



Implications of Dual Use on Modern Oral Tobacco Product Clinical AL/PK Study Design

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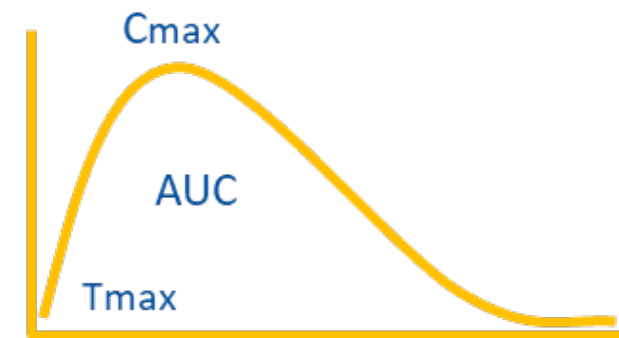
Modern Oral Background

- Oral tobacco products range from traditional smokeless tobacco to modern oral products that contain nicotine derived from tobacco or synthetic nicotine.
- Modern oral pouched products are similar in size and shape to pouched snus but contain purified nicotine and an inert filler material, but no tobacco leaf.
- Nicotine pouch products have substantially reduced levels of several harmful and potential harmful chemicals (HPHCs), which are believed to be the primary cause of smoking-related diseases.
- Modern oral pouched products are the largest growing category of tobacco products
 - 2020: \$452.8 million (US only)
 - 2023: \$1.06 billion (US only)
 - 2034 (Projected): \$20 billion (US only)

Modern Oral Nicotine Products Market Size, Share & Trends Analysis Report By Product (Nicotine Pouches, Nicotine Gums, Nicotine Patches), By Flavor (Original/Unflavored, Flavored), By Strength, By Distribution Channel, By Region, And Segment Forecasts, 2024 – 2030; Grand View Research, 2023

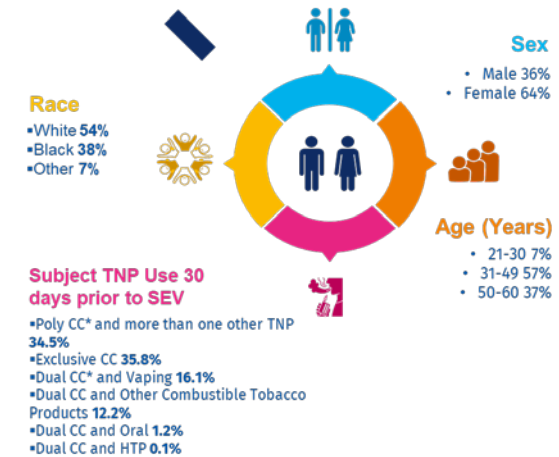
Tobacco Product Clinical Abuse Liability (AL) Studies

- Many physiological, pharmacological, and behavioral components influence AL
 - Pharmacokinetic (PK) and Pharmacodynamic (PD) help understand potential for abuse
- Commonly assessed PK endpoints
 - Baseline adjusted plasma nicotine concentration over time following (single/defined) product use/session
 - Maximum plasma nicotine concentration (C_{max})
 - Time from start of product use C_{max} (T_{max}), or rate of systemic absorption
 - Area under the Plasma Nicotine Curve / to Maximum plasma nicotine concentration
- Commonly assessed PD endpoints
 - Physiological effects
 - Heart rate
 - Blood pressure
 - Subjective effects
 - Product Liking/Satisfaction/Intent to Use Again/Modified Cigarette Evaluation Questionnaire
 - Urge to Smoke/Questionnaire on Smoking Urges-Brief



Participant Tobacco Use Demographics

- Tobacco Use History
 - Current Tobacco Use
 - Tobacco Product Characteristics (e.g., menthol)
 - Frequency of Tobacco Use
 - Length of Tobacco Use of each Tobacco Product Class



TNP: Tobacco or nicotine-containing product; SEV: Screening and Enrollment Visit; CC: Combustible Cigarettes

* "Poly-usage" and "dual-usage" may refer to a transitional period where adult (age 21+) consumers of traditional tobacco products move towards a complete switch to potentially reduced-risk nicotine products by reducing traditional tobacco consumption and adding potentially reduced-risk nicotine products to their consumption.

- US CDC defines, any use of tobacco in past 30 days is considered dual user
- Felicione et al., 2022 reported among MO users: 65% daily use, 16% weekly, 18% less than weekly
- Stratifying use by daily and non-daily use of products used to track use transitions (Sharma et al., 2024)
 - ENDS use lead to transition of daily cigarette use to non-daily use

Jamal et al., Tobacco Product Use Among Middle and High School Students — National Youth Tobacco Survey, United States, 2024; MMWR, 2024

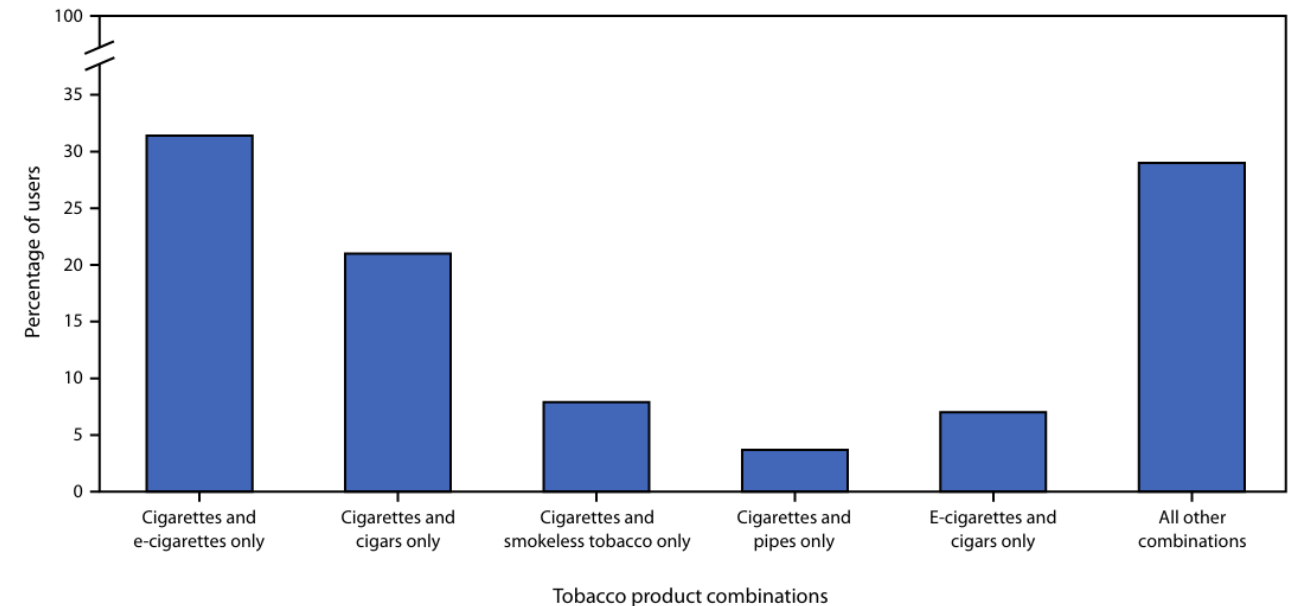
Sharma et al., Cigarette and ENDS dual use longitudinal transitions among adults in the PATH Study Waves 4-5. Addict Behav Rep, 2024

Felicione et al., Oral Nicotine product awareness and use among people who smoke and vape in U.S. Am J Prev Med, 2022

Use History Profile of Dual Users

- Approximately 30% of US adult tobacco users were dual users in 2021 (Cornelius et al., 2023)
- Any use of another tobacco product within the past 30 days
- 33.4% of US adult tobacco users reported being dual users of cigarettes and MO in 2021 (Reyes-Guzman et al., 2025)

FIGURE 1. Percentage of persons aged ≥ 18 years who reported use of two or more tobacco products, by the top five product combinations — United States, 2021^{*,†,§}



Abbreviation: e-cigarettes = electronic cigarettes.

* Smoking and tobacco product use refers to use of commercial tobacco products and not to tobacco used for medicinal and spiritual purposes by some American Indian communities.

† Current smokeless tobacco product use was defined as using chewing tobacco, snuff, dip, snus, or dissolvable tobacco at least once during a person's lifetime and now using at least one of these products "every day" or "some days."

§ "All other combinations" refers to use of other combinations of two or more products.

Cornelius et al., Tobacco Product Use Among Adults – United States, 2021. MMWR, 2023

Reyes-Guzman et al., Patterns of Emerging Tobacco Product Use Among US Adults 2019-2022. Am J Prev Med, 2025



Mere-Exposure Effect

Mere-Exposure Effect

- Familiarity principle
- Increased liking of a product with more exposure to a product
- Robert Zajonic – Popularized this phenomenon
 - Group of people interested in learning a new language were shown Chinese-like characters (nonsense characters) in varying frequency. At the end, the people were told the characters were adjectives, the characters more frequently shown were rated more favorable
- Further demonstrated with the following experiment by Dr. Goetzinger (Zajonic 1968)
 - A person was dressed in a black bag with only their feet showing for a class. Over time the students' attitude changed from hostility to curiosity then to friendship
- Longer the exposure leads to increased liking from baseline
- Meta review of literature by Bornstein proposed peak effect occurred between 10 – 20 presentations



Zajonic, Attitudinal Effects of Mere Exposure. J Res Per, 1968

Bornstein, Exposure and affect: Overview and meta-analysis of research 1968-1987, Psyc Bul 1989

Current Examples of Mere-Exposure Effect

- Cell Phone Preferences
 - Samsung vs. Apple Users



- Product Placement in Movies (Ruggieri and Boca 2013)
 - Increased positive attitude towards brands regardless if product is recognized or not
- Repeated Listening of Songs (Madison and Schiölde 2017)
 - Increased liking of songs regardless of complexity

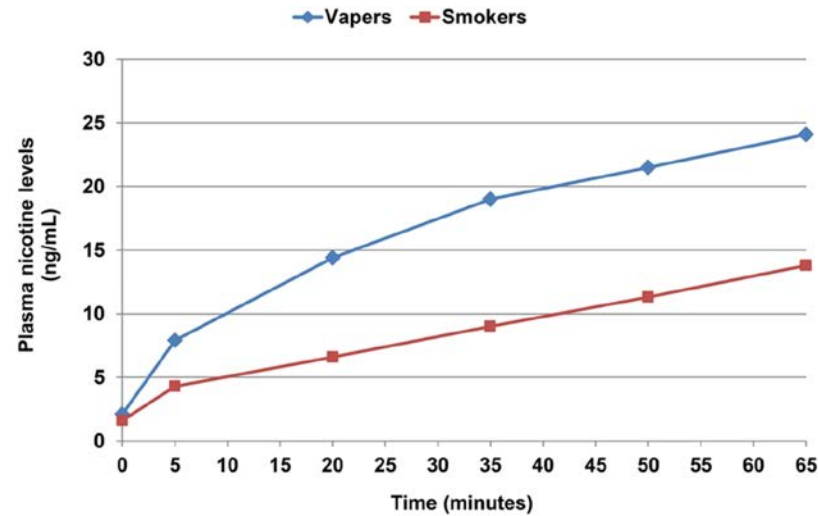
Ruggieri and Boca, At the Roots of Product Placement: The Mere Exposure Effect. Eur J Psych 2013

Madison and Schiölde, Repeated Listening Increases Liking for Music Regardless of its Complexity, Front Neurosci. 2017

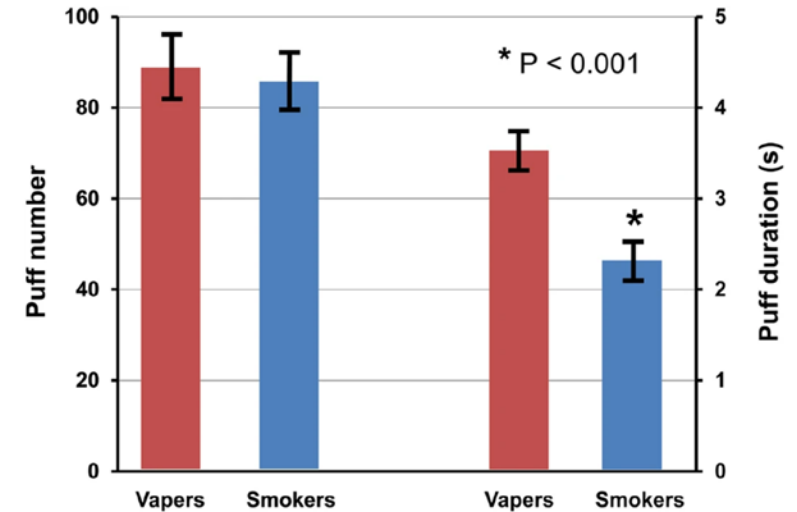


Potential Impact in Tobacco Clinical Studies

Familiarity impact ENDS Clinical Studies



Farsalinos et al., 2015



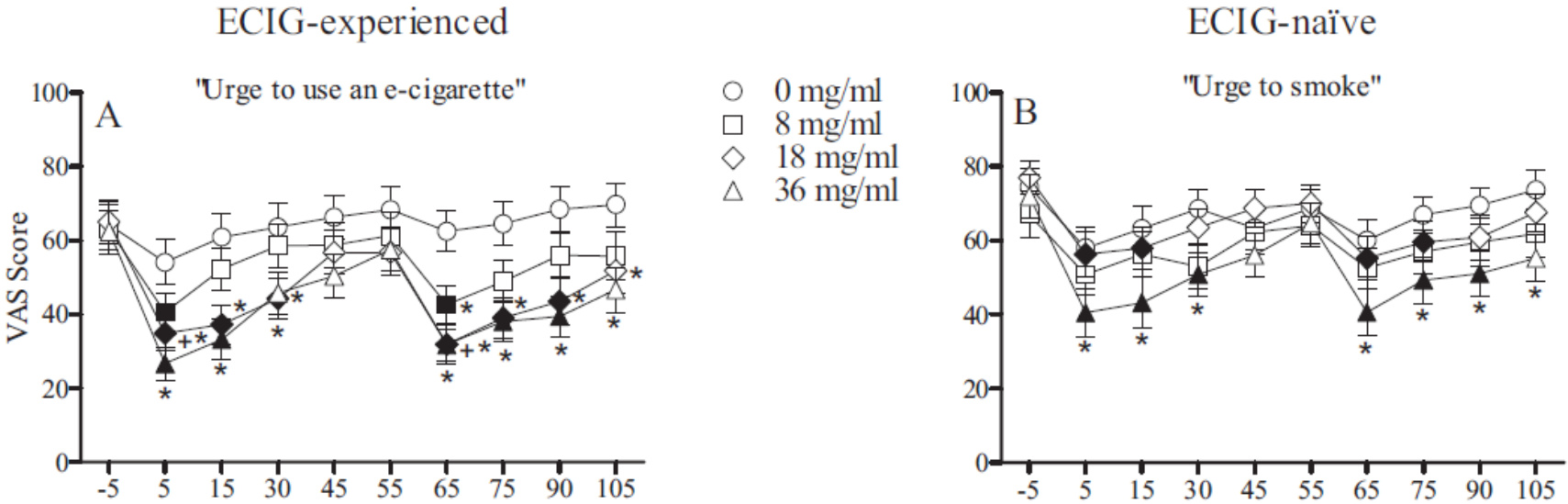
Farsalinos et al., 2015

- Participants were given limited instructions on ENDS device
- Nicotine Pharmacokinetic differences between naïve and current users of ENDS (Farsalinos et al., 2015)
 - Potentially due to shorter puff duration or depth of inhalation

Farsalinos et al., Nicotine absorption from ENDS: comparison between experienced and naïve users, Sci Rep 2015

Familiarity impact in ENDS Clinical Studies

- Experienced ENDS users and exclusive smokers (ENDS-naïve) were instructed on a prescribed puffing regimen and Urge to Smoke was measured at defined times (Hiler et al., 2017)



Filled symbols indicate significant difference from baseline (-5 time point), asterisks indicate significant differences between from 0 mg/mL condition at that time point. Plus signs indicate significant between-group differences at that time point for that concentration ($p < 0.05$).

Hiler et al., Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects. Exp Clin Psych 2017

Familiarity impact in ENDS & MO Clinical Studies

- Nicotine dependence between dual users of cigarette and ENDS similar to exclusive cigarette only users, but lower than exclusive ENDS users (Kaplan et al., 2020)
- Different product use behavior has been proposed between exclusive smokers/moist smokeless tobacco users versus dual users of cigarettes and moist smokeless tobacco (Liu et al., 2022)
- Dual users of cigarette and moist smokeless tobacco reported to have lower urine cotinine on days using only one product vs. both (Felicione et al., 2020)
- Conflicting reports on cigarettes per day for dual users of cigarettes and moist smokeless tobacco and exclusive smokers (Felicione et al., 2020)

Liu et al., Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users. Psych (Berl), 2022

Felicione et al., Cigarette smokers' concurrent use of smokeless tobacco: dual use patterns and nicotine exposure. Tob Control 2020

Kaplan et al., A comparison of product dependence among cigarette only, ENDS only, and dual users: Findings from Wave 3 (2015–2016) of the PATH study. Drug and Alcohol Depend 2020

Potential Impacts to AL Study Design/Summary

- Growth of Modern Oral and ENDS has led to a growing population of dual users of these products and cigarettes
- Should Dual User definition change reflect evolving marketplace?
- Greater familiarity with ENDS shown differences between nicotine pharmacokinetics, topography, and urge to smoke reductions.
 - Does this trend exist in Modern Oral or other categories?
 - Verify level of user familiarity?
- Biochemical verification of current product usage?