

A proposal for capturing, categorizing,
and organizing adverse events of
interest in clinical trials for New Drug
Applications

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Adverse Event Working Group

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Overview

- It is unclear which list of adverse events should be considered for abuse and dependence potential evaluation
 - FDA guidance lists certain terms however some are broad (e.g. psychotomimetic effects)
 - Multiple versions of lists have been circulating amongst the public domain and industry members
 - Each list differs; containing both common and unique terms
- Data presentation style that is efficient for review should be considered
 - Typically NDA submissions have required narration of each abuse or dependence related AE for evaluating abuse potential
 - Narration of terms that are further removed from abuse/dependence may add development and review burden

Objectives

1. Develop an 'official' list of relevant 'abuse' and 'dependence' related AEs of interest
 - Living document such as MedDRA
2. Work with the FDA to understand their review process when evaluating abuse potential data in an NDA, and identify an efficient way to present these data

Identifying Adverse Events of Interest

- Currently abuse and dependence related AEs have been identified in 4 distinct industry lists, a poster by Love and Sun (2013)¹, and the draft Guidance for Industry²
 - Each list contains common and unique terms ranging from 67 to 213 terms
 - Some lists include terms of varying specificity e.g. lower level terms, preferred terms, high-level terms, and Standardized MedDRA Queries (SMQ)

1. Love L.A. and Sun S. Proposed Query to Capture Abuse-Related Adverse Events. (abstract) College on Problems of Drug Dependence – 75th Annual Meeting, San Diego, CA, June 2013.

2. Guidance for Industry. Assessment of Abuse Potential of Drugs. US Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research (CDER) January 2010.

Proposed Query to Capture Abuse Related AEs

(Love and Sun, 2013)

Abnormal behaviour	Delirium	Euphoric mood	Maternal use of illicit drugs	Sensory disturbance
Abnormal dreams	Delusion	Executive dysfunction	Memory impairment	Sensory level abnormal
Abnormal sleep-related event	Delusion of grandeur	Fear	Mental disability	Sleep sex
Accidental death	Delusion of reference	Feeling abnormal	Mental disorder	Sleep terror
Accidental overdose	Delusion of replacement	Feeling drunk	Mental impairment	Slow speech
Accidental poisoning	Delusional perception	Feeling jittery	Mental status changes	Somatic delusion
Acute psychosis	Delusional disorder, erotomanic type	Feeling of despair	Miosis	Somatic hallucination
Affect lability	Delusional disorder, grandiose type	Feeling of relaxation	Mood altered	Somnolence
Affective disorder	Delusional disorder, jealous type	Flashback	Multiple drug overdose	Staring
Aggression	Delusional disorder, mixed type	Flat affect	Multiple drug overdose accidental	Steroid withdrawal syndrome
Agitation	Delusional disorder, persecutory type	Flight of ideas	Multiple drug overdose intentional	Stupor
Alice in wonderland syndrome	Delusional disorder, somatic type	Formication	Muscle relaxant therapy	Substance abuse
Altered state of consciousness	Delusional disorder, unspecified type	Hallucination	Mydriasis	Substance abuser
Altered visual depth perception	Delusions, mixed	Hallucination, auditory	Nasal necrosis	Substance use
Amnesia	Dependence	Hallucination, gustatory	Nasal septum perforation	Substance-induced mood disorder
Amnesic disorder	Depersonalisation	Hallucination, olfactory	Nasal septum ulceration	Substance-induced psychotic disorder
Amphetamines	Depressed level of consciousness	Hallucination, synaesthetic	Needle track marks	Suicidal behaviour
Amphetamines positive	Depressive delusion	Hallucination, tactile	Neonatal complications of substance abuse	Suicidal ideation
Analgesic therapy	Derailment	Hallucination, visual	Overdose	Suicide attempt
Anger	Derealisation	Hallucinations, mixed	Panic attack	Suspiciousness
Anhedonia	Disinhibition	Hangover	Panic reaction	Tangentiality
Anterograde amnesia	Disorientation	Homicidal ideation	Paramnesia	Thinking abnormal
Antisocial behaviour	Dissociation	Homicide	Paranoia	Thought blocking
Antitussive therapy	Dissociative amnesia	Hostility	Parasomnia	Thought broadcasting
Anxiety	Dissociative identity disorder	Hypervigilance	Paroxysmal perceptual alteration	Thought insertion
Anxiolytic therapy	Disturbance in attention	Hypnagogic hallucination	Persecutory delusion	Thought withdrawal
Apathy	Disturbance in social behaviour	Hypnopompic hallucination	Personality change	Toxicity to various agents
Asocial behaviour	Dopamine dysregulation syndrome	Ideas of reference	Personality disorder	Transient global amnesia
Asthenia	Dopaminergic drug therapy	Illogical thinking	Physical assault	Transient psychosis
Attention-seeking behaviour	Drug abuse	Illusion	Poisoning	Treatment noncompliance
Balance disorder	Drug abuser	Impaired driving ability	Polysubstance dependence	Urine amphetamine
Belligerence	Drug dependence	Impaired reasoning	Prescription form tampering	Urine amphetamine positive
Benzodiazepine drug level	Drug dependence, antepartum	Impulsive behaviour	Product tampering	Violence-related symptom
Blunted affect	Drug dependence, postpartum	Inappropriate affect	Product used for unknown indication	
Bradypnea	Drug detoxification	Incoherent	Psychomotor hyperactivity	
Central nervous system stimulation	Drug diversion	Intentional drug misuse	Psychomotor retardation	
Cognitive disorder	Drug screen positive	Intentional overdose	Psychomotor skills impaired	
Completed suicide	Drug tolerance increased	Intentional self-injury	Psychotic behaviour	
Compulsions	Dysphoria	Irritability	Psychotic disorder	
Confabulation	Dysphoria	Jamais vu	Reactive psychosis	
Confusional arousal	Elevated mood	Jealous delusion	Restlessness	
Confusional state	Emotional disorder	Judgement impaired	Retrograde amnesia	
Consciousness fluctuating	Emotional distress	Loose associations	Sedation	
Coordination abnormal	Energy increased	Magical thinking	Self-injurious behaviour	
Deja vu	Erotomanic delusion	Mania	Self-injurious ideation	

213 Terms

Terms with Probable or Definite Association to 1° Abuse Potential

- Using a consensus process, Sellers and Romach¹ found that
 - Only 3% of terms relate to reinforcing properties and only ~20% of terms have probable or definite association to primary abuse potential
 - Presumed core reinforcing associated terms included: Elevated mood, Energy increased, Euphoric mood, Feeling drunk, Feeling of relaxation, Sedation, and Somnolence
 - Terms with probable or definite saliency included:

Saliency Definite		Saliency Probable	
Dependence	Prescription form tampering	Elevated mood	Multiple drug overdose accidental
Drug abuse	Product tampering	Euphoric mood	Multiple drug overdose intentional
Drug abuser	Substance abuse	Accidental overdose	Mydriasis
Drug dependence	Substance abuser	CNS stimulation	Nasal necrosis
Drug dependence, antepartum	Substance use	Drug screen positive	Nasal septum perforation
Drug dependence, postpartum	Substance-induced mood disorder	Intentional drug misuse	Nasal septum ulceration
Drug detoxification	Substance-induced psychotic disorder	Maternal use of illicit drugs	Neonatal complications of substance abuse
Needle track marks		Miosis	Urine amphetamine
Polysubstance dependence		Multiple drug overdose	Urine amphetamine positive

1. Romach MK, Sellers EM. A standardized approach to adverse event terminology in abuse potential evaluation; the next iteration. (abstract) ASCPT 2014. www.dlglobalpartners.com

FDA Draft Guidance

- Evaluate AE profile (MedDRA) from clinical trials for a signal of abuse potential
 - Systematic categorization, tabulation and analysis of safety data for mood elevation, sedation, and **psychotomimetic events**.
 - Incidence of euphoria-type AEs (including euphoria, euphoric mood, elevated mood, mood altered, feeling drunk, feeling abnormal) and hallucinations (visual & auditory)
 - Inappropriate affect (elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation)
 - A prospective evaluation of withdrawal AEs after abrupt discontinuation

Standardized MedDRA Queries (SMQ)

Table 1. Standardized MedDRA Queries (Version 18.0) for Drug Abuse, Dependence, and Withdrawal; Preferred Terms

Drug Abuse and Dependence SMQ (broad)				Drug Withdrawal (SMQ) broad
Intentional product misuse	Overdose	Dependence	Drug tolerance	Drug withdrawal convulsions
Drug abuse	Accidental overdose	Drug dependence	Drug tolerance decreased	Drug withdrawal headache
Drug abuser	Drug level above therapeutic	Drug dependence, antepartum	Drug tolerance increased	Drug withdrawal maintenance therapy
Substance abuse	Drug level increased	Drug dependence, postpartum	Prescribed overdose	Drug withdrawal syndrome
Substance abuser	Intentional overdose	Polysubstance dependence	Prescription form tampering	Drug withdrawal syndrome neonatal
Drug administered at inappropriate site	Multiple drug overdose	Toxicity to various agents	Substance use	Rebound effect
Drug rehabilitation	Multiple drug overdose accidental	Intentional product use issue	Substance-induced mood disorder	Steroid withdrawal syndrome
Drug screen	Multiple drug overdose intentional	Maternal use of illicit drugs		Withdrawal arrhythmia
Drug screen positive	Drug detoxification	Substance-induced psychotic disorder		Withdrawal syndrome
Disturbance in social behavior	Drug toxicity	Drug diversion		
Needle track marks	Therapeutic agent toxicity	Medication overuse headache		
Neonatal complications of substance abuse	Dopamine dysregulation syndrome	Narcotic bowel syndrome		

Additional AEs of Interest

- Additional Adverse events that are referenced by Romach and Sellers (Sun and Love) but do not appear in industry lists:
 - Product tampering (maps to Product Quality Issues)
 - CNS stimulation
 - Miosis
 - Nasal necrosis
 - Nasal septum ulceration,
 - Urine amphetamine
 - Urine amphetamine positive.

AEs Assessing Potential Withdrawal

Table 2. List of AE Terms Derived from Four Industry Lists Assessing Withdrawal Following Abrupt Drug Discontinuation (N=25 Terms)

• Agitation	• Depression	• Early morning awakening	• Morose	• Pain
• Anhedonia	• Diarrhoea	• Feeling of despair	• Nausea	• Poor quality sleep
• Anxiety	• Dysphoria	• Headache	• Negative thoughts	• Syncope
• Chills	• Dyssomnia	• Hyperhidrosis	• Nervousness	• Tremor
• Depressed Mood	• Dysthymic disorder	• Insomnia	• Obsessive thoughts	• Vomiting

Abuse Potential-Related AEs

- Collectively, amongst industry lists, 83 abuse potential-related terms were identified
 - Of these, 41 are specified in the guidance as being related to *mood elevation, sedation, psychotomimetic effects, euphoria, inappropriate affect, or hallucinations*

Abuse Related AE Terms

Table 3. List of AE Terms Derived from Four Industry Lists and Referenced in the FDA 2010 Draft Guidance for Industry (N=41 Terms)

• Abnormal behavior	• Detachment	• Flight of ideas	• Mood altered/alteration	• Thinking Abnormal
• Abnormal thinking	• Disturbance in attention	• Hallucination (visual and auditory)	• Mood disorders and disturbances	
• Agitation	• Elation inappropriate	• Inappropriate affect	• Mood swings	
• Cognition disorder	• Elevated mood	• Inappropriate elation	• Paranoia	
• Concentration impaired	• Emotional disorder	• Inappropriate laughter	• Poor concentration	
• Concentration loss	• Euphoria/Euphoric mood	• Inappropriate mood elevation	• Psychosis	
• Confusion and disorientation	• Exhilaration inappropriate	• Irritability	• Psychotic Disorder	
• Confusional state	• Feeling abnormal	• Memory impairment	• Sedation*	
• Delirium	• Feeling drunk	• Mental Disorder	• Sensory disturbances	
• Delusional disorder unspecified type	• Feeling happy inappropriately	• Mental impairment	• Stupor	

Terms NOT Referenced

Table 4. List of AE Terms Derived from Four Industry Lists but NOT referenced in the FDA guidance (N=42 Terms)

• Aggressive	• Dizziness	• Feeling of relaxation	• Impatience	• Substance-related disorders
• Affective disorders	• Dopiness	• Feeling spacey	• Intoxicated	• Tranquilization
• Amnesia	• Drowsiness	• Feeling talkative (logorrhea)	• Mental dullness	
• Anger	• Dysarthria	• Felt giddy or giddiness	• Muscle rigidity	
• Attention disorder	• Emotional distress	• Floating	• Personality disorder	
• Bradyphrenia	• Energy increased	• Forgetfulness	• Psychomotor hyperactivity	
• Depersonalization	• Exaggerated well-being	• Groggy	• Restlessness	
• Derealization	• Fatigue	• Habituation	• Rush	
• Disinhibition	• Feeling dazed	• Hostility	• Somnolence	
• Dissociation	• Feeling jittery	• Hypervigilance	• Stoned	

Additional Considerations

- Some higher level terms are broad and may require further specificity to determine if these are applicable to a drug's abuse potential
 - *e.g. psychotomimetic effects, mood disorders and disturbances, mental disorder, psychotic disorder*
- FDA guidance refers to sedation but does not include somnolence.

Organizing AEs for Abuse Potential Evaluation

- Table summaries provide easier format for at-a-glance information
- *Narratives can be generated for specific information*
- *Suggestions:*
 1. *Limit all terms to Treatment Emergent Adverse Events*
 2. *Provide overall summary tables segregated according to treatment, population types (i.e. healthy volunteers, non-dependent recreational drug users, patients, others) and single vs multiple dose exposure*
 3. *Develop narratives for all events related to abuse potential (i.e. SMQs; 41 abuse-related adverse events)*
 - *Some events may be effectively summarized in table format rather than narrative e.g. sedation, euphoria in abuse potential studies*
 4. *Whenever possible, subject verbatim description should be included to further characterize the event.*

Organizing AEs for Abuse Potential Evaluation

- Table summaries would include at minimum, the following subheadings:
 - *Medical history*
 - *Demographics (age, sex)*
 - *Dosage/ Regimen*
 - *Treatment assignment*
 - *Duration of treatment*
 - *Time to onset*
 - *Duration of event*
 - *Severity*
 - *Subject verbatim terms*
 - *Actions taken*
 - *Drug relatedness*
 - *Concomitant medications*
 - *Disposition*
 - *Other temporally related adverse events*
 - *Outcome*

AE Work Group Recommendations

1. As per FDA guidance, the following terms should be considered for the evaluation of abuse and dependence potential of CNS drugs:
 - i. SMQ for Drug Abuse, Dependence, and Withdrawal [Table 1]
 - ii. Adverse event terms assessing abrupt drug withdrawal (N=25 terms) [Table 2]
 - iii. Abuse potential-related terms specified in the Draft FDA Guidance (N=41 terms) [Table 3]

Does the agency agree with this approach?

AE Work Group Recommendations

2. To evaluate drug related effects, only Treatment-Emergent AEs should be considered for Abuse potential evaluation. Does the agency agree?
3. AEs that are NOT listed in the draft Guidance [Table 4], can be included as part of the safety summary but NOT as part of the abuse potential evaluation.
 1. Does the agency agree?
 2. If not, can these terms be summarized in table format instead of full narration?