Pinney Associates

Abuse Liability Assessment of CNS-Active Drugs in Development: History and Overview

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Presented at: *Virtual CORESTA CROM Symposium 2023 – Abuse Liability*

13 February 2023

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Disclosures

Through **Pinney**Associates, Inc., I provide scientific, clinical, and regulatory consulting to support new drug applications (NDAs) and risk management programs for a broad range of CNS active-substances and drug products including new chemical entities and alternative formulations and routes of delivery. **Pinney**Associates also provides consulting services on tobacco harm reduction on an exclusive basis to Juul Labs, Inc.

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What is Abuse Potential and Why Assess It?

From 2017 FDA Guidance, Assessment of Abuse Potential of Drugs:

- "**Drug abuse** is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, **abuse potential** refers to **the likelihood that abuse will occur with a particular drug product or substance with CNS activity**."
- "Throughout this guidance, the **term abuse potential will be used, although abuse liability represents a similar concept**."

- **Why assess it?**
  - Required by law per the Controlled Substances Act (1970) to assist with scheduling and labeling of approved medications
  - Part of the overall safety assessment of a drug in development
  - To protect the public health by controlling the prescribing and use of drugs that may have addictive potential, but not limit their access by patients who need them

U.S. Food and Drug Administration (2017). Assessment of Abuse Potential of Drugs: Guidance for Industry. FDA Clinical/Medical Guidance.

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AP Assessment of Drugs: Key Historical Events

Early 20th Century: "Narcotic/Opium" problems led to 1914 Harrison Narcotic Act, and then research to finding medicines with reduced "addiction liability."

1935: Addiction Research Center established in Lexington, KY, as part of a U.S. Public Health Service (USPHS) hospital; became part of National Institute on Drug Abuse (NIDA) in 1974

1950s: World Health Organization and CPDD provided general guidance for evaluating substances for "dependence" or "abuse" potential.

1970: Controlled Substances Act (CSA) included **8 Factors for "abuse potential"** and established NIDA in 1971 in part to provide the science for scheduling recommendations by FDA and DEA

- Provides model for multi-factored evaluation of AL as exemplified in tobacco product guidances
- Exempts tobacco and tobacco products from scheduling

1990: 1st FDA Draft Guidance by FDA's Drug Abuse Advisory Committee & NIDA – "*Draft Guidelines for Abuse Liability Assessment*"

2002: CPDD, NIDA & FDA Conference on the Assessment of CNS Drugs – contributed to development of the first formal FDA abuse potential assessment guidance (see special issue of *Drug & Alcohol Dependence*, 2003)

2010: FDA issues Draft *Guidance on Assessment of Abuse Potential of Drugs*– **Finalized in 2017 – now the roadmap for CNS-active drug developers**

2015: FDA issues *Guidance on Abuse-Deterrent Opioids - Evaluation and Labeling* - describes the types of studies that may be relevant to tobacco product developers, including tampering, PK & subjective effects (abuse potential studies), & post-marketing assessments

2020: FDA ENDS Enforcement Priorities Guidance – "However, for many individual addicted cigarette smokers, the potential for ENDS to act as a substitute for cigarettes, thereby encouraging smokers to seek to switch completely away from combustible cigarettes, ***may be dependent, in part, upon the product having acceptability and abuse liability more comparable to a cigarette.***" (from p. 20)

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Drug Abuse Potential vs Tobacco Abuse Liability

	Drug Abuse Potential (AP)	Tobacco Abuse Liability (AL)
Legal basis	1970 Controlled Substances Act (CSA)	2009 Family Smoking Prevention & Tobacco Control Act (FSPTCA)
FDA Center	Center for Drug Evaluation and Research (CDER)	Center for Tobacco Products (CTP)
Purpose	Guide CSA drug scheduling recommendations for all CNS drugs including nicotine drug products and drug labeling instructions & warnings	Exempt from scheduling but may include evaluations for risk of initiation, dependence, difficulty quitting, and in vulnerable populations, e.g., for consideration for Substantial Equivalence, or designation as a Modified Risk Tobacco Product (MRTP)
Drug/product focus	Active chemical entity main focus of study (evaluation of product is important for ADF opioids)	Product is main focus, but other ingredients and design features are also studied
Nonclinical studies	Includes receptor binding and CNS effects	Nicotine is already well characterized (contributions of other constituents less so)
Animal behavioral pharmacology	Mainly self-admin. & drug discrimination. Also place preference & intracranial self-stimulation.	Similar techniques being adopted for product extracts and non-nicotine constituents (e.g., acetaldehyde, MAOIs, minor tobacco alkaloids)
Primary human data	Human AP (HAP) studies – "gold standard" clinical trial measures of abuse and physical dependence/withdrawal/PK; also, AEs from RCTs	Nicotine delivery/absorption/PK for new products; many options depending on product, state of development questions and goals of sponsor. Can include HAL, clinical trials, & surveys
Product factors	Physiochemical properties that influence abuse potential and abuse deterrence	Sensory factors including flavors and other factors that may affect attractiveness, consumer appeal & satisfaction

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From FDA Abuse Potential Guidance to NDA

Per FDA's 2017 AP guidance, assessing the AP of a drug under IND development is viewed as a safety issue and is conducted when a drug:

- Has central nervous system (CNS) activity
- Is chemically or pharmacologically similar to other drugs with known abuse potential
- Produces effects such as euphoria, sedation, stimulation, hallucinations, and mood changes

Key decision points and recommended studies: Step-wise approach guides study planning & priorities, e.g., need for human abuse potential (HAP) study

NDA content and structure: The guidance details 5 modules of the Abuse Potential Section of the NDA needed by FDA to develop its **8 Factor Analysis (8FA)** and drug scheduling recommendation.

- DEA makes final scheduling decision after drug is approved by FDA
- Goal for most pharmaceuticals (unlike tobacco products) is to have as close to **ZERO** abuse potential as possible

U.S. Food and Drug Administration (2017). Assessment of Abuse Potential of Drugs: Guidance for Industry. FDA Clinical/Medical Guidance.

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Abuse Potential (aka, Liability) Terminology

Drug abuse: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.

Abuse potential [note: synonymous with abuse liability] refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Desired psychological effects can include euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood.

Dependence*:* physical or psychological dependence. ***Physical dependence…*** develops as a result of physiological adaptation… to repeated drug use, manifested by ***withdrawal*** signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Psychological (or psychic) dependence: state… [of] impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug.

U.S. Food and Drug Administration (2017). Assessment of Abuse Potential of Drugs: Guidance for Industry. FDA Clinical/Medical Guidance.

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Examples of Drug Products Evaluated for AP by FDA

- Analgesics
- Treatments for neuropathic pain
- Treatments for postherpetic neuralgia
- Treatments for cough and cold
- Treatments for GI motility
- Anti-emetics
- Anesthetics
- Anti-anxiety drugs
- Anti-convulsants
- Muscle relaxants
- Treatments for Attention Deficit Hyperactivity Disorder
- Treatments for sleep disorders
- Treatments for narcolepsy
- Treatments for weight management
- Treatments for Alzheimer's Disease
- Treatments for Parkinson's Disease
- Treatments for smoking cessation
- Antidepressants
- Antipsychotics
- Treatments for sexual dysfunction in men and women
- Treatments for androgen insufficiency
- Treatments for drug abuse and dependence
- Novel formulations that may reduce abuse potential

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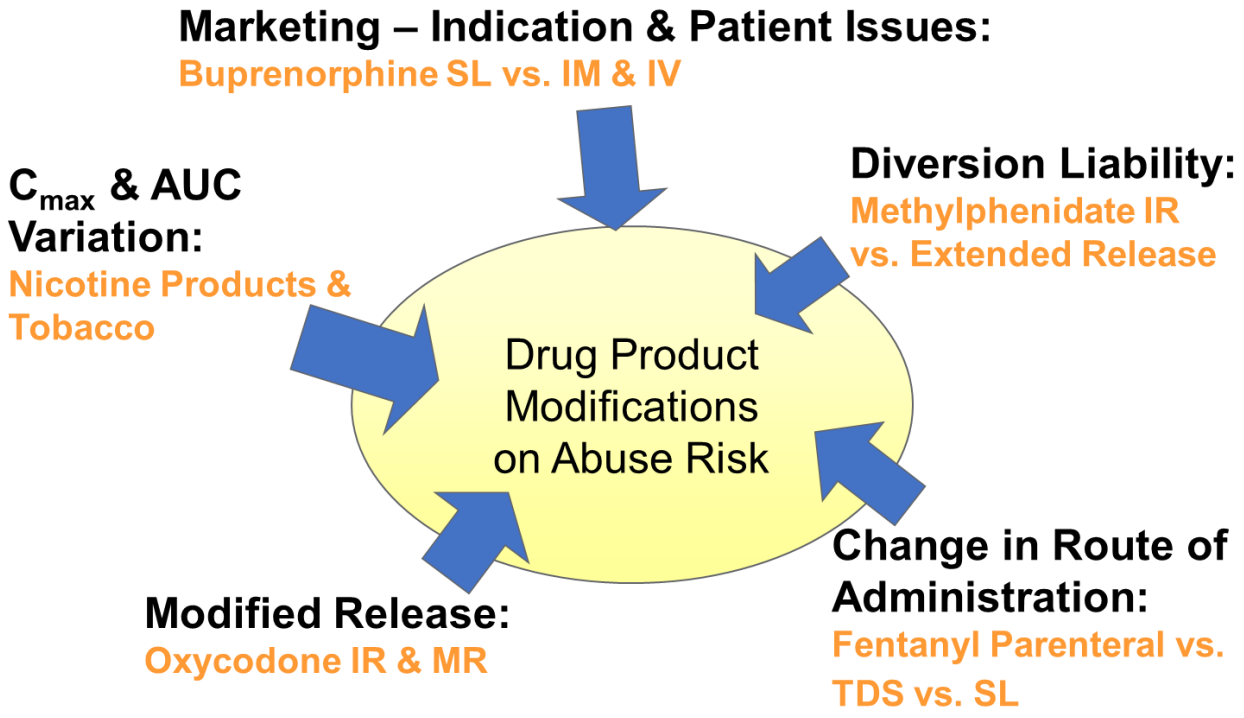
Drug Factors that Influence Abuse Potential

- **Chemical structure**
  - Similarity to known drugs of abuse
- **Dose**
- **Pharmacokinetics**
  - Route of administration
  - Speed of delivery
  - Relative distribution to the brain vs. systemic
  - Penetration of the brain
- **Pharmacodynamic**
  - Subjective effects
  - Behavioral effects
  - Cognitive effects
  - Physiological effects
- **Safety and toxicity**
  - Substance
  - Formulation

Formulation Influences on AP:**



Note: Figure adapted from Mike Klein, FDA @ DIA 2008

**Also see FDA's 2015 *Guidance on Abuse-Deterrent Opioids — Evaluation and Labeling*

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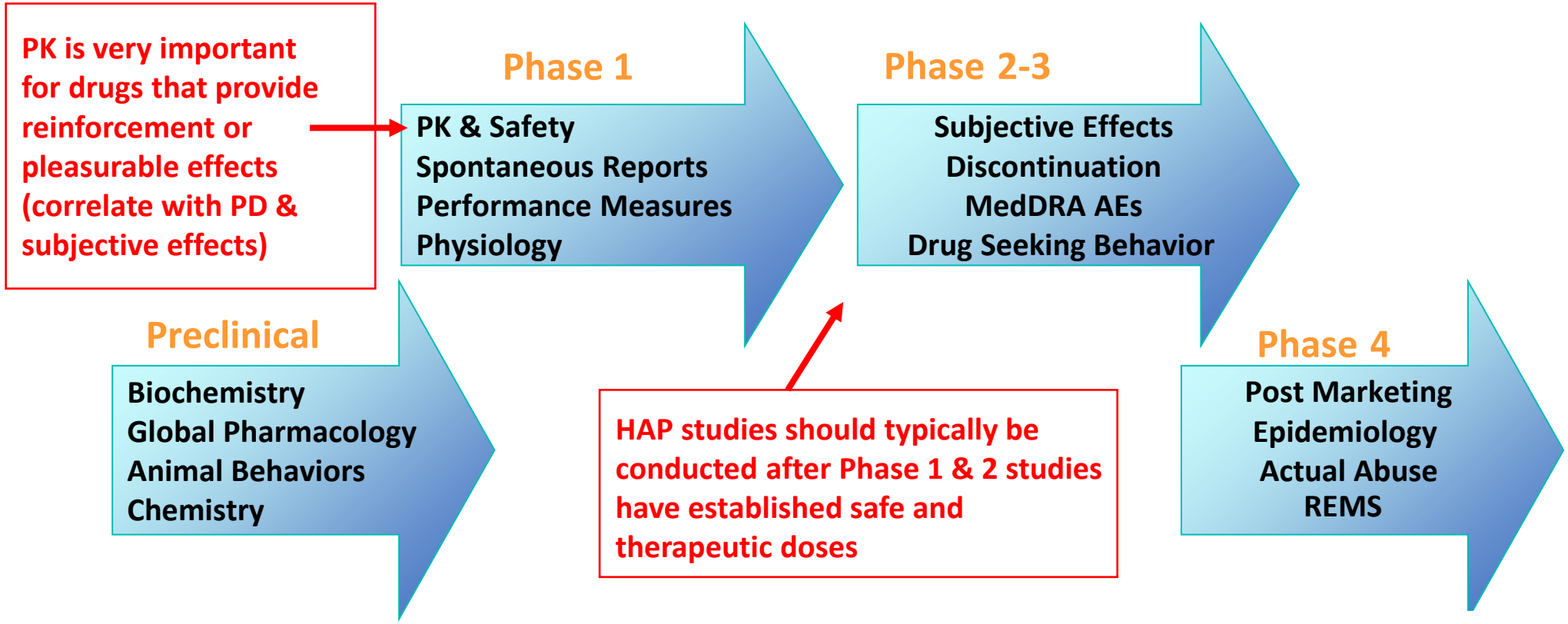
Abuse Potential Assessment During Drug Development

Data on the drug's abuse potential can be obtained at critical times throughout the drug development process



Note: Figure adapted from Mike Klein, FDA @ DIA 2008

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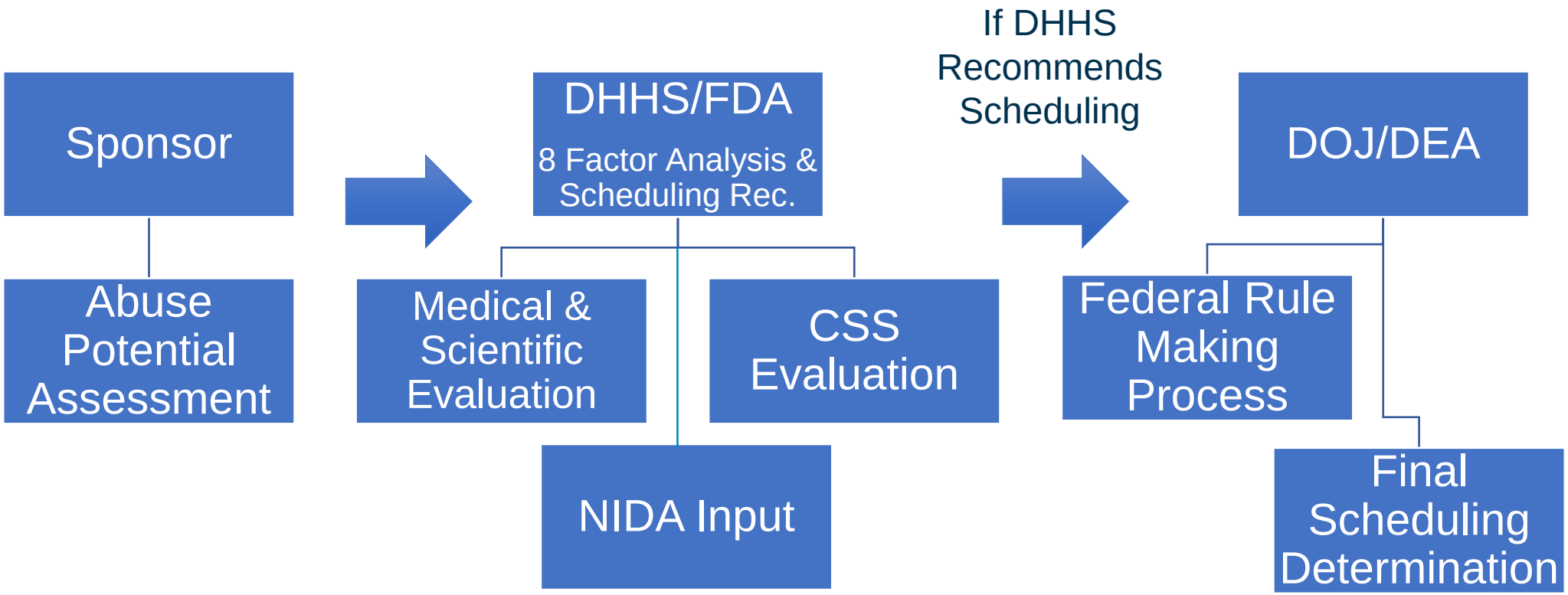
Drug Approval and Scheduling Process



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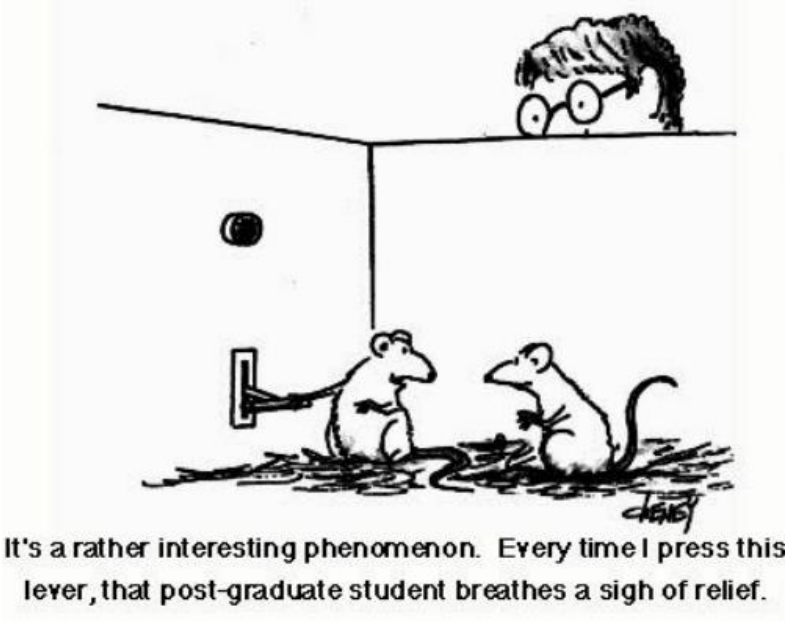
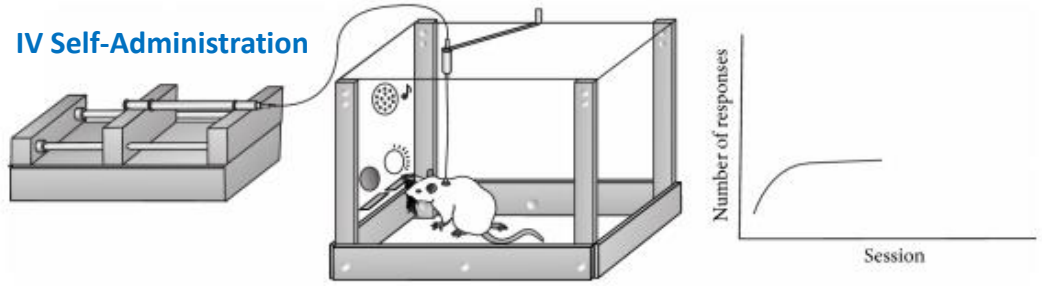
Preclinical Abuse Potential Assessment Methods

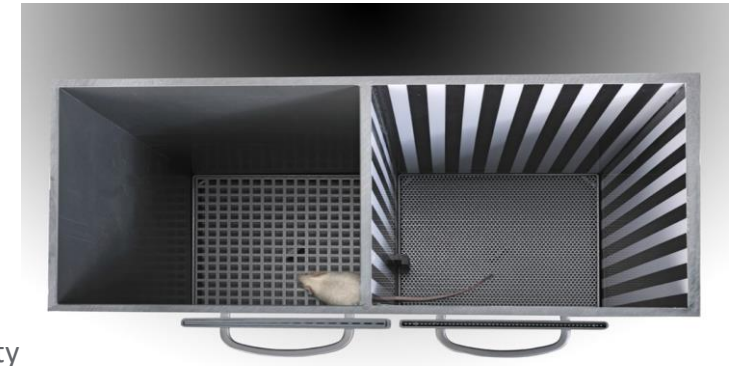
- 1st stages include chemistry, in vitro and animal studies
- Receptor binding (affinity and functional) studies can tell us if a drug's effects will likely be similar to other known drugs of abuse
- **Animal abuse potential studies** can predict psychoactive effects in humans – however, humans are complex and will abuse drugs for certain effects that animals will not (e.g., hallucinogens, nicotine)



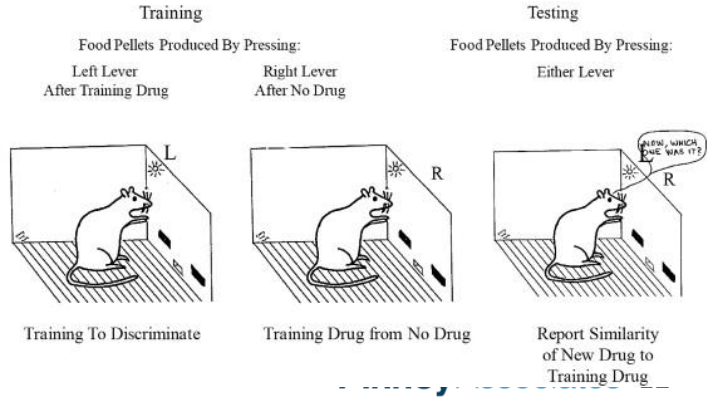
IV Self-Administration



Conditioned Place Preference



Drug Discrimination



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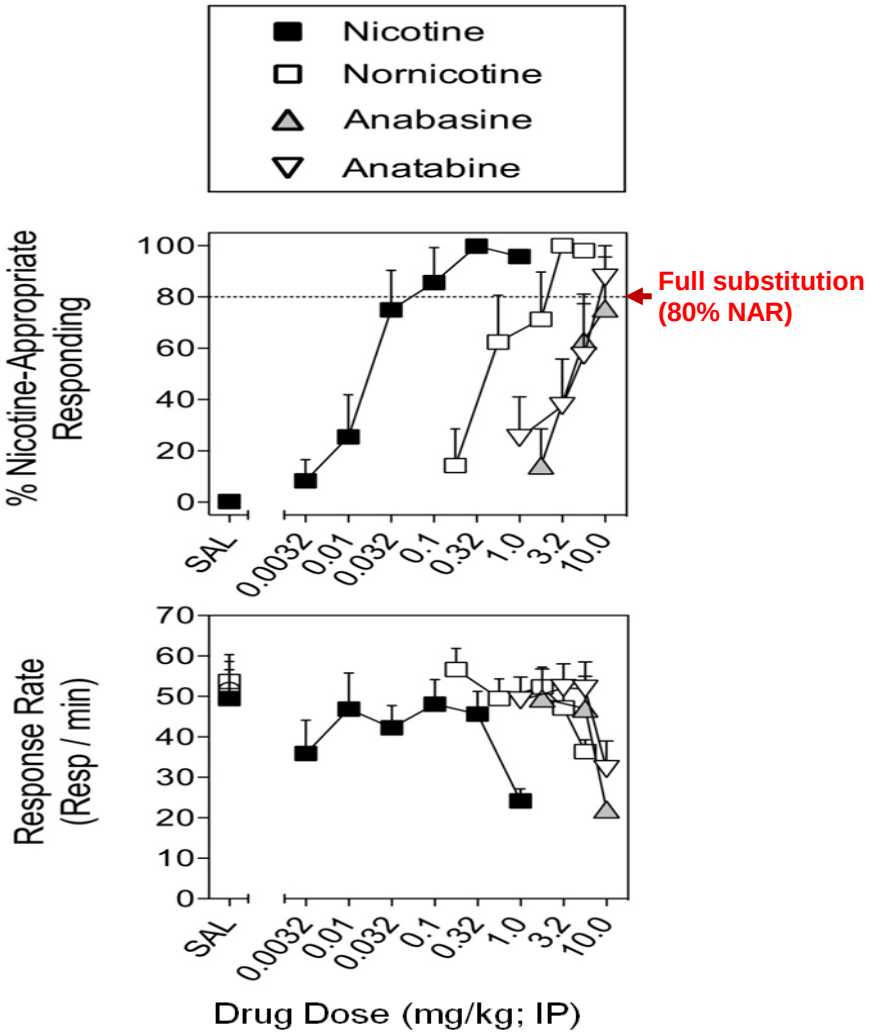
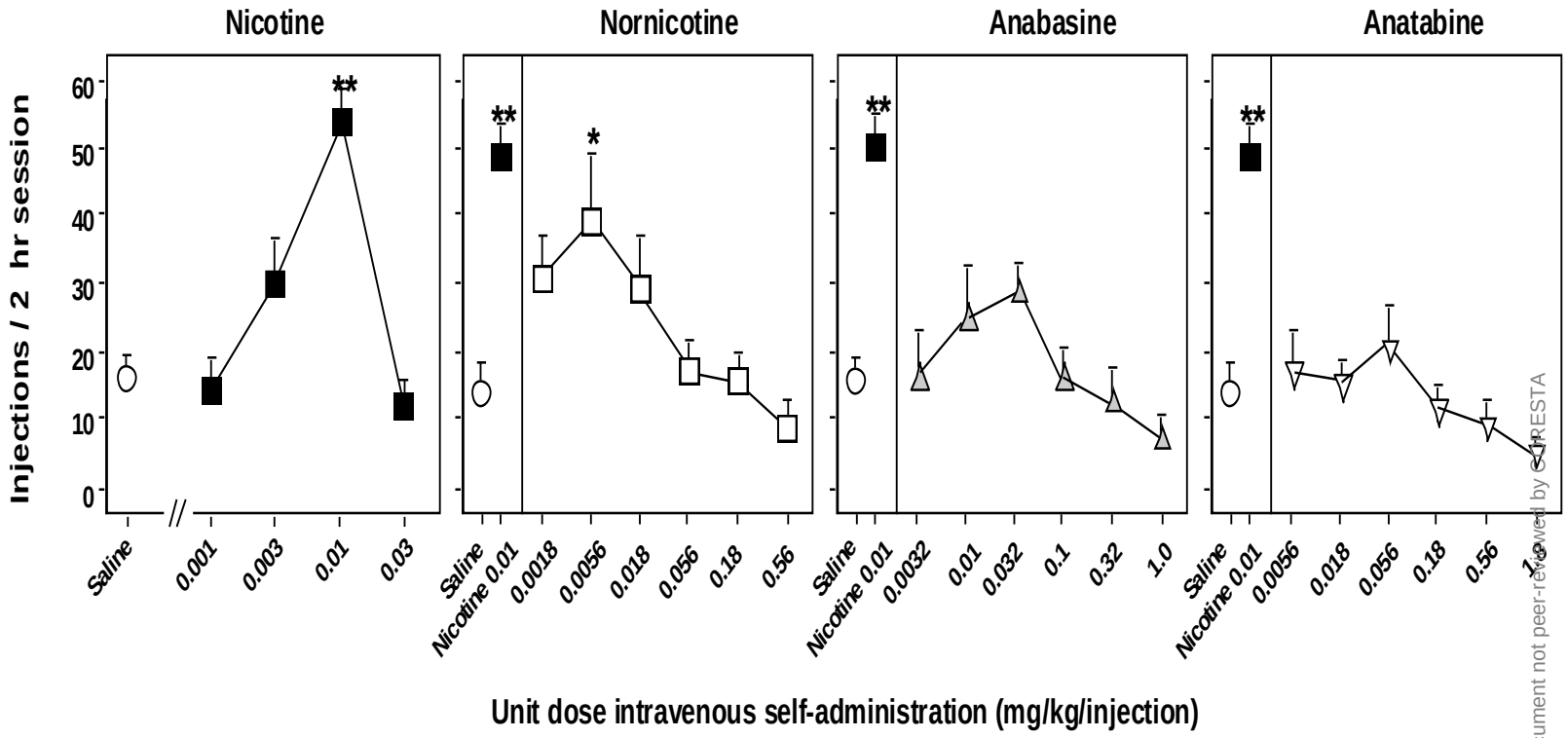
Preclinical Abuse Potential Assessment Methods

Drug Discrimination (Sub.)



IV Self-Administration (Sub.)



Caine SB et al. *Exp Clin Psychopharmacol.* 2014;22:9-22.

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Human Abuse Potential Studies - Summary

Parameter	HAP Studies
Phase of development	Typically, after Phase 2 (establish therapeutic doses)
Key objectives	Evaluate abuse potential & safety (not efficacy)
Study subjects	Recreational drug users experienced w/same pharma class, otherwise healthy, non-physically dependent
Study size & sites	N<100 (depends on drug), single site, typically Phase 1 unit (usually a CRO), controlled lab environment, usually inpatient
Design	Multi-phase, multi-period, single doses, placebo and active-controlled crossover
Doses of new drug tested	Highest therapeutic dose up to 3x (i.e., supratherapeutic)
Outcomes of interest	• Subjective measures (Liking, High, Take Again, etc.) • Safety (AEs), PK & physiological (O2 sat, pupillometry, vitals) • Cognitive & performance

Drug HAP & tobacco product HAL assessment differences (adapted from Sigmon et al. CPDD poster, 2018):

- Tobacco products are **relatively complex** as compared to single component New Molecular Entities (NMEs)
- Traditional AP assessments do not typically evaluate **perceptual effects and appeal** (e.g., advertising, promotions, and other marketing tactics used to increase sales of tobacco products)
- **Blinding:** the complex sensory stimuli of tobacco products presents significant issues in blinding study subjects in clinical evaluations (e.g., taste, smell, and other sensory effects)
- **Dosing:** generally, tobacco products are used ad lib, confounding selection and comparisons of different "doses" of tobacco products (dose may be based on nicotine levels)
- **Translatability:** There are limited data comparing outcome measures (and difference in outcome measures) to "real world" effects and use.
- Selecting an active **comparator** ("usual brand" cig or an alternative comparator) is not standardized – also often use negative control (e.g., nicotine gum) instead of inert placebo

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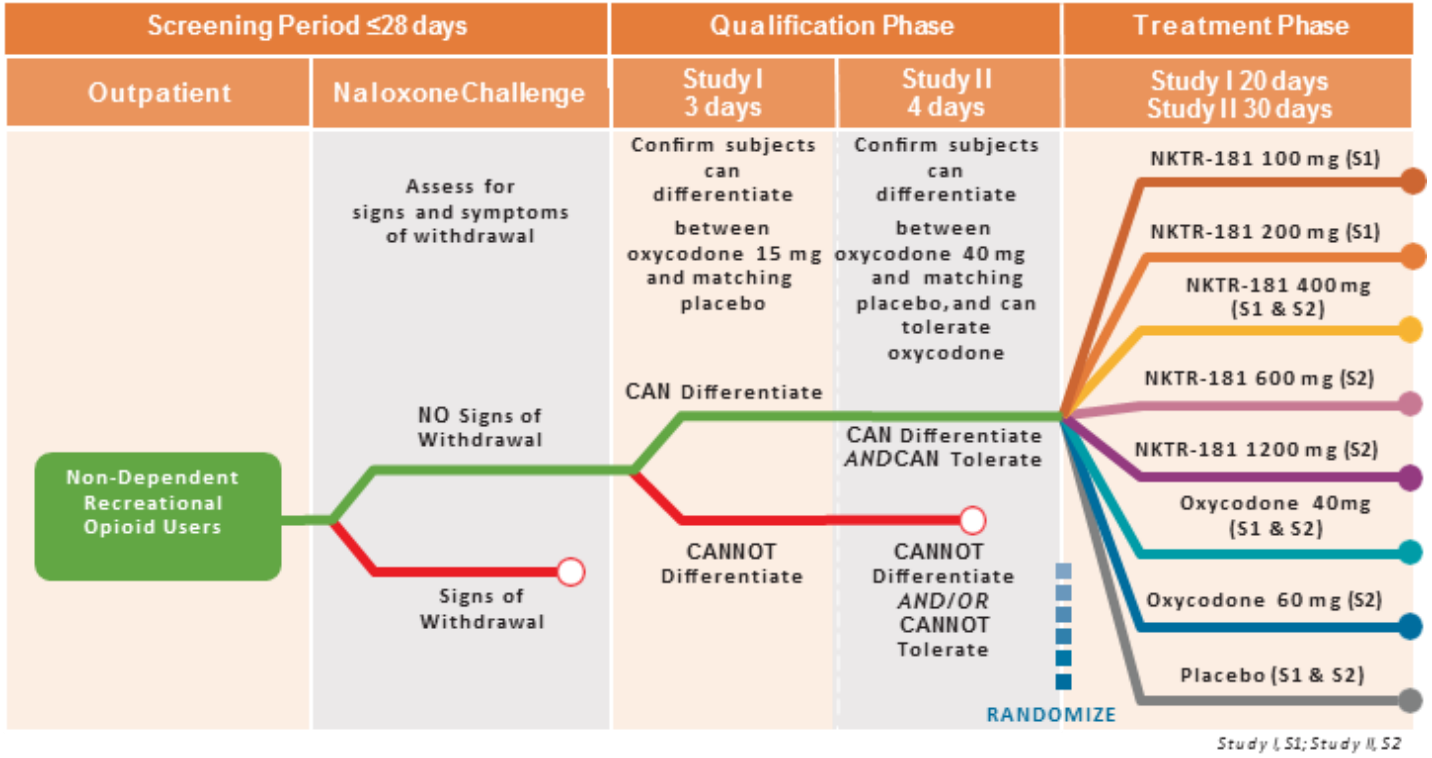
Human Abuse Potential Studies – Methods

- HAP studies are multi-phase, multi-period, single doses, placebo and active-controlled crossover design
- Test highest therapeutic dose up to 3x
- Standard methods are described in FDA's 2017 guidance



Category	Subjective Measure	VAS Type	0–100 mm VAS (0 / 50 / 100)
Balance of Effects	"At this Moment" Drug Liking	Bipolar	At this moment, my liking for this drug is: Strong Disliking / Neutral / Strong Liking
	Overall Drug Liking		Overall, my liking for this drug is: Strong Disliking / Neutral / Strong Liking
	Take Drug Again	Unipolar	I would take this drug again: Definitely Not / Definitely So
Positive Effects	Feeling High		I am feeling high: Definitely Not / Definitely So
	Good Effects		I can feel good drug effects: Definitely Not / Definitely So
Negative Effects	Bad Effects		I can feel bad drug effects: Definitely Not / Definitely So
	Feeling Sick		I am feeling sick: Definitely Not / Definitely So
Other Subjective Effects	Any Effects		I can feel any drug effect: Definitely Not / Definitely So
Sedative Effects	Drowsiness/ Alertness	Bipolar	My mental state is: Very Drowsy / Neither drowsy nor alert / Very Alert

Harris SC et al. *Pain Medicine,* 2016; 17(1):820-831; Henningfield JE et al. CPDD Poster 2018

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Human Abuse Potential Studies – Methods

Figure 2. Time Course of Mean Drug Liking "At This Moment," Mean E_{max}, and Drug Liking AUE Summary Data

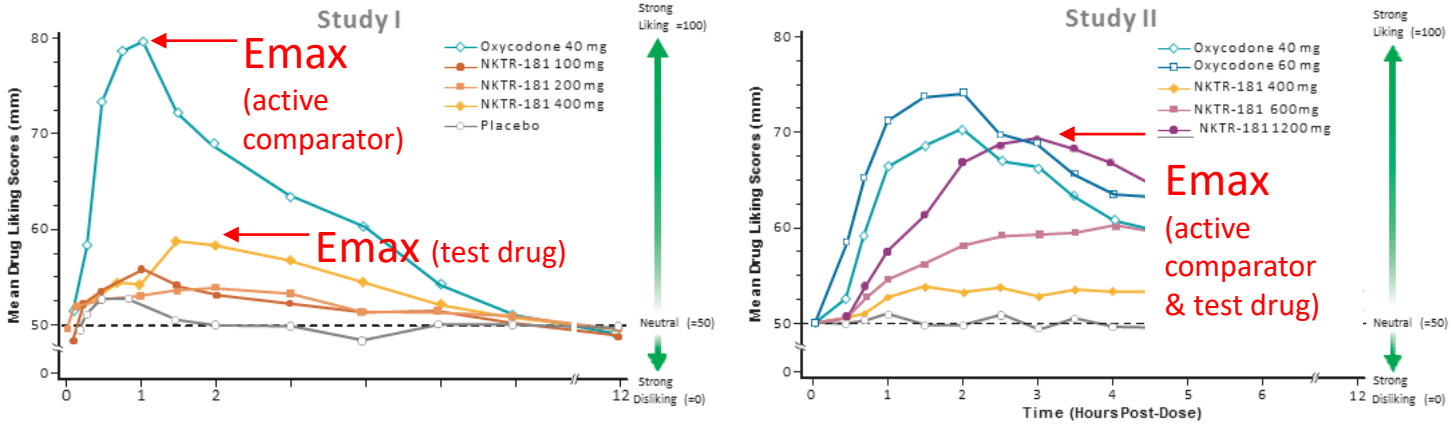
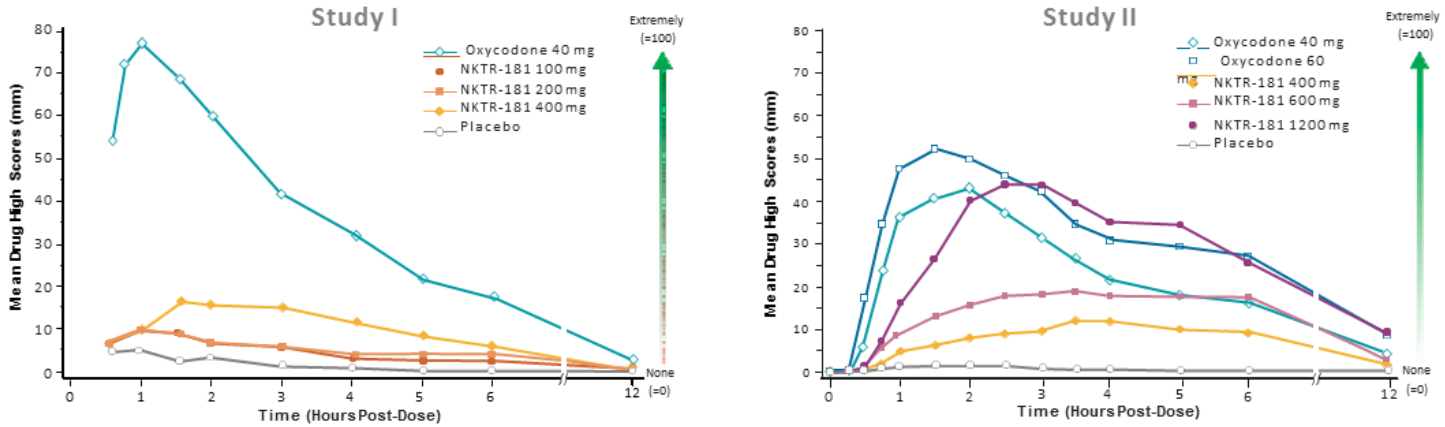
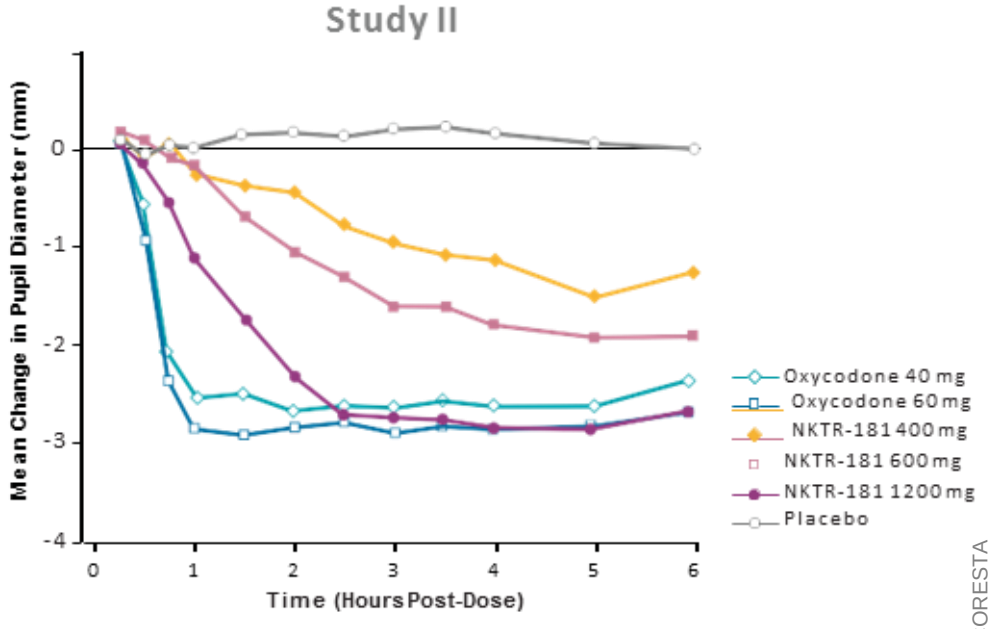


Figure 3. Time Course of Mean Drug High, Mean E_{max}, and Drug High AUE Summary Data



Figures from: Henningfield JE et al., CPDD Poster 2018

Figure 4. Time Course of Mean Change in Pupil Diameter from Baseline



Pre-Toad (psychedelic)

Post-Toad

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Assessment of Abuse Potential in Clinical Trials

FDA Guidance 2017:

"All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes."

- Sponsors should prospectively identify potentially abuse-related **AEs in Phase 2 & 3 studies** that may indicate abuse potential (e.g., ***euphoria, feeling abnormal, hallucinations***) & train investigators and staff to monitor for those events & record details in real-time
  - Goal is to **capture sufficient data** to allow sponsors and FDA to **distinguish signals of abuse potential from other plausible explanations**
- Monitoring for ***drug accountability discrepancies*** (e.g., missing drug) may indicate diversion or abuse
- Conduct post-study MedDRA queries (e.g., Drug Abuse, Dependence and Withdrawal SMQ)

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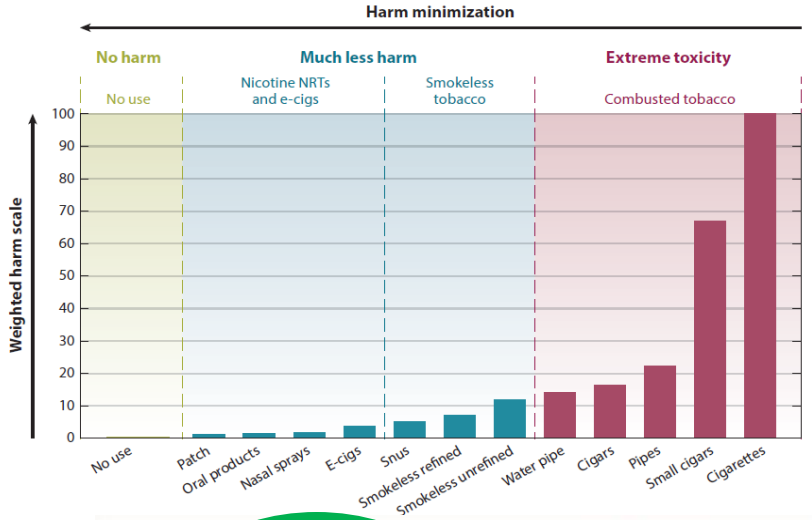
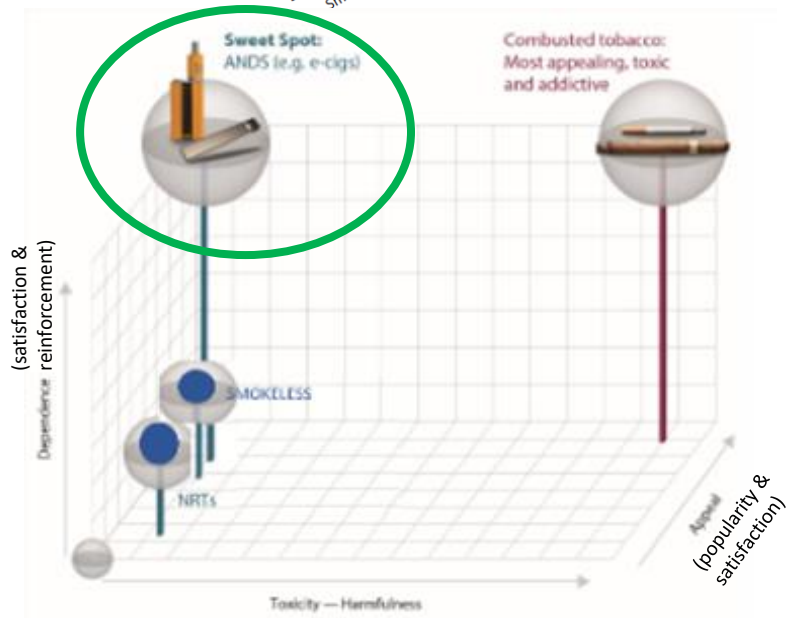
Harm Reduction as it Relates to Abuse Potential

- **Harm reduction** is an approach that attempts to *reduce the adverse consequences of drug use among persons who continue to use drugs*[1]
- Among the best examples are FDA-approved opioid medications for treating OUD – **methadone** and **buprenorphine**
  - Another example: **clean needle exchange programs** (reduce toxicity/infectious disease)
- To develop a safer, less harmful ***substitute*** for a drug of abuse (such as opioids or stimulants), and to promote patient adherence, the product must provide sufficient ***reinforcement*** and ***reduce or eliminate cravings*** – i.e., some level of abuse potential is needed
  - A drug with greater abuse potential or no abuse potential might not be an appropriate substitute
- The same concept applies for nicotine & tobacco products





[1]Single E. *Drug Alcohol Rev. 1995*;14(3):287-90.
Figures from: Abrams DB et al. *Annu Rev Public Health.* 2018;39:193-213.

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Summary and Conclusions

- Long history of drug AP research has led to standardized, reliable, & valid methodologies that are being adapted for tobacco product AL assessments (ALA)
- FDA's 2017 final abuse potential guidance provides important guidelines for pharma industry
- AP assessment of drugs has several notable differences from tobacco ALA, and purpose/goal is to provide information re: scheduling and labeling (e.g., directions for prescribing and use) of approved pharmaceuticals
- Thorough AP assessment requires data from many sources collected throughout drug development, including post-marketing and real-world surveillance of product use/abuse
- Harm reduction approaches & goals are similar for patients (drug abusers) & consumers (tobacco users) who choose to continue using drugs or nicotine/tobacco products
  - In these cases, some level of AP/AL is necessary (how much is debatable)

The science of abuse potential assessment is constantly evolving

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Thank you! Questions?

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