Challenges of Abuse Liability Evaluation During Drug Development and Approval Of New Compounds

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Outline

• Introduction
  Speakers

• Why Drug Abuse Liability at NESOT?

• What constitutes “Abuse Potential/Liability”?

• Why is the pharmaceutical industry concerned with abuse potential and liability?

• What does the pharmaceutical industry have as its challenges regarding drug development and abuse liability?
Speakers

• Richard Alper, Global Safety Pharmacology, Pfizer Inc
  – Introduction to Abuse Liability Assessments in Drug Safety/Toxicology: Perspectives from Industry

• Steven Negus, Dept of Pharmacology and Toxicology, VCU
  – Preclinical Approaches to Abuse Liability Assessment

• Roger Weiss, Dept of Psychiatry, Clinical Director, Alcohol and Drug Abuse Treatment Program, Harvard/McLean Hospital
  – Treatment of Substance Abuse Disorders

• Michael Klein, Controlled Substances Staff, FDA
  – Abuse Liability Assessment: FDA Perspective
Why this symposium at NESOT?

- **Toxicology**: the study of the adverse effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects [SOT]

- **Addiction**: a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences [NIDA]
  - Treatments for addiction are considered Drug Discovery
  - To understand the likelihood that a new drug can lead to addiction (i.e. an adverse effect) and/or abuse is now generally considered Drug Safety
    - Most in the industry include Safety Pharmacology within Drug Safety along with the more standard Toxicology disciplines
    - Have been discussions in regulatory guidelines around the issue of GLP
Why is abuse liability assessment important?

– Commitment to protecting and improving public health
– Regulatory requirements
  • Increased attention to this topic by regulatory agencies around the world
– Many novel CNS targets
– Abuse liability represents a risk to the development portfolio
  • Absence of abuse potential may represent a commercial benefit
  • May lead to project delay or termination
    – Costly in terms of time and money
    – Potential to delay product introduction due to negotiations with Authorities
    – Delayed project termination if early “signals” cannot be interpreted clearly
  • Added cost/complexity in inventory management, distribution, risk management programs for marketed controlled substances
  • Increased complexity in physician prescription process (limited # refills etc.)
Regulatory Environment: US

- **US Controlled Substances Act of 1970**: Levels of Drug Control: Schedules I – V
  
  I. Heroin, LSD, marijuana – no accepted medical use
  
  II. Amphetamines, methylphenidate (Ritalin®), opioids including morphine – high potential for abuse and can lead to severe psychological and physical dependence
  
  III. Ketamine, Tylenol® with codeine, dronabinol (Marinol®) – less potential for abuse and may lead to some psychological or physical dependence
  
  IV. Benzodiazepines (diazepam, Valium®; zolpidem, Ambien®), sibutramine (Meridia®) – less potential for abuse and limited risks of dependence
  
  V. Dilute narcotic preparations (Lomotil®), pregabalin (Lyrica®) – low potential for abuse and continued use may lead to limited dependence
Abuse potential and liability

Prescription drugs are abused or used for **nonmedical** reasons (“reward” and subjective feelings such as euphoria)

Prescription drugs can lead to physical dependence and withdrawal

Prescription drugs can produce hallucinations (animal models?)

Examples of drug categories associated with abuse
- Opioids
- Benzodiazepines
- Barbiturates
- CNS stimulants
- Cannabinoids
- Anabolic steroids
Abuse potential and liability

• Preclinical studies evaluate abuse potential of a compound
  – Explore situations in animals you cannot evaluate in humans (high doses, IV administration, antagonist-precipitated withdrawal)
  – Can be misleading (i.e. doses required to produce reward might produce adverse effects humans that are not detected in animals, such as dizziness, nausea and emesis)

• In early clinical trials, assess the pattern of adverse events
  – Focus on CNS adverse events such as euphoria, mood elevation

• Clinical studies designed specifically to assess abuse liability in drug abusers

• Long-term clinical studies can include end-points to assess physical dependence and withdrawal

• Postmarketing experiences can also lead to scheduling
Pre-clinical abuse potential strategy development

• One size does NOT fit all
• Work with the project team to develop a comprehensive strategy to assess abuse liability
  – Review
    • Marketing/commercial considerations
      – competitors
    • Indication
      – “guilt by association” (e.g. ADHD, insomnia, anxiety)
    • Target/mechanism of action
      – Novel CNS
      – Known target associated with drugs of abuse
      – Species-specific target expression
    • Literature
    • In-house data (*in vitro* and *in vivo*)
      – Pharmacokinetics (species variations in metabolism)
      – Receptor binding/functional profile (secondary pharmacology)
      – Behavioral effects (increases in locomotor activity)
    • Clinical experiences
      – Available only at later stage of development
Relevant Targets

- Dopamine receptors and transporter: stimulant effects
- μ-Opioid receptors: morphine-like effects
- 5-HT$_{2A}$ receptors: hallucinogen effects of agonists such as LSD
- Cannabinoid CB$_1$ receptors: marijuana ($\Delta^9$-THC)
- GABA/benzodiazepine receptor complex: CNS depressant effects
- NMDA receptors: phencyclidine-like effects
- Neuronal nicotinic acetylcholine receptors: tobacco products
- Novel mechanisms
Drug Self-Administration

**Question:** Is the NCE reinforcing, and how does it compare to known drugs of abuse?

Animal trained to respond on a lever for a compound with known abuse potential (e.g. cocaine)

↓

Test drug substituted for the training drug

↓

Does responding continue?

(Positive signal: dose with significant increase in drug infusions compared to vehicle)

↓

Responding on a progressive ratio (how many times will the rat press for one drug infusion) can give an indication of reinforcing efficacy vs. standards
Drug Discrimination

Question: Is the NCE perceived as similar to known drug of abuse?

Animal trained to respond on a lever to obtain food

Administered drug/vehicle prior to session

when drug stimulus perceived, must press one lever to obtain reward
when no drug stimulus perceived, must press alternative lever

% cocaine-appropriate responding

mg/kg i.p.

- cocaine
- U50488 (kappa agonist)
- amphetamine

training
**Physical Dependence & Withdrawal (PD&W)**

**Question:** Does discontinuation of NCE administration result in a withdrawal syndrome?

- Chronic compound administration (typically 2-4 weeks)
- Cessation of drug administration (spontaneous or precipitated withdrawal)

- Monitoring of behavioral and physiological parameters throughout both treatment and withdrawal periods
- Choice of endpoints driven by pharmacological class of NCE where possible
- Appropriate positive control included to validate chosen endpoints
Clinical Evaluation of Abuse Potential

• Components
  – Spontaneous reports of adverse events suggestive of abuse (Euphoria, other CNS AEs)
  – Assessment of medication discontinuation or withdrawal effects (evidence of physical dependence)
  – Assessment of the development of tolerance
  – Clinical Pharmacology/ Human Laboratory Study in drug abusers
Challenges

• Which compounds require an assessment?
  – Any mechanism affecting the CNS
    • not only psychotherapeutic drugs!!!
  – Compounds for “at-risk” indications (ADHD, anxiety)
  – Other evidence, i.e. AE reports of euphoria, etc

• When should preclinical and clinical assessments be complete?
  – Regulatory Agencies: Prior to filing of NDA
  – Industry
    • Preclinical: No later than end of Phase II
    • Clinical: No later than submission of the NDA (i.e. during Phase III)

• What assessments are needed?
  – Develop strategy on case-by-case basis

• What constitutes a positive signal that may lead to scheduling of a product?
  – Subjective decision based on totality of data

• What is the impact of scheduling?
  – Commercial viability, manufacturing, distribution, and prescribing practices
## Impact of Scheduling

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Summary

- Abuse liability assessment cannot be made upon results from a single measure or study (aggregate data needed)

- Current understanding of pre-clinical models does not allow to predict level of scheduling

- Clinical experiences can trump all
  - Reports of euphoria

- Final scheduling is determined by the Drug Enforcement Agency (Department of Justice) following scientific review and recommendation from the FDA and the Controlled Substances Staff (CSS)
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