Identifying Relevant Adverse Events of Interest and Recommendations for Analysis and Presentation of Data in the NDA Submission

Steven Galati, MD
Controlled Substance Staff

Disclaimer

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Objectives

- Present the key adverse events (AEs) recommended for analysis in the assessment of a drug's abuse potential
- Present recommendations as to how AEs should be analyzed in the New Drug Application (NDA) submission
- Discuss special considerations, e.g., with psychedelics

Background

- Abuse potential assessment is based on numerous data sources
  - Analysis of AEs from clinical trials is only one component
- Some CNS-related AEs do not necessarily indicate a potential for abuse; however, assessment of these AEs is still important because…
  - Provides an early indication a drug may ultimately have abuse potential, as more specific abuse-related AEs (e.g., euphoria) are less frequently observed in clinical trials
  - Helps characterize the drug class (e.g., stimulant, depressant, psychedelic) – relevant for selecting a comparator in a human abuse potential (HAP) study

FDA Retrospective Review of Abuse-Related PTs to Inform Abuse Potential Assessment

Introduction

- We conducted an informal exploratory retrospective comparison of abuse-related AEs, many of which are MedDRA preferred terms (PTs), reported in NDAs for drugs that were evaluated for scheduling under the CSA
- FDA guidance for industry *Assessment of Abuse Potential of Drugs*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-abuse-potential-drugs, provides examples of abuse-related terms that could inform the abuse potential of a drug
- Because this list in the guidance is not exhaustive, we compiled a more comprehensive list of AEs based on our previous experience with drug development programs
  - This list was then compared between scheduled and unscheduled drugs

Methods

A total of 10 scheduled and unscheduled drugs were compared with respect to the frequency of certain abuse-related AEs reported in clinical trials

- Two drugs from each Schedule (II, III, IV, and V) and two unscheduled drugs were selected for comparison
    - **Schedule II**: Lisdexamfetamine (CNS stimulant) and Tapentadol (opioid analgesic)
    - **Schedule III**: Perampanel (anticonvulsant non-competitive AMPA glutamate receptor antagonist) and Sodium Oxybate (sedative)
    - **Schedule IV**: Solriamfetol (dopamine and norepinephrine reuptake inhibitor) and Eluxadoline (gastrointestinal agent—mu-opioid receptor agonist)
    - **Schedule V**: Lasmiditan (antimigraine agent— serotonin (5-HT) 1F receptor agonist) and Brivaracetam (anticonvulsant)
    - **Unscheduled**: Cariprazine (atypical antipsychotic) and Brexpiprazole (atypical antipsychotic)
- One Phase 1 study and one Phase 2/3 study was examined from each NDA

Abuse-Related Adverse Events (MedDRA PTs) for Comparison

Preferred Terms						
Abnormal Behavior	Confusional state	Drug Abuse	Euphoric mood	Hypervigilance	Mood swings	Somnolence
Affect Liability	Delirium	Dependence	Feeling abnormal	Inappropriate affect	Paranoia	Stupor
Aggression	Delusion	Diversion	Feeling drunk	Intentional overdose	Personality disorder	Suicidal ideation
Agitation	Depersonalization	Drug withdrawal syndrome	Feeling jittery	Irritability	Physical assault	Thinking abnormal
Anger	Depression	Dysphoria	Feeling relaxation	Logorrhea	Psychomotor activity	
Anxiety	Derealization	Elevated mood	Flight of ideas	Mania	Psychotic disorder	
Bradyphrenia	Disinhibition	Emotional disorder	Hallucination	Memory impairment	Restlessness	
Cognitive disorder	Disorientation	Energy increased	Homicidal ideation	Mental disorder	Sedation	
CSSR-S abnormal	Disturbance of attention	Euphoria	Hypersomnia	Mood altered	Sensory disturbance	

Results

- Overall, there were more abuse-related AEs reported in scheduled drugs compared to unscheduled drugs
  - E.g., about 50% of the abuse-related AEs were seen in scheduled drugs compared to under 10% in unscheduled drugs
  - The difference between scheduled and unscheduled drugs was more prominent in healthy volunteer studies (i.e., Phase 1)
- Abuse-related AEs that occurred only in studies of selected unscheduled drugs was less than 1%, providing additional support for the utility of the selected terms in the abuse-related AE analysis
- However, several abuse-related AEs were not reported in scheduled drugs, likely due to the limited sample size, controlled setting, and overlapping terms

Conclusions on the Retrospective Review

- There is utility in evaluating this list of abuse-related AEs given the frequencies we observed in scheduled versus unscheduled drugs
- The healthy volunteer studies appear most useful, possibly due to
  - Lack of confounding by symptoms of the underlying disease process (i.e., psychiatric, neurologic) and concomitant medications more typical of Phase 2/3 studies
  - Use of supratherapeutic doses
- Analysis of abuse-related AEs in clinical trials does not provide a definitive signal of abuse potential but rather is a component of the full abuse potential assessment

Recommendations for Abuse-related AE Analysis

Recommended List of Abuse-Related AEs to Assess Abuse Potential - MedDRA PTs (1/2)

- **Euphoria-related terms**:
  - *Elevated mood, euphoria, euphoric mood, feeling drunk, feeling of relaxation*

- **Dissociative/psychotic-related terms**:
  - *Abnormal behavior, amnesia, delirium, delusion, delusion of grandeur, delusional perception, mixed delusion depersonalisation, derealization, disturbance in attention, hallucination, hypnagogic hallucination, hypnopompic hallucination, hallucination auditory, hallucination gustatory, hallucination olfactory, hallucination synaesthetic, hallucination tactile, hallucination visual, hallucinations mixed paranoia, psychotic disorder, acute psychosis, transient psychosis, substance-induced psychotic disorder, sensory disturbance, thinking abnormal*

- **CNS stimulation terms**:
  - *Affect liability, aggression, agitation, anxiety, disinhibition, energy increased, feeling jittery, flight of ideas, hypervigilance, irritability, psychomotor hyperactivity, restlessness*

- **CNS depression terms**:
  - *Bradyphrenia, depression, dysphoria, hypersomnia, hypersomnia related to another mental condition, sedation, infant sedation, neonatal oversedation, post-injection delirium sedation syndrome, sedation complication, sedative therapy, somnolence, somnolence neonatal, stupor*

Recommended List of Abuse-Related AEs to Assess Abuse Potential - MedDRA PTs (2/2)

- **General terms:**
  - *Drug abuse, drug abuser, substance abuser, substance abuse, drug use disorder, drug use disorder antepartum, drug use disorder postpartum, substance use disorder, drug diversion, drug dependence, dependence, drug dependence antepartum, drug dependence postpartum, substance dependence, drug withdrawal syndrome, drug withdrawal convulsions, drug withdrawal headache, drug withdrawal maintenance therapy, drug withdrawal syndrome neonatal, withdrawal arrhythmia, withdrawal catatonia, withdrawal hypertension, withdrawal syndrome*

- **Terms not captured elsewhere**:
  - *CSSR abnormal, confusional state, disorientation, emotional disorder, feeling abnormal, homicidal, inappropriate affect, overdose, logorrhea, mania, memory impairment, mental disorder, mood altered, mood disorder, mood disorder due to a general medical condition, substance induced mood disorder, substance-induced mood disorder, mood swings, suicidal ideation, intentional misuse of drug delivery system, intentional product misuse, prescription form tampering, product tampering, suspected product tampering*

Presentation of Abuse-Related AEs in the NDA

- Tabulation of abuse-related AEs should be by dose and population
  - Phase 1 studies are of particular importance, especially analysis of supratherapeutic doses which tend to produce a greater degree of abuse-related AEs
  - Phase 2 and 3 studies include populations with a disease state (e.g., psychiatric) which may make detection of certain AEs more difficult.

- Abuse-related AE data should be analyzed and described to determine if AE patterns exist within different human populations following administration of the test drug

- AEs should be also be presented as pooled studies and as individual studies
  - HAP study AE data should be tabulated separately because involves supratherapeutic doses and different population studied (e.g., recreational abuse)

Presentation of Abuse-Related AEs in the NDA (continued)

- All studies should include analysis of reasons for discontinuation and how related to abuse potential
  - E.g., was discontinuation secondary to dose change? lack of efficacy? subject self-titration?
  - If relevant to abuse potential, should include a narrative
- Additionally, if certain AEs identified, a more detailed narrative should be provided from case report forms

Narratives are recommended for Certain Abuse-Related AEs (MedDRA PTs)

1. Affect Lability
2. Aggression
3. Delusion
4. Depersonalisation
5. Derealisation
6. Disinhibition
7. Drug abuse
8. Drug diversion
9. Drug dependence, drug withdrawal syndrome
10. Elevated mood
11. Energy increased
12. Euphoria, euphoric mood
13. Feeling drunk
14. Feeling jittery
15. Feeling of relaxation
16. Flight of ideas
17. Hallucinations
18. Hypersomnia
19. Hypervigilance
20. Intentional overdose
21. Intentional product misuse
22. Psychomotor hyperactivity
23. Psychotic disorder
24. Sedation
25. Somnolence

Components of a Narrative

- A valuable narrative is written similarly to a medical discharge summary with a complete synthesis of available data and informed discussion of the case and include:
  - Age and sex
  - Signs and symptoms of AE being discussed
  - Relationship of exposure to drug and AE
  - Medical history
  - Concomitant meds with relative start dates to AE
  - Key physical exam findings
  - Pertinent test results (e.g., labs)
  - Discussion of diagnosis
  - Differential diagnosis
  - Re-challenge results (if applicable)
  - Outcomes and resolution

Special Considerations

- Certain drugs, e.g., psychedelics, pose a unique situation with assessing abuse-related AEs
  - Sponsors often inquire whether elements of the mystical experience should be considered AEs
- As codified in the IND safety regulations (21 CFR 312.32), an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
- We request that Sponsors capture ALL AEs that are not a direct part of the clinical outcome (improvement in disorder via a validated measure)
- For example, euphoria and hallucinations might not be considered aversive to a subject, but they represent effects that are not part of the direct treatment response outcome measure of the disease state and are important for characterizing the safety of a drug and informing labeling.

Thank you