

Clinical studies of abuse
deterrent opioid analgesics:
*Definitions, current approaches, and
critical issues*

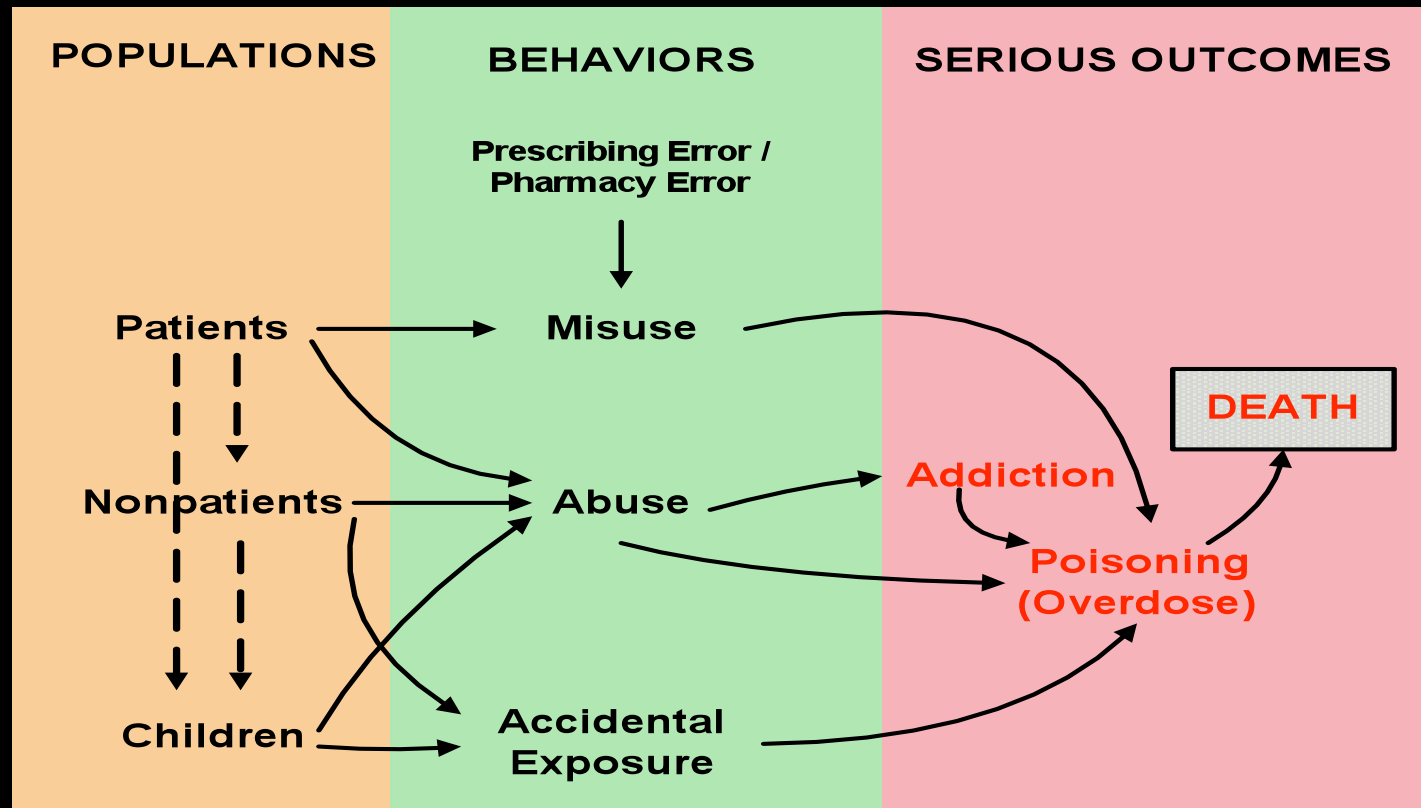
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Topics

- **Phenomenology:** What problems are we trying to deter?
- **Drugs:** Is “abuse deterrence” a property of a drug?
- **Terminology:** What words best label these problems?
- **Evidence:** What types of evidence persuade us about abuse deterrence?
- **Studies:** What methodological challenges arise in conducting these studies?

Relationships Between Misuse, Abuse, Diversion & Overdose

DIVERSION



Reasons for fatal & nonfatal exposures TESS 2004

REASON	NUMBER	%
<i>Fatal</i>		
Therapeutic error	41	3.5
Unintentional misuse	4	.34
Abuse	151	12.8
<i>Nonfatal</i>		
Therapeutic error	222644	9.4
Unintentional misuse	96124	3.9
Abuse	45562	1.9

Alcohol-opioid co-ingestion

- NMU of Rx opioids about 5x more likely among college students with alcohol dependence
- About 1/25 college students report past yr co-ingestion of alcohol with Rx opioids (40% reporting 3 or more episodes)
- Over half (56%) of those with current Rx opioid disorder have current alcohol dependence
- Nearly half of those diagnosed with alcohol dependence were prescribed opioid medications in one-year period
- 50/250 drug overdose deaths in Palm Beach County due to co-ingestion of alcohol with Rx opioids

Opioid attractiveness scale

Intrinsic drug properties

- Ease of extractability
- Rapidity of onset
- Duration of effect
- Presence of impurities
- Ease of hiding

Extrinsic drug properties

- Price
- Availability
- Availability of alternatives
- Stigma



Terminology

Consensus

- Tolerance
- Physical dependence
- Addiction
(dependence)

No consensus

- Misuse
- Abuse
- Diversion

Misuse

- “the use of any drug in a manner other than how it is indicated or prescribed” (Butler et al, Pain, 2007)
- “An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic or euphoric effect.” (Watson et al, Toxicology, 2005)
- “Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not” (Katz et al, CJP, 2007)

Abuse

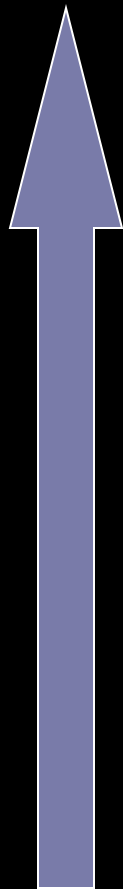
- “the use of any substance when such use is unlawful, or when such use is detrimental to the user or the others.” (Butler et al, Pain, 2007)
- “the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect.” (Watson et al, Toxicology, 2005)
- “Any use of an illegal drug; the intentional self-administration of a medication for a non-medical purpose such as altering one’s state of consciousness, eg, getting high” (Katz et al, CJP, 2007)

Abuse: DSM-IV-TR

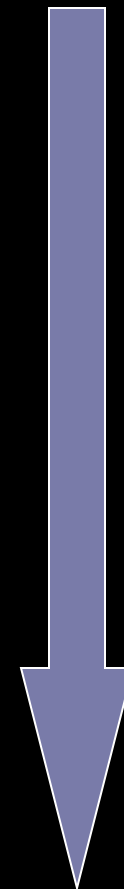
- *“a maladaptive pattern of opioid use leading to clinically significant impairment or distress occurring in any of the following areas, within a 12-month period.*
 - *Failure to fulfill major job obligations at work, school, or home*
 - *Recurrent opioid use in hazardous situations, such as driving or operating heavy machines while impaired*
 - *Opioid-related legal problems*
 - *Social and interpersonal problems caused by or exacerbated by opioid use*

Abuse Liability: Levels of evidence

Internal
Validity



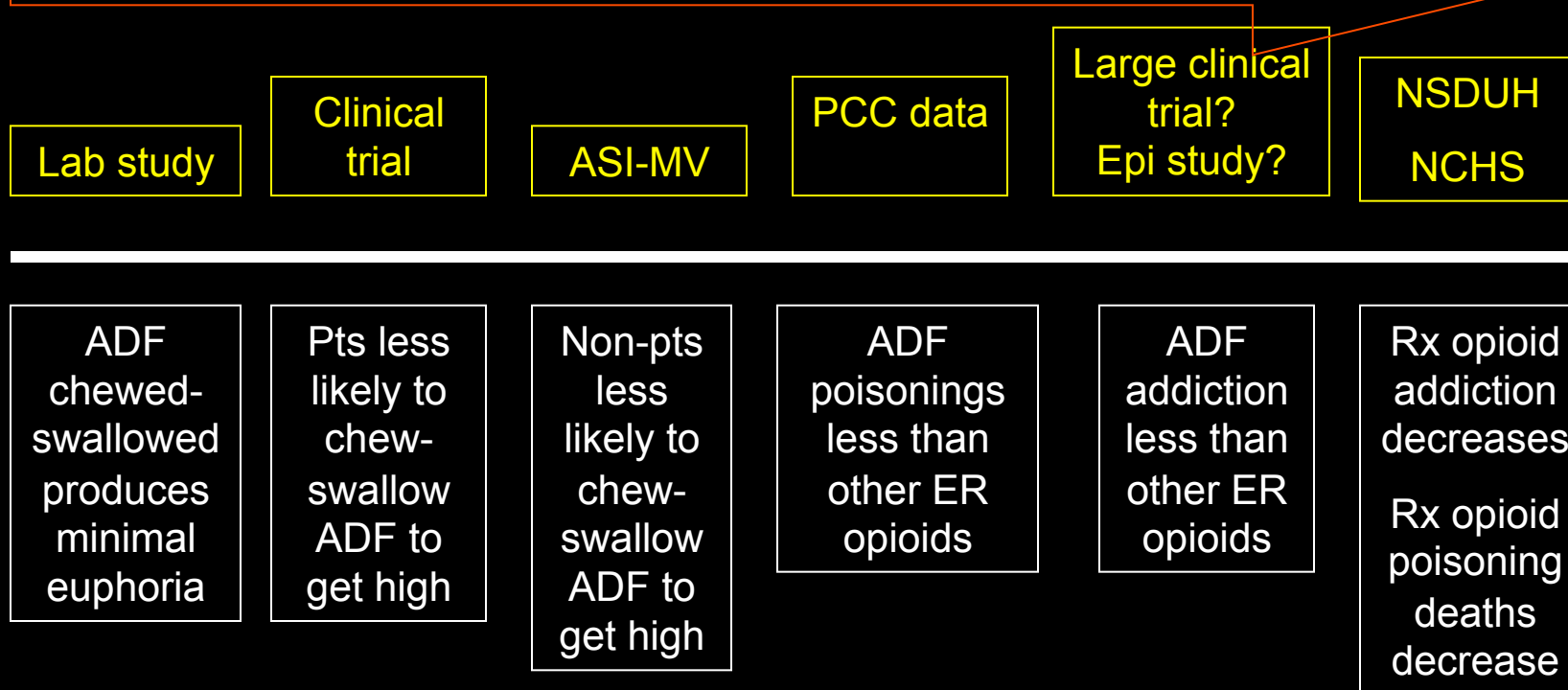
- In vitro extractability
- Preclinical studies
- Human laboratory abuse liability studies
- Human “kitchen chemistry” studies
- Clinical trials
- Epidemiology



External
Validity

Likelihood of demonstration of benefit is related to how closely the outcome measure is connected to the properties of the drug

More clinically relevant.....less likely to be positive.....



Abuse studies checklist

- Construct: what are you trying to measure?
- Measure: is your measure of that construct valid? Do you know what a CID is?
- Population: implications for generalizability? For sample size?
- Exchangability: are your groups comparable?

Human abuse liability studies

- Main focus tends to be euphoria under different treatment conditions
- Unclear predictive validity for “real-world” drug abuse
- Validity of commonly used measures unclear
- Target population rarely if ever studied

Clinical trials for analgesia

- Prospective measures related to abuse rarely implemented
- Appropriate method for deriving predictive measures of abuse from AEs unclear (unlike PUBs or CV events)
- High-risk patients typically excluded

Clinical trials for abuse

- Few precedents exist
- Need to choose which construct to measure
- Unclear which measures to choose; none validated in active vs. active studies
- Sample size requirements unclear
- Impact of study population on (1) generalizability of results and (2) sample sizes are unclear

Measures

- COMM
- PMQ
- PDUQ
- DSM-based measures
- Urine drug screens
- Aberrant behaviors (ABC)
- “Ambiguous drug handling events”

Epidemiologic Studies

- Multiple types: claims data, observational studies, surveillance systems, etc.
- Are groups exchangeable?
- Choice of outcome measures
- Sampling frame
- Generalizability

Conclusions

- Clinical studies of “abuse-deterrent opioids” need to define exactly what outcome (construct) they are trying to measure
- If the purpose of the study is to define some property of the drug, the design should avoid confounding by “extrinsic factors” that influence the extent or manner of abuse of that drug
- Persuasive demonstration of benefit requires a “mosaic” of studies
- Demonstration of benefit requires connecting study outcome measures to properties of the drug
- Multiple types of studies are feasible and precedents exist, but require careful methodological choices
- We have to be thoughtful about setting the bar higher for ADFs than for other classes of drugs