Altreos
Research Partners

Clinical Abuse Potential Assessments: What Can We Learn from Tobacco Research?

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Scientific consulting and writing
Abuse liability, CNS drug development, clinical pharmacology and neuroimaging

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Presenter Disclosure

- Presenter: Megan J. Shram, Ph.D.
  - Director and co-founder of Altreos Research Partners, Inc.

- Relationships with commercial interests:
  - Consultant to various pharmaceutical and biotech companies, and clinical research organizations in the area of CNS drug development and abuse liability/abuse deterrence.
  - Consultant to companies developing new tobacco products, including electronic nicotine delivery systems (eg, e-cigarettes) and very low nicotine (VLN) products, in the area of abuse liability assessment.

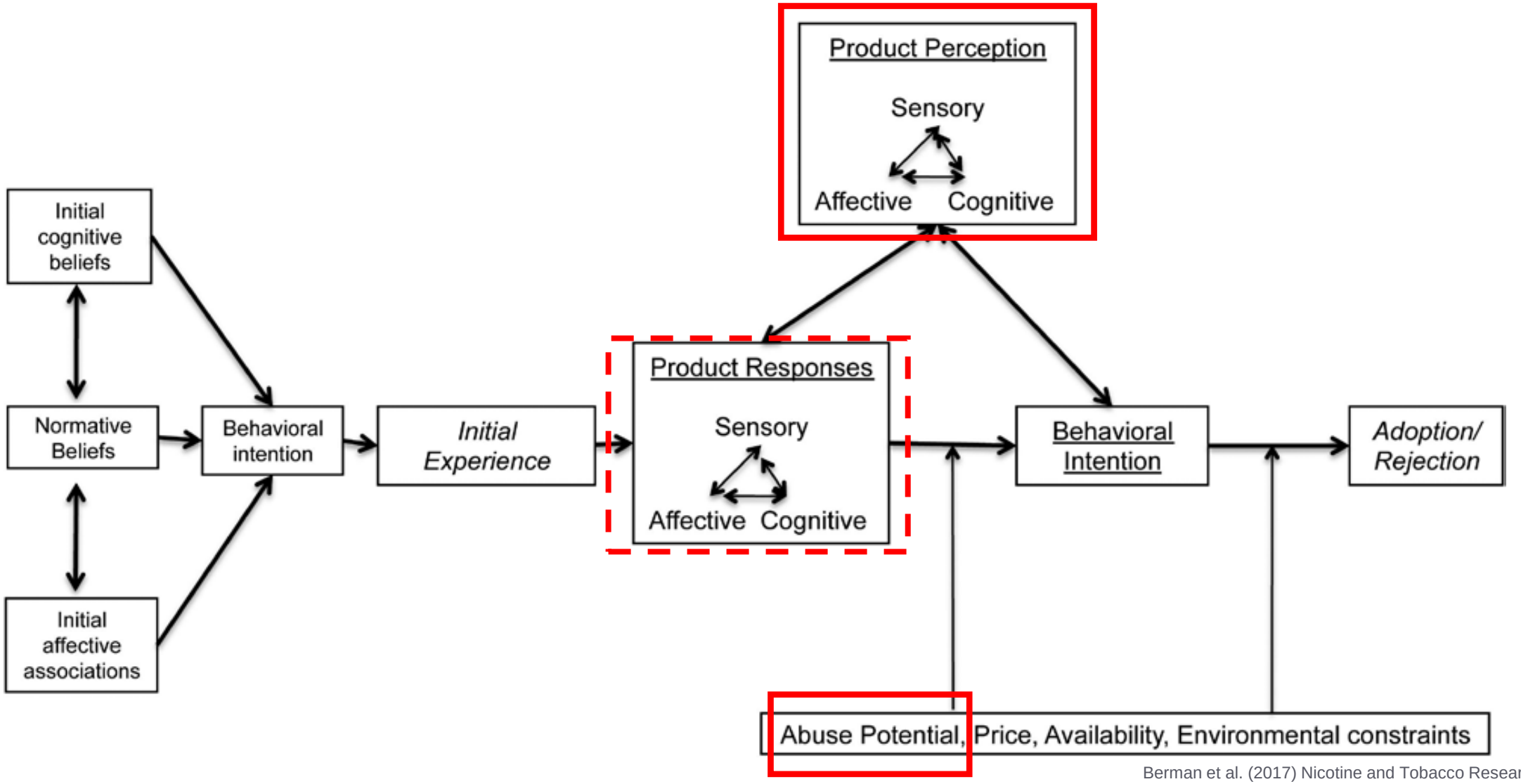
Overview

- Regulatory requirements for new and modified risk tobacco products
- Behavioral intentions: Abuse liability and perceptions of tobacco products
  - Clinical abuse liability
  - Consumer perceptions
  - Behavioral economics: The Experimental Tobacco Marketplace
- Potential application to new chemical entities (NCEs)
  - Compare and contrast of tobacco products vs. new chemical entities

Background

- FDA granted authority to regulate tobacco products under the Family Smoking Prevention and Tobacco Control Act passed in 2009
  - New tobacco products must receive a marketing order from FDA prior to marketing
  - Products must be evaluated, as appropriate, for the protection of the public health
- Three draft FDA Guidances:
  - Modified Risk Tobacco Product Applications (2012)
  - Applications for Premarket Review of New Tobacco Products (2011)
  - Premarket Tobacco Applications for ENDS (2016)
- Guidances outline regulatory recommendations, including assessments of abuse liability and perceptions of tobacco products to understand impact on use

Factors Influencing Behavior and Product Use



Berman et al. (2017) Nicotine and Tobacco Research

Abuse Liability

- …“is the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product… Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently.” (FDA MRTP Guidance)
- Abuse liability of nicotine-containing products is influenced by multiple factors, including:

Pharmacokinetics	Availability	Price
Social Factors (eg, peer use)	Marketing	Environment (eg, other products)

Carter et al. (2009) Cancer Epidemiol Biomarkers Prev.; Henningfield et al. (2011) Drug Alcohol Depend

Consumer Perceptions

- Consumer perceptions of a product are associated with:
  - Attitudes, knowledge, and beliefs about a product
  - Sensory perceptions of and prior experiences with a product.

- Perception is both absolute and relative to other categories of tobacco products

- Both abuse liability and perceptions, as well as other factors, contribute to tobacco product appeal, and potential uptake and continued use.

Abuse Liability: Clinical Assessment of Tobacco Products

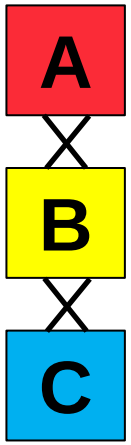
- Objective: To understand abuse liability of product relative to other marketed products
  - Place along a continuum of abuse liability risk
- Randomized, typically open-label, crossover design in tobacco product users
  - Product familiarization period
  - Ad libitum use
  - Controlled and uncontrolled use sessions
- Comparators can include:
  - Combustible cigarette – a “high” abuse liability
  - Nicotine gum – a “low” abuse liability product

Sample Methodology

Stage 1

Ad Libitum Use

- Familiarization
- Amount of product used
- Subjective effects (eg, craving reduction)



Stage 2a

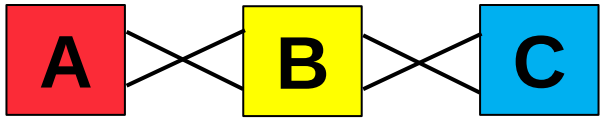
Controlled Use AM

- Single use, pre-specified puffing regimen
- Subjective effects (eg, direct effects)
- Pharmacokinetics

Stage 2b

Uncontrolled Use PM

- Single use, subject's pace
- Subjective effects
- Pharmacokinetics



Stage 3

Product Choice Procedure

- Subject presented with products and must make choice
- Subject uses chosen product ad libitum for up to 30 minutes
- Multiple choice presentations over day

A=E-cigarette; B=combustible cigarette; C=nicotine gum

Subjective Measures vs. Choice Procedure

- Study evaluating cigarettes of varying nicotine content
  - 0.4, 2.4, 5.2, 15.8 mg

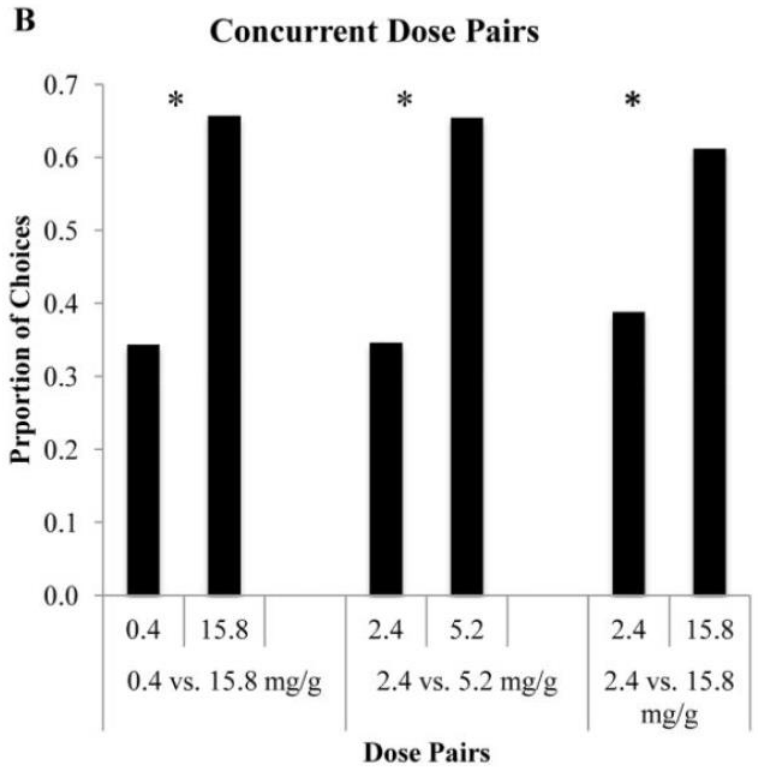
Subjective Measures

- Satisfaction:
  - 0.4 < 15.8 mg nicotine
  - No other differences
- No difference in ratings of:
  - Reward
  - Craving reduction
  - Withdrawal symptom alleviation

Subjective effects and choice behavior can present different picture

Choice Procedure

Cigarettes containing 0.4 and 2.4 mg nicotine chosen less often vs. 15.8 mg nicotine



Higgins et al. (2017) Psychopharmacology

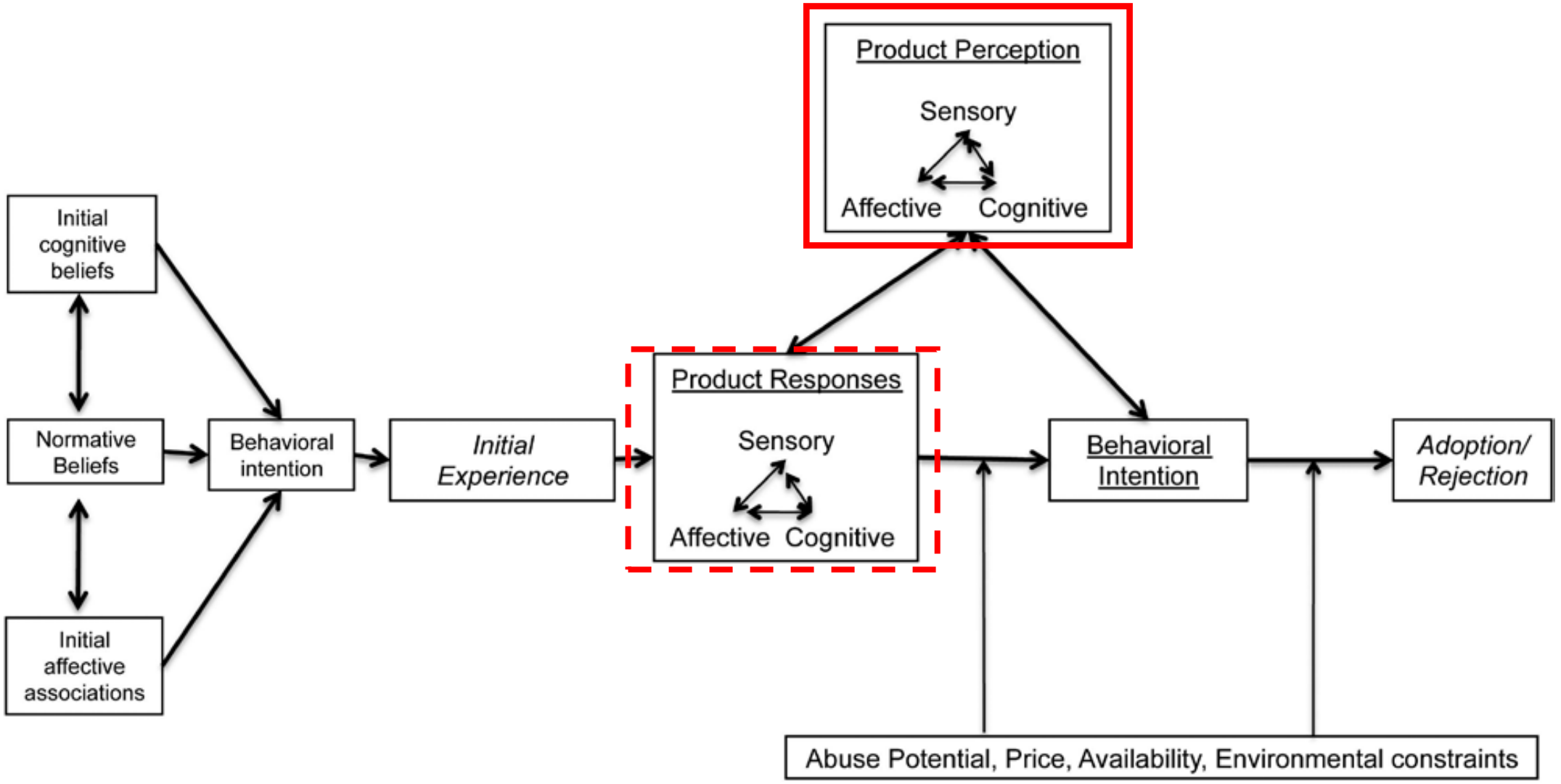
Abuse Liability Measures

- Subjective effects
  - Similar to indirect measures used in human abuse potential studies of pharmaceutical products
- Product choice procedures
  - More direct measure of reinforcement, provides some “real-world” relevance
  - Subjects previously exposed to test and reference products (Stage 1 and Stage 2), therefore have some experience to determine preference
  - Does not address multitude of other products on market, but choice can be made relative to low and high abuse liability products
  - Methodology also used in drug studies, primarily academic, not new!
- Differential responses based on direct and indirect measures

Product Choice Procedure: Application to NCEs/Reformulations and Challenges

- Considers subject choice in controlled environment, focusing on pharmacological/sensory response to products
- However, subjects need to be able to identify the products in order to make the choice (vs. blinded human abuse potential study design)
  - How many sampling sessions needed?
  - Dose selection, particularly of drug with potentially low signal/mixed effects?
  - Previously conducted with drugs of abuse, anorectics, etc. (eg, Johanson and Uhlenhuth, 1980; Chait et al., 1987), results also indicate some dissociation between reinforcing effects (i.e., choice behavior) and subjective effects
- Requires additional stage in or completely separate clinical study
  - Cost, time, practicality?
  - Risk-benefit?

Factors Influencing Behavior and Product Use



Berman et al. (2017) Nicotine and Tobacco Research

Consumer Perceptions of Tobacco Products

- Objective: To understand consumer perceptions of product alone and relative to other marketed products

- Topics of interest:
  - Product “concept”
  - Awareness, attitudes and beliefs (health risks, addictiveness, social acceptability)
  - Appeal, importance of features and design (eg, cost, flavors)
  - Reasons for trial and continued use
  - Health risk warnings and influence on perceptions/intentions
  - Advertising/marketing and influence on perceptions/intentions

Rees et al., 2009 Cancer Epidemiol Biomarkers Prev
FDA, 2016

Consumer Perceptions of Tobacco Products

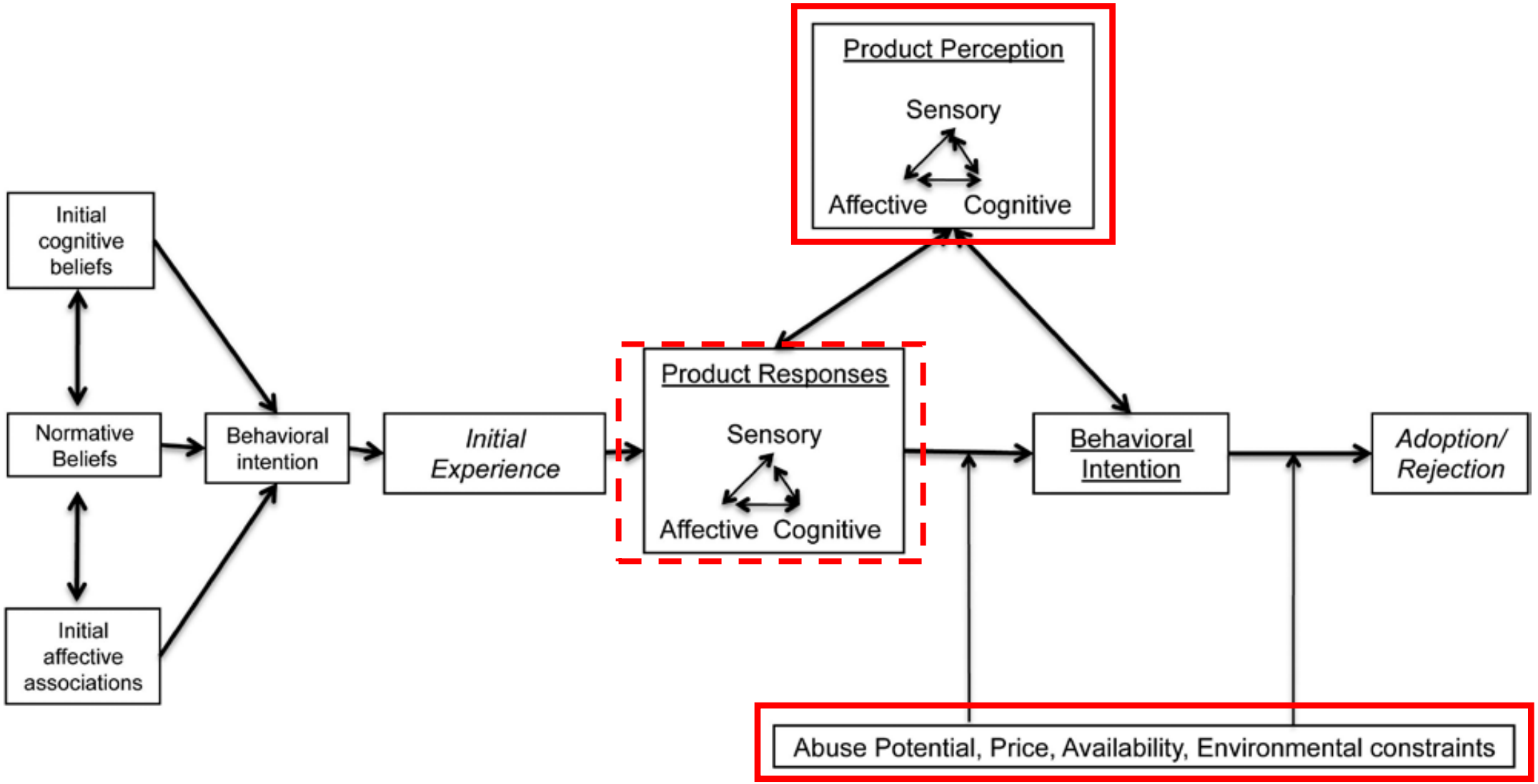
- Methodology:
  - Semi-structured interview-based assessments
  - Focus groups (n=6-10 per group)
  - Surveys (web, telephone, paper)
  - Discrete-choice experiments (stated-preference)

- Field testing to enhance validity of responses
  - Measure perceptions and behavioral intentions before and after product use
  - Responses based on information alone may not reflect response following actual experience (Schneider et al., 2008)

Consumer Perceptions: Application to NCEs/Reformulations and Challenges

- Methods have already been applied to ADFs (eg, Oxycontin; Sellers et al., 2013)
  - Provide theoretical drug information to subjects to gain understanding of perceptions, relative attractiveness
  - Rate and rank variables of interest
  - Allow subjects to tamper with formulations
  - Can assess appeal of formulations, eg, solution vs. tablet
- Application to NCEs
  - Unintended user (vs. assessing perceptions of intended tobacco product consumer)
  - Premarket assessment → lack of experience with drug under development
- Consumer perceptions studies may be more practically applied to reformulations/ADFs rather than pre-market evaluation of NCEs
  - ie, product-specific characteristics of reformulations/ADFs vs. intrinsic abuse potential of the substance

Factors Influencing Behavior and Product Use



Berman et al. (2017) Nicotine and Tobacco Research

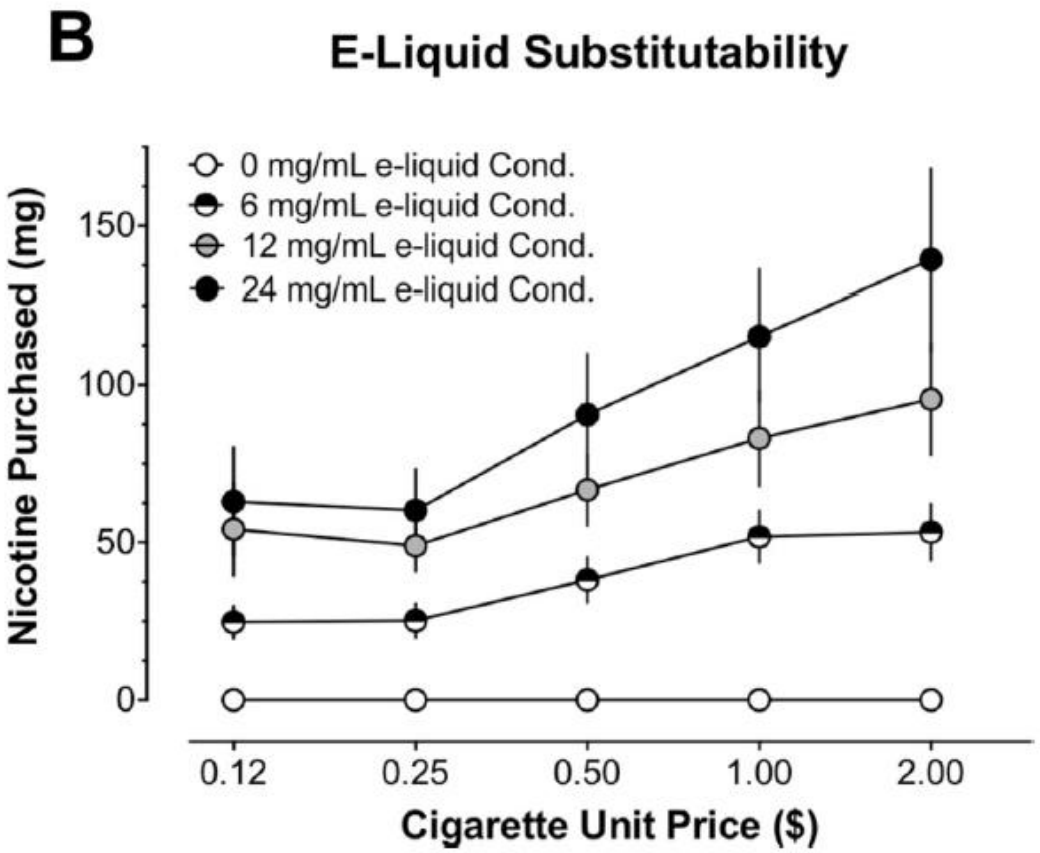
Behavioral Economics (BE)

- Multiple non-nicotine factors influence tobacco use behavior
  - Price, availability, other marketed products, labeling, product characteristics
- BE laboratory assessments can evaluate the effect of such factors on tobacco product consumption and choices (Tidey et al., 2016)
- Two key concepts:
  - Demand elasticity (sensitivity of purchasing to price)
  - Demand intensity (purchasing unconstrained by price)

The Experimental Tobacco Marketplace

- Participants (eg, smokers) provided with experimental income to purchase real-world supplies of new (eg, e-liquid) and existing (eg, cigarette) tobacco products
- Sampling session to gain experience with new tobacco product prior to purchasing experiment
- Potential manipulations:
  - Price and consumer budget
  - Product descriptions (eg, low or high nicotine content; flavors)
  - Availability of other products (multiple concurrent choices)
  - Narratives (eg, reduced exposure to toxins)
  - Consumer characteristics (eg, smoking frequency, risk perceptions, gender)

The Experimental Tobacco Marketplace



Among smokers:

- E-liquid showed nicotine concentration-dependent substitutability for cigarettes
- Snus, dip, nicotine gum or nicotine lozenge did not substitute for combustible cigarette

Pope et al. (2018) Tobacco Control

Behavioral Economics: Application to NCEs/Reformulations and Challenges

- Permits assessment of multiple pharmacological and non-pharmacological factors that influence drug taking behavior
- A more complex approach vs. other methods
  - Interpretation?
  - Practicality of “real” purchasing task with investigational drug?
- Will results have potential to shift over time with changes in market, price, other drugs, etc.?
  - How would this impact scheduling and labeling?
- Simplified version (theoretical money vs. drug choice procedure) has previously been implemented directly in human abuse potential studies

Overall Summary

- Product effects, consumer perceptions and other factors can influence tobacco product use/intentions
  - These factors also apply to drug abusers and their choices
- Multiple methods can be utilized to evaluate pharmacological and non-pharmacological factors associated with tobacco product use
- Together, results of such studies can inform on the risk to public health of a specific new tobacco product, both absolute and relative to currently marketed products

Implications for Pre-market Assessment of NCEs

- Tobacco products are consumer products intended to be used for “satisfaction” vs. NCEs, for which potential abuse is an unintended consequence
- Several tobacco products (eg, e-cigarettes) are already marketed, and consumer perceptions of new products are much more readily assessed “in situ,” as has been done for decades
  - How do these methods apply to a NCE at the pre-market stage?
- Product Choice Procedures
  - Provide some “real-world” relevance in a controlled environment
  - Some observed dissociation between subjective responses and choice behavior in tobacco and drug literature suggests additional supportive assessment may be useful
    - ie, determining relative (schedule placement) vs. absolute (scheduling vs. no scheduling) abuse potential
  - Implementation would likely require separate, fairly lengthy, clinical study

Implications for Pre-market Assessment of NCEs

- Consumer perceptions
  - Useful in assessing perceptions of reformulations/ADFs (vs. NCE) among drug abusers
  - Addition of single-trial period could provide more meaningful outcomes based on actual experience with product
- Behavioral economics:
  - Fairly complex procedures/analysis, with currently unknown function in assessing intrinsic abuse potential of drug, eg, with weak/mixed effects (for scheduling purposes)
  - Other, simpler options previously implemented directly in human abuse potential studies
- Implementation should consider goal of assessment
  - Scheduling is based on intrinsic abuse potential of a substance, outside the shifting marketplace and fads
  - Differential labeling opportunities?