Classification of Abuse-Related Events in Analgesic Clinical Trials: Recommendations and Research Agenda

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Issues

- What constructs/classification system are appropriate?

- What measurement approaches are appropriate?

- What are the primary purposes to which these measures are put?

- Which measurement approaches should be used under which circumstances?

Types of Constructs

- Behaviors/observations/adverse events
- Disorders/diseases
- Diversion
- Tampering

Approach:
- Use existing terms/definitions when possible
- Use or adapt existing classification systems when possible

AAPCC Classification

- Unintentional general
- Environmental
- Occupational
- Therapeutic error
- Unintentional misuse
- Bite/sting
- Food poisoning
- Unintentional unknown

- Suspected suicidal
- Intentional misuse
- Intentional abuse
- Intentional unknown
- Contaminant/tampering
- Malicious
- Withdrawal
- Adverse reaction

Tampering and route of administration are captured

Bornstein et al 2007

Table 3. Clinician versus PCC ratings of prescription opioid intentional exposure cases[2], and (percent agreement), fourth quarter 2002 through second quarter 2004

$n = 4{,}321$

Clinician	PCC					
	Abuse	Misuse	Suicide	Withdrawal	Int. Unk.[1]	Total
Abuse	577	67	174	22	75	915
	(62.92)	(10.44)	(8.01)	(29.73)	(14.51)	
Misuse	19	188	39	3	32	281
	(2.07)	(29.28)	(1.80)	(4.05)	(6.19)	
Suicide	22	12	1125	0	44	1203
	(2.40)	(1.87)	(51.82)	(0.00)	(8.51)	
Withdrawal	4	1	0	47	0	52
	(0.44)	(0.16)	(0.00)	(63.51)	(0.00)	
Int. Unk.[1]	295	374	833	2	366	1870
	(32.17)	(58.26)	(38.37)	(2.70)	(70.79)	
Total	(100.00)	(100.00)	(100.00)	(100.00)	(100.00)	4321
	(917)	(642)	(2171)	(74)	(517)	

Weighted Kappa Coefficient: 0.44   95% Confidence Limits: 0.42–0.46

[1]Int. Unk. = Intentional unknown/insufficient data for further categorization.
[2]Prescription opioids included: buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone extended release, other oxycodone.

Smith M et al, 2006

Intentional misuse

- 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.

Intentional abuse

- An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included.

Substance-Related Disorders

- DSM Substance Use Disorders
  - Substance Dependence and Substance Abuse
- Alternative 1
  - ASAM/APS/AAPM Addiction
- Alternative 2
  - DSM-V Addiction
- Specify Drug Relationship
  - Drug-specific (e.g. alcohol or opioid)
  - General
  - Polysubstance

DSM-4-TR

Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance

(2) withdrawal

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Substance Abuse

- *"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*

Diversion

- The intentional removal of a medication from legitimate distribution and dispensing channels
  - Can be operationalized based on Purdue approach

Katz N, et al, Clinical Journal of Pain, 2007

Tampering

- Route/method
  - IV, nasal, chewing/swallowing, smoking, other
  - "Successful" or not

Recommendation: Clinical Classification Proposal

- Therapeutic error
- Unintentional unknown
- Suspected suicidal
- Intentional misuse
- Intentional abuse
- Intentional unknown
- Contaminant/ tampering

- Malicious
- Withdrawal
- Adverse reaction
- Addiction (abuse or dependence)
- Diversion
- Specify drug(s) or polysubstance
- Tampering (type)

Other potential constructs

- Baseline risk for abuse in study sample
- Subjective effects (euphoria, high)
- Craving
- Others?

Baseline risk for abuse in sample

- SOAPP
- COMM
- SISAP
- History
- Physical exam
- Urine drug screen

Recommendation

- In analgesic clinical trials where the analgesic has any abuse potential, the baseline risk of the study sample for developing abuse-related complications should be characterized.

- The recommended approach is to simply capture personal hx of substance abuse, of abuse of the drug class being studied, of mental illness, and family hx of substance abuse, and quantitative urine drug screen

- Specific instruments can be added

Liking in opioid pain studies

Responses to the drug liking index suggested that active placebo was preferred to morphine, but the difference was not statistically significant (p=0·08). 4 patients (8·7%) reported drug craving for morphine and 2 (4·3%) for placebo. All patients appeared compliant with their dosing regimens and interview with others in the domestic environment did not suggest drug-seeking behaviour.

Moulin D, Lancet, 1996

ARCI/MBG in people with pain who did vs. did not develop addiction

Figure 1: Mean score of the modified 46-Item ARCI MBG subscale between cases and controls

Bieber C et al, J Clin Exp Psychopharm, 2008
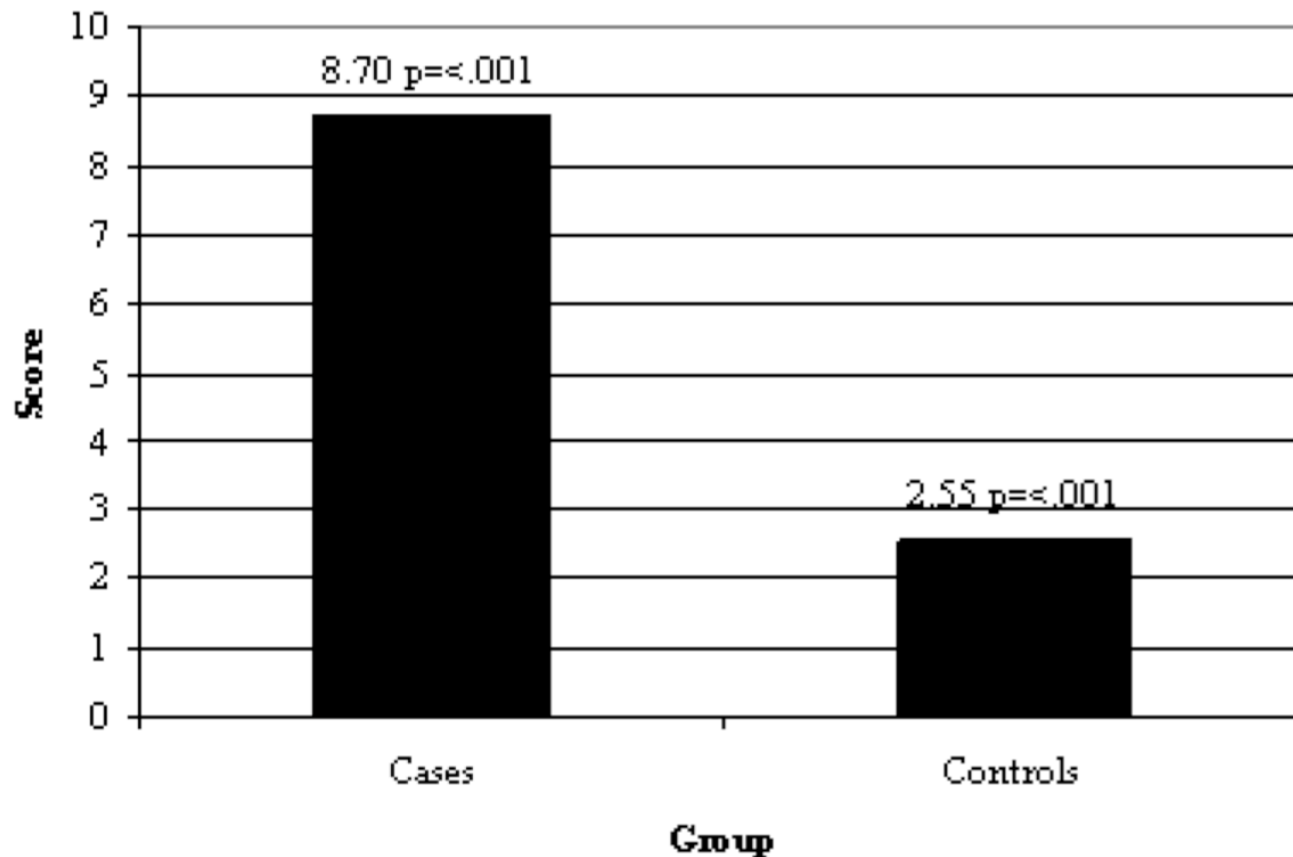
Recommendation

- In clinical trials where abuse-related phenomena are important, subjective experience of individual drug doses should be studied for exploratory and research purposes

- There are limited data on the best approach or interpretation of available measures

"Craving" in in people with pain who did vs. did not develop addiction

Item	Case		Control		p-value
Please rate how strong your desire was to use prescription opioids	6.40	2.817	3.30	3.164	0.002
Please rate how strong your urges were for prescription opioids when something in the environment reminded you of it	6.65	2.681	1.20	2.142	$\leq$0.001

Five approaches to comparing abuse-related phenomena

1. Ad hoc sorting of AEs (e.g. Fentora)

2. Standardized sorting of AEs (e.g. SMQ)

3. Expert classification of retrospective data (e.g. C-CASA)

4. Expert classification of retrospective + prospective/prompted data (e.g. Purdue)

5. Prospective evaluation of key outcomes using validated instruments (Haythornthwaite)

Recommendations

One or more of the following approaches should be considered for each clinical trial in which abuse-related outcomes is important:

- Drug Abuse Dependence & Withdrawal SMQ (supportive)

- Ad hoc **structured** query for key outcomes of interest in individual studies with clear and transparent methods (e.g. tampering) (supportive)

- Use structured query to pull cases for expert adjudication according to Clinical Classification (C-CASA)

- Create a prompted CRF for events of interest with expert adjudicated classification using Clinical Classification

- Prospective structured investigation and adjudication of diversion events

- Prospective use of validated instruments for relevant key constructs

Recommendations

- The choice of methods to evaluate abuse-related outcomes should be fit to the purpose of the method. Examples:

  – Objective of the study

  – Early-phase vs. late-phase development

  – Putative abuse-deterrent opioid vs. standard abusable opioid

  – New analgesic with potential abuse liability

  – New formulation with potentially higher abuse liability than standard

  – Whether a regulatory claim will be sought

Recommendations

- Drug Abuse Dependence & Withdrawal SMQ, or fully described and tested ad hoc structured queries, should be considered for the purpose of identifying case records for further review (to support other methods)

- The use of AE query based approaches as **measures** of any abuse-related phenomenon should be considered exploratory and require validation

Recommendations (2/2)

- For CLAIMS, prospective use of a validated measure is required

- If you don't have one, develop one

- Options include:

  - Patient-reported measure

  - Observer-rating scale

  - Laboratory test

  - Combination

Research Agenda

- Validate and refine SMQ for Drug Abuse, Dependence, & Withdrawal

- Develop and validate SMQs for other key constructs

- Develop consensus Clinical Classification of Abuse-Related Phenomena

- Develop and validate C-CASA-like approach for abuse-related phenomena

- Develop standardized investigator prompted CRF to support adjudication of events

- Develop consensus on best measures for abuse-related constructs for clinical trials