Challenges of Capturing and Reporting Adverse Events to Assess Abuse Potential in Clinical Trials

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- All views presented are mine and not necessarily those of my employer
- All data presented are available in the public domain

Overview

- Specifying Abuse-related AEs
- Analyzing AEs Using MedDRA
- Impact of Drug Pharmacology
- Impact of Type of Study
- Narratives – Triggers and Content
- Supplementary Methods to Assess Abuse Potential

FDA 2017 Guidance

Abuse-related AEs from clinical studies are listed as one source of abuse-related data from human studies.

- *"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."*

Abuse-Related Adverse Events as AESIs

- Share challenges with other types of AESIs
  - Prespecifying specific terms to be analyzed
  - Constraints of MedDRA
  - Potential for the need for additional information to be collected
- Additional complicating factors for abuse-related AEes are that we are trying to predict future use of the drug:
  - In a population not included in the studies (those with previous drug abuse most often excluded)
  - For use outside of the proposed/approved indication
  - Most likely at doses higher than what is proposed/approved

Identifying Abuse-Related Adverse Event - The List

- Company/product specific requests
- 2010 FDA draft abuse potential guidance
- 2013 Love and Sun poster
- 2015 Industry proposal (CCALC)
- 2017 FDA final guidance
- 2023 ‘updated’ list

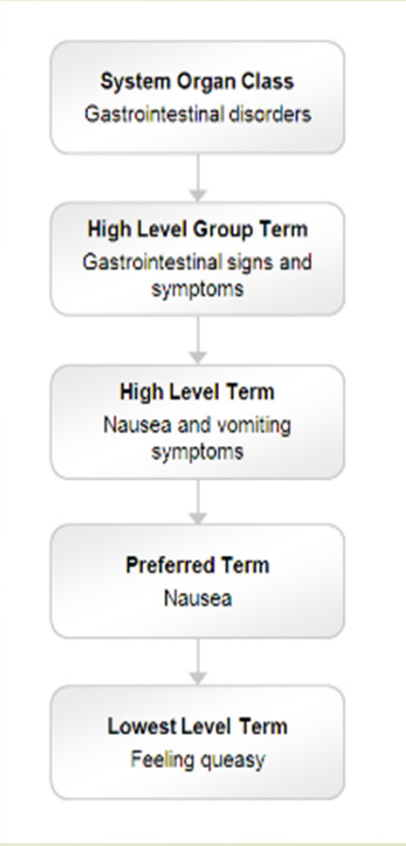
Abuse-Related Terms FDA Guidance-2017

- ***Euphoria-related terms:*** *Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect*
- ***Terms indicative of impaired attention, cognition, and mood:*** *Somnolence; Mood disorders and disturbances*
- ***Dissociative/psychotic terms:*** *Psychosis; Aggression; Confusion and disorientation*
- ***Related terms not captured elsewhere:*** *Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders*

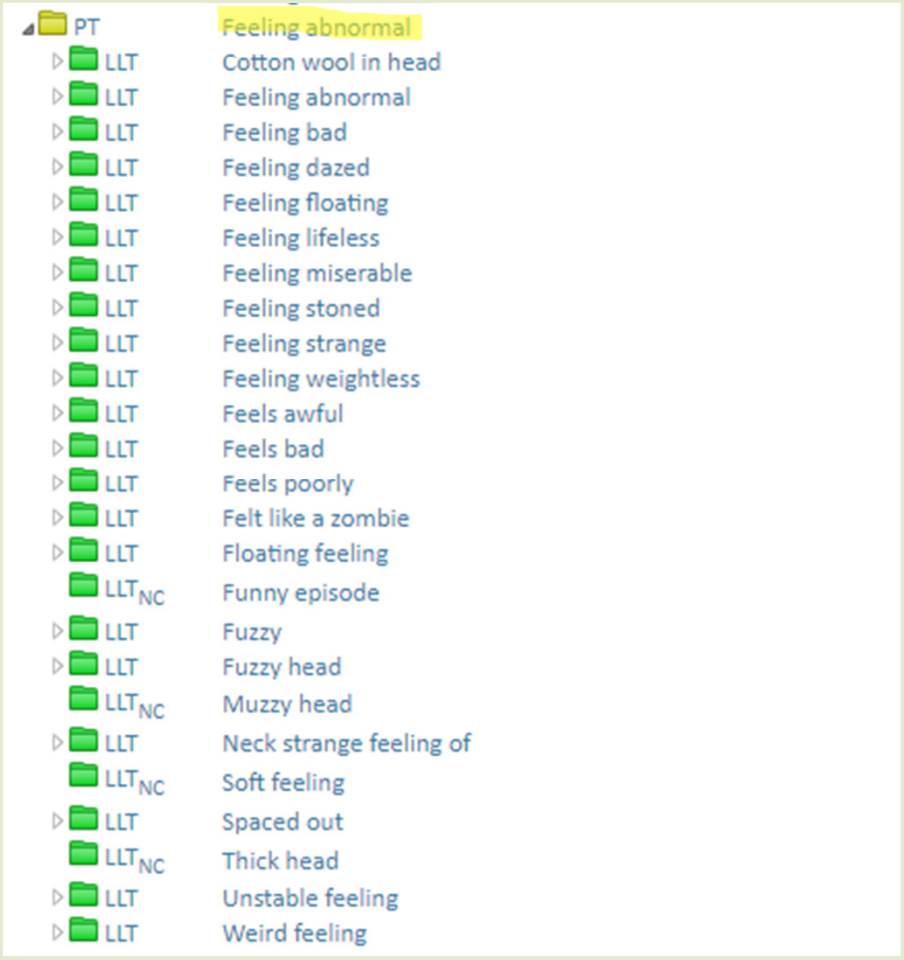
- *Terms represent MedDRA coded events that fall in the General disorders and administration site conditions SOC, Nervous system disorders SOC, and Psychiatric disorders SOC .*

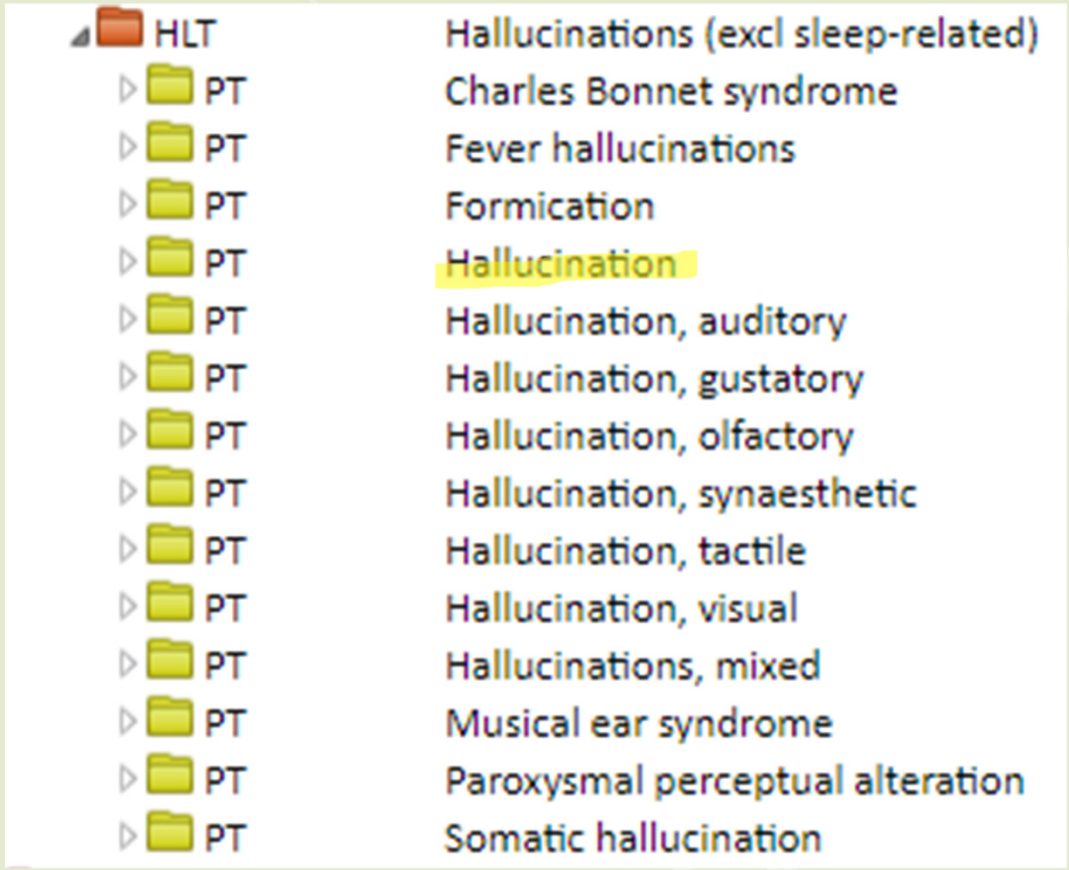
Identifying Abuse-Related AEs Using MedDRA

- **"Lowest Level Terms"** (LLTs), there are more than 80,000 terms which parallel how information is communicated. **(Euphoria**)
- Each LLT is mapped to a **"Preferred Terms" (PTs)**, which is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. (**Euphoric mood**)
- Related PTs are grouped together into **"High Level Terms" (HLTs)** based upon anatomy, pathology, physiology, aetiology or function. (**Emotional and mood disturbances NEC**)
- HLTs, related to each other by anatomy, pathology, physiology, aetiology or function, are in turn linked to **"High Level Group Terms" (HLGTs)** (**Mood disorders and disturbances NEC**)
- HLGTs are grouped into "**System Organ Classes" (SOCs)** which are groupings by aetiology (e.g. *Infections and infestations*), manifestation site (e.g. *Gastrointestinal disorders*) or purpose (e.g. *Surgical and medical procedures*), issues pertaining to products and contain social circumstances. (**Psychiatric disorders**)



Abuse-Related PTs





MedDRA Abuse SMQ

SMQs are groupings of MedDRA PTs related to a defined medical condition or area of interest; they are intended to aid in the identification and retrieval of potentially relevant Individual Case Safety Reports. The terms in an SMQ may represent diagnoses, syndromes, symptoms, physical findings, procedures, laboratory and other physiological test data, all related to the condition or area of interest.

- Benefits: facilitate comparison across product, organizations, over time.
- Limits: may miss cases of interest, may identify case not relevant

- Broad vs Narrow Scope
- Narrow constrained to terms highly likely to represent condition of interest (narrow search = narrow)
- Broad less specific, more likely to return irrelevant cases (broad search = includes broad + Narrow)

https://cioms.ch/sd7fdh93gewd882ds/78yudej8fddqd6s-red-book/CIOMS-MedDRA-RedBook-SECURED.pdf

MedDRA Abuse SMQ

Narrow	Drug abuse
Narrow	Drug abuser
Narrow	Drug dependence
Narrow	Drug dependence, antepartum
Narrow	Drug dependence, postpartum
Narrow	Intentional drug misuse
Narrow	Intentional overdose
Narrow	Maternal use of illicit drugs
Narrow	Multiple drug overdose intentional
Narrow	Neonatal complications of substance abuse
Narrow	Polysubstance dependence
Narrow	Substance abuse
Narrow	Substance abuser

Broad	Accidental overdose
Broad	Dependence
Broad	Disturbance in social behaviour
Broad	Drug administered at inappropriate site
Broad	Drug detoxification
Broad	Drug level above therapeutic
Broad	Drug level increased
Broad	Drug screen
Broad	Drug screen positive
Broad	Drug tolerance
Broad	Drug tolerance decreased
Broad	Drug tolerance increased
Broad	Drug toxicity
Broad	Multiple drug overdose
Broad	Multiple drug overdose accidental
Broad	Narcotic intoxication
Broad	Needle track marks
Broad	Overdose
Broad	Therapeutic agent toxicity

Coding Issues

suvorexant medical review

- *….the incidence of hallucinations in this program was small, and published literature cited by the sponsor indicates prevalence of hypnagogic and hypnopompic hallucinations can be as high as 12.5% in the general population. The review concludes that* ***the small numbers of cases in this program make it difficult to determine the relationship of hallucinations with suvorexant****, while seeming to note that the events might be dose-related.*

- *Increased incidence of nightmares and abnormal dreams is associated with narcolepsy, and could be related to the anti-orexin effect of suvorexant. Suvorexant also caused hypnagogic/hypnopompic hallucinations, and* ***it isn't clear if hallucinations around the time of sleep/wake transition could have been recorded as nightmares and abnormal dreams instead of as hallucinations.***

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204569Orig1s000MedR.pdf

Coding Issues

brivaracetam safety review

- Comment: After reviewing the AE datasets for the 3 pivotal Phase 3 studies in adults with POS to assess the coding of the verbatim terms to the MedDRA preferred terms, the coding process overall seemed appropriate and allowed for reliable estimates of AE risks. However, there were rare cases that appeared to be **coding omissions and miscoding**. For example, the verbatim term of "broken brace after fall" was only coded to the PT device breakage (and not also to fall), "pre. syncope" was coded to the PT dizziness, and "increase energy" was coded to the PT asthenia. Additionally, there were multiple verbatim terms such as "tingeling and mumbness in her feet" that were coded to the PT unevaluable event (full list and Applicant's explanation provided in Section 7.4.1 of this review). Furthermore, there were also instances where the coding process resulted in **splitting likely related AEs into separate SOCs leading to an underestimation of the true incidence for a particular event or syndrome**.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205836Orig1s000_205837Orig1s000_205838Orig1s000MedR.pdf

Narratives: Triggers

May not be practical to prepare narratives for all abuse-related AEs

- 'Short list' of individual PTs or constellations of abuse-related AEs
  - Consider class of drug
  - Disease under study
  - Specificity of the term

Narratives: Content

Potential components of a narrative

- Verbatim terms from participant
- Medical history
- Concomitant medications
- Concomitant AEs
- Extenuating circumstances
- Other assessments tools
- Temporal onset relative to drug administration
- Duration of effect

Some information may not be available from CRF pages so would need to be planned for in advance.

Abuse-Related AEs Based on Drug Pharmacological

>1% SYNDROS (dronabinol) oral solution (Cannabinoid)

System Organ Class	Adverse Reactions
General	Asthenia
Cardiovascular	Palpitations, tachycardia, vasodilation/facial flush
Gastrointestinal	Abdominal pain*, nausea*, vomiting*
Central Nervous System	dizziness*, euphoria*, paranoid reaction*, somnolence*, thinking abnormal*, amnesia, anxiety/nervousness, ataxia, confusion, depersonalization,

*Actual Incidence 3% to 10%

BELSOMRA® (suvorexant) tablets (Orexin antagonist)

Table 2: Percentage of Patients with Adverse Reactions Incidence ≥2% and Greater than Placebo in 3-Month Controlled Efficacy Trials (Study 1 and Study 2)

	Placebo	BELSOMRA (20 mg in non-elderly or 15 mg in elderly patients)
	n=767	n=493
Gastrointestinal Disorders		
Diarrhea	1	2
Dry mouth	1	2
Infections and Infestations		
Upper respiratory tract infection	1	2
Nervous System Disorders		
Headache	6	7
Somnolence	3	7
Dizziness	2	3
Psychiatric Disorders		
Abnormal dreams	1	2
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1	2

The rate of euphoria was 0% for 75 mg and 0.2% (2/1032) for 100 mg and the rate of feeling drunk was 0.1% (1/807) for 75 mg and 0.1% (1/1032) for 100 mg.

VIBERZI (eluxadoline) tablets (Opioid mu and kappa agonist)

Table 1: Common* Adverse Reactions in the Placebo-Controlled Studies in IBS-D Patients

Adverse Reactions	VIBERZI 100 mg twice daily (N= 1032) %	VIBERZI 75 mg twice daily (N=807) %	Placebo (N=975) %
Constipation	8	7	3
Nausea	7	8	5
Abdominal Pain**	7	6	4
Upper Respiratory Tract Infection	5	3	4
Vomiting	4	4	1
Nasopharyngitis	3	4	3
Abdominal Distention	3	3	2
Bronchitis	3	3	2
Dizziness	3	3	2
Flatulence	3	3	2
Rash***	3	3	2
Increased ALT	3	2	1
Fatigue	2	3	2
Viral gastroenteritis	1	3	2

* Reported in > 2% of VIBERZI-treated patients at either dose and at an incidence greater than in placebo-treated patients

Abuse-Related AEs Based on Study Type -
Study Phase

Table 6: Incidence of Euphoric Mood across Phase 1 and Phase 2/3 Clinical Studies with Lorcaserin at 0.1 to 60 mg doses, relative to Placebo

Study	Dose	Placebo	Lorcaserin Daily Dose (mg)									
			0.1	1	3	5	10	15	20	40	60	Total
Phase I	Single	0 of 20 (0%)	0 of 5 (0%)	0 of 5 (0%)			0 of 35 (0%)		0 of 12 (0%)	4 of 6 (67%)	6 of 31 (19%)	
Phase I	Multiple	0 of 117 (0%)			0 of 6 (0%)		1 of 34 (2.9%)	4 of 60 (6.7%)	6 of 54 (11%)	7 of 64 (11%)		
Phase II & III	Multiple	1 of 3389 (0 03%)		0 of 90 (0%)		0 of 89 (0%)	4 of 918 (0.4%)	0 of 205 (0%)	6 of 3311 (0.18%)			
Total		2 of 3526 (0 06%)	0 of 5 (0%)	0 of 95 (0%)	0 of 6 (0%)	0 of 89 (0%)	5 of 987 (0.5%)	4 of 265 (1.5%)	12 of 3377 (0.4%)	11 of 70 (16%)	6 of 31 (19%)	38 of 4926 (0 8%)

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000OtherR.pdf

Abuse-Related AEs Based on Study Type -
Safety/Efficacy vs HAP

Table 2. Treatment-Emergent AEs for Psychiatric Disorders (euphoric mood, thinking abnormal and hypervigilance) Clinical Study Report INS-13-017 (Human Abuse Liability Study)

Preferred Term	Placebo (N=39)	Marinol (10mg) (N=35)	Marinol (30mg) (N=37)	Dronabinol (10mg) (N=36)	Dronabinol (30mg) (N=40)	All Marinol (N=72)	All Dronabinol (N=76)	p-value[2]
Euphoric Mood	3 (7.7)	24 (68.6)	30 (81.1)	26 (72.2)	35 (87.5)	54 (75%)	61 (80%)	p=0.55
Thinking abnormal	0	0	0	1 (2.8)	2 (5.0)	0	3	p=0.25
hypervigilance	0	1 (2.9)	0	0	2 (5.0)	1	2	p>0.99

Table 3. Treatment-Emergent AEs for Psychiatric Disorders (euphoric mood, thinking abnormal and hypervigilance) from Pharmacokinetic Studies[a]

Preferred Term	Study INS-08-008			Study INS-10-012		Study INS-12-015		Study INS004-15-059		
	SYNDROS 10 mg	Dronabinol Oral Solution 10 mg[b]	Marinol 10 mg	SYNDROS 5 mg	Marinol 10 mg	SYNDROS 4.25 mg	Marinol 5 mg	SYNDROS 4.25 mg Fed	Marinol 5 mg Fed	Marinol 5 mg Fasted
	N=18	N=18	N=18	N=169	N=171	N=104	N=104	N=52	N=54	N=53
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Euphoric Mood	0	0	0	1 (0.6)	0	0	1(1.0)	2 (3.8)	0	1 (1.9)
Thinking Abnormal	0	0	0	0	0	0	0	0	0	0
Hyper vigilance	0	0	0	0	0	0	0	0	0	0

[a]Integrated Summary of Safety, NDA 205525
[b]Previous test formulation of Dronabinol Oral Solution

http://www.accessdata.fda.g
OtherR.pdf

Supplementing Spontaneously Reported AEs to Better Identify Abuse Potential during Clinical Trials

Considering the challenges and limitations of using abuse-related AEs to determine abuse potential perhaps there are additional ways to capture the information.

Scales/questionaires are used to probe for safety issues other than abuse, eg, the CSSRS for suicidality. We use that scale in clinical studies in circumstances where there could be a causal association with the drug and in studies where the population is at high risk for suicide.

Supplementing Spontaneously Reported AEs to Better Identify Abuse Potential during Clinical Trials

Not a new idea, Brady, Lydiard and Brady 2003:

Suggested:

- Development and testing of brief subjective rating scales to be used in human volunteers who are not experienced drug users. The language and wording of items would need to be tailored to fit a nonsubstance-using population. Both positive and negative effects should be rated

Mentioned:

- Assessments commonly used to study subjective effects of drugs include the Single Dose Questionnaire (SDQ), the Drug Effects Questionnaire (DEQ), the Subjective Effects Questionnaire (SEQ) and a number of visual analogue scales.

Concluded:

- There remains much groundwork to be done in developing and validating appropriate assessment instruments and determining ''threshold'' levels for concern

Drug and Alcohol Dependence 70 (2003) S87/S95

Would a scale/questionnaire be helpful for assessing abuse potential in clinical studies? And would the benefits outweigh the burdens to both sponsors and study participants?

Thank you!

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