not start
• Prediction: 5 million smokers would quit within 1 year of implementation, and 13 million with 5 years
Tengs Simulation of Population Health Impact of Mandatory Nicotine Reduction

Smoking prevalence likely to decline to 5%, with resultant gain of 137 million QALYs over 50 years

“Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population.”