Identifying appropriate outcome measures and methodology to evaluate the abuse, misuse, and dependence of CNS-active drugs in patient and post-marketing trials.

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Disclosures

- I am an employee of INC Research and provide consultation services to various pharmaceutical and biotech companies
- I am a former employee of King Pharmaceuticals and Pfizer
Introduction

- Studies have shown that aberrant drug taking behaviors are prevalent in patient populations
- Rates vary depending on population/study type/duration, ranging from 11 to 80.5%\(^1\)\(^-\)\(^4\)
  - Higher ranges generally found when lifetime behaviors assessed
- Monitoring these signals during clinical trial development is relevant to patient safety and drug safety evaluation

Opioid Misuse and Dependence in Chronic Pain Patients

- Kahan et al.\(^1\), completed a literature review to identify “opioid misuse” and “addiction” in chronic pain patients:
  - Few studies identified; based on retrospective chart reviews
  - Reported prevalence of opioid dependence among chronic pain patients varies among clinical settings; ranged from 3-19% across various studies.\(^2,3\)
  - In 3 retrospective chart reviews in primary care clinics, 7 to 31% of charts documents opioid misuse and drug abuse was diagnosed in 6% or these patients.\(^4-6\)

Regulatory Requirements

• As outlined in the FDA Draft Guidance\textsuperscript{1}, for Phase 3 clinical trials sponsors should make every effort to do the following:

1. “Set criteria, collect data, and tabulate the abuse, misuse, noncompliance, and diversion cases across the studies and study sites with special attention to aberrant drug behaviors that may be indicative of drug abuse, misuse and/or diversion.\textsuperscript{2,3}

2. Provide complete information, including case report forms and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study.

3. Provide information on the risks of addiction, abuse, misuse, overdose, and drug diversion in the study populations.”


\textsuperscript{3} http://sbirt.samhsa.gov/ Screening and brief intervention (SBI) can identify the severity of the “problem” in study participant and identify the appropriate level of intervention.
Definitions$^{1,2,3}$

- **Abuse**
  - Any intentional, non-therapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect.

- **Misuse**
  - Any intentional, therapeutic use of a drug in an inappropriate way. Misuse specifically excludes those events that meet the definition of abuse.

- **Diversion**
  - Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession.

- **Aberrant drug-related behavior**
  - Using a controlled substance medication in a manner that is not prescribed

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Domains of Interest

- Abuse
- Misuse
- Tolerance
- Drug Diversion
- Overdose
- Physical Dependence
- Impairment (e.g. driving)

Aberrant Behaviors
Risk Assessment Tools

- Assess potential risk or presence of aberrant behaviors

### Addiction-Related Assessment Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDIS</td>
<td>alcohol and drug diagnostic instrument</td>
</tr>
<tr>
<td>ASI</td>
<td>addiction severity index</td>
</tr>
<tr>
<td>Atluri six-point screening tool</td>
<td>problem-oriented screening instrument for teenagers</td>
</tr>
<tr>
<td>CAGE/CAGE-AID</td>
<td>cut down, annoyed, guilty, eye-opener/adjusted to include drugs</td>
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<tr>
<td>CCI</td>
<td>chemical coping inventory</td>
</tr>
<tr>
<td>Chabal five-point prescription opiate abuse checklist</td>
<td>substance abuse subtle screening inventory</td>
</tr>
<tr>
<td>COMM</td>
<td>current opioid misuse measure</td>
</tr>
<tr>
<td>CUAD</td>
<td>chemical use, abuse, and dependence scale</td>
</tr>
<tr>
<td>DAPA-PC</td>
<td>drug abuse problem assessment for primary care</td>
</tr>
<tr>
<td>DAST</td>
<td>drug abuse screening test</td>
</tr>
<tr>
<td>DIRE</td>
<td>diagnosis, intractability, risk, efficacy</td>
</tr>
<tr>
<td>KMSK scale</td>
<td>Kreek-McHugh-Schluger-Kellogg scale</td>
</tr>
<tr>
<td>ORT</td>
<td>opioid risk tool</td>
</tr>
<tr>
<td>PDUQ</td>
<td>prescription drug use questionnaire</td>
</tr>
<tr>
<td>PMQ</td>
<td>pain medication questionnaire</td>
</tr>
<tr>
<td>POSIT</td>
<td>problem-oriented screening instrument for teenagers</td>
</tr>
<tr>
<td>RAFFT</td>
<td>relax, alone, friends, family, trouble</td>
</tr>
<tr>
<td>SASSI</td>
<td>substance abuse subtle screening inventory</td>
</tr>
<tr>
<td>SCID-P</td>
<td>alcohol and drug sections of the DSM-III-R</td>
</tr>
<tr>
<td>SISAP</td>
<td>screening instrument for substance abuse potential</td>
</tr>
<tr>
<td>SMAST-AID</td>
<td>short Michigan alcoholism screening test/adapted to include drugs</td>
</tr>
<tr>
<td>SOAPP</td>
<td>screener and opioid assessment for patients with pain</td>
</tr>
<tr>
<td>STAR</td>
<td>screening tool for addiction risk</td>
</tr>
<tr>
<td>SUDDS</td>
<td>substance use disorder diagnostic schedule</td>
</tr>
<tr>
<td>TICS</td>
<td>two-item conjoint screen</td>
</tr>
</tbody>
</table>

Urine Drug Testing

• Urine Drug Test
  • Positive for drugs of abuse
  • Negative for investigational drug
• Usually implemented frequently during clinical study
• Aberrant results should be probed to determine what was taken, why, and when?
• Quantitative testing may be warranted to confirm results
• Tampering of urine should be noted (e.g. temperature, diluted urine)
  – Spontaneous UDT, retesting
• May indicate abuse, misuse, or diversion AND non-compliance

Drug Accountability

- **Site level**
  - Missing drug supply
  - Determine who, what, where, when and why?
  - Intentional vs unintentional loss?

- **Patient level**
  - Missing pills
    - Non-compliance
    - Further query to understand why, when, how and who?
    - May be suggestive of inappropriate use (misuse or abuse), lack of efficacy, increased tolerance, diversion, or accidental loss
  - Too many pills
    - Non-compliance
    - Further query to understand why, when, and how?
    - Adverse events, dose too high (e.g. splitting doses), improvement in condition/less severe condition?
    - Patient eligibility should be reviewed; dose adjustments may be considered
  - Missing bottle
    - Intentional or unintentional
    - Probe on use, provide warning to patient for compliance with study procedures
Physical Signs and Indicators

• Physical signs of drug abuse, misuse, or dependence (e.g.):
  – Needle track marks
  – Withdrawal signs
  – Constricted pupils (in absence of environmental trigger)
  – Toxicity, Overdose
  – Impairment, erratic behavior

• Indicators of aberrant behaviors (e.g.):
  – Frequent calls for refills
  – Doctor shopping
  – Requests for specific medications
  – Malingering
  – Early discontinuation (depending on reason)
  – Require further probing/data collection, as needed
Adverse Events

- Systematic categorizations, tabulation and analysis of safety data for:
  - Mood elevation
  - Sedation
  - Psychotomimetic effects
  - Euphoria-type AEs (euphoria, euphoric mood, mood alteration, feeling drunk, feeling abnormal)
  - Hallucination (visual and auditory)
  - Inappropriate affect (elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation)
  - Withdrawal adverse events
# Standardized MedDRA Queries (SMQ) Terms

<table>
<thead>
<tr>
<th>Abuse / Misuse</th>
<th>Dependence</th>
<th>Withdrawal</th>
<th>Tolerance</th>
<th>Overdose /Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intentional drug misuse</td>
<td>Dependence</td>
<td>Drug withdrawal convulsions</td>
<td>Drug tolerance</td>
<td>Overdose</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>Drug dependence</td>
<td>Drug withdrawal headache</td>
<td>Drug tolerance decreased</td>
<td>Accidental overdose</td>
</tr>
<tr>
<td>Drug abuser</td>
<td>Drug dependence, antepartum</td>
<td>Drug withdrawal maintenance therapy</td>
<td>Drug tolerance increased</td>
<td>Drug level above therapeutic</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Drug dependence, postpartum</td>
<td>Drug withdrawal syndrome</td>
<td></td>
<td>Drug level increased</td>
</tr>
<tr>
<td>Substance abuser</td>
<td>Polysubstance dependence</td>
<td>Drug withdrawal syndrome neonatal</td>
<td></td>
<td>Intentional overdose</td>
</tr>
<tr>
<td>Drug administered at inappropriate site</td>
<td></td>
<td>Rebound effect</td>
<td></td>
<td>Multiple drug overdose</td>
</tr>
<tr>
<td>Drug rehabilitation</td>
<td></td>
<td>Steroid withdrawal syndrome</td>
<td></td>
<td>Multiple drug overdose accidental</td>
</tr>
<tr>
<td>Drug screen</td>
<td></td>
<td>Withdrawal arrhythmia</td>
<td></td>
<td>Multiple drug overdose intentional</td>
</tr>
<tr>
<td>Drug screen positive</td>
<td></td>
<td>Withdrawal syndrome</td>
<td></td>
<td>Drug detoxification</td>
</tr>
<tr>
<td>Disturbance in social behavior</td>
<td></td>
<td></td>
<td></td>
<td>Drug toxicity</td>
</tr>
<tr>
<td>Needle track marks</td>
<td></td>
<td></td>
<td></td>
<td>Therapeutic agent toxicity</td>
</tr>
<tr>
<td>Neonatal complications of substance abuse</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Assessing Adverse Events

- Methodology for collecting abuse-related AEs requires standardization; differentiation from misuse important
  - Standardized clinical probes/training for eliciting AEs
  - Collection of consistent and meaningful details for case narratives
  - Sample classification of abuse-related AE types (chronological)
    1. ‘Psychoactive effects’ (e.g. elevated mood, feeling drunk)
    2. ‘Behavior’ (e.g. drug abuse, drug diversion)
    3. ‘Physical signs of abuse’ (e.g. needle marks, drug screen positive)
    4. ‘Outcomes’ (e.g. accidental death, accidental overdose)
  - Clinical probes will vary according to type of AE (e.g. ‘outcomes’ event will require different information compared to ‘psychoactive effect’ event)
Interpreting Adverse Events

• Clinical probes (standardized questionnaires/checklists) need to collect information consistently across studies to include (not limited to):
  – Non-leading, non accusatory questions
  – Collection at all time-points (AEs are not coded in real time hence probes cannot be triggered in real time)
  – Summarize all aberrant events observed in individual patient over time
  – Intentionality
  – Types of drugs involved; investigational vs. concomitant vs. contraband
  – Causality: drug-related; co-morbidity; other drug?
  – Duration of event
  – Medical history
  – Motive (behavioral)- related to abuse or misuse?
  – Triggering additional data collection e.g. UDT
  – Defining threshold of what is clinically relevant
Case Example

- A 48 year old female patient arrives at the clinic reporting pain and anxiety. A pill count reveals that a 1 week supply of pain medication is missing. The patient has no prior known history of substance abuse.

Abuse?

Misuse? Tolerance?

Diversion?
Self-Reported Misuse, Abuse and Diversion (SR-MAD) Instrument

- Confidential, self-reported questionnaire
- Probes past behavior and motive in order to classify aberrant behaviors into categories of abuse, misuse, or diversion
- Original version probes for opioid use but flexibility to adapt to other classes of drugs
- Adapted version to be used in a large post-marketing requirement study for long acting/extended release opioids

Withdrawal Scales

• Opioids (e.g.)
  – Clinical Opiate Withdrawal Scales (COWS)
  – Objective Opiate Withdrawal Scale (OOWS)
  – Subjective Opiate Withdrawal Scale (SOWS)
• Stimulants (e.g.)
  – Amphetamine Withdrawal Assessment Scale
• Benzodiazepines (e.g.)
  – Benzodiazepine Withdrawal Scale
• Alcohol (e.g.)
  – Clinical Institute Withdrawal Assessment of Alcohol Scale
• Cannabis (e.g.)
  – Cannabis Withdrawal Scale (CWS)
• General (e.g.)
  – Diagnostics and Statistical Manual (DSM-IV TR) - Dependence and Withdrawal
Additional Considerations

• Aberrant behaviors are not always related to the investigational drug
• Abuse is not the same as misuse although the aberrant behaviors may be similar
• Adverse events may be related to patient condition and not to the investigational drug (TEAEs* that are drug related are most relevant to assessing abuse potential)
• Patient verbatim terms and reports are important in characterizing the nature of the event

*Treatment emergent adverse events
Mitigation & Prevention Strategies

• Exclusion criteria for high risk patients
• Withdrawal from study
• Referring patient to treatment/addiction support
• Reinforcing importance of proper drug storage and disposal (e.g. lock box)
• Identifying events related to abuse, misuse, and diversion are challenging in patient trials
• Clinician/Investigator training is essential to identify and probe for events that may be associated with abuse, misuse, or diversion
• Clinical probes must be non-leading and consistent across study sites
• Mitigation plans must be implemented to ensure patient safety and data integrity
Discussion Points

• What can be done to address patient dishonesty (e.g. my dog ate my pills)?
• How is this data reviewed by regulatory agencies?
• How reliable is this data in concluding that abuse/misuse has actually occurred?
• Do all events need to be classified into abuse or misuse categories? What if there is not enough information to make the assessment?