Retrospective analyses of abuse-related outcomes in clinical trials of analgesic drugs and their interpretation

IMMPACT-X Abuse Deterrent Opioid Analgesics

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Opioid Products for Treatment of Pain – Primarily Extended Release – Risk Management Concerns

1. Use by non-tolerant individuals
2. Misuse, abuse and diversion
3. Unintended exposure

Pre-Market Product Review

New Drug Review

- Investigational New Drug (IND)
  - Process by which a sponsor advances to the next stage of drug development known as clinical trials
    - Animal Pharmacology and Toxicology Studies
    - Manufacturing Information
    - Clinical Protocols and Investigator Information
- New Drug Application (NDA)
  - Formal application to the FDA for approval of a new drug

Predictive Human Abuse & Diversion Potential Data: In Drug Development

- Human Pharmacology Laboratory Study
  - "Human Abuse Potential Study"
- Controlled and Open Label Clinical Studies – Efficacy and Safety Studies (Phases 1 – 3)
  - Safety Assessment
    - *Euphoria, mood elevation*
    - *Sedation, stimulation, hallucinations*
    - *Other relevant behavioral events*
  - **Evidence of actual abuse and diversion**

Concerns

- With **prospective evaluation**, procedures and criteria are defined and the clinical investigator receives appropriate training in the identification and coding of the behaviors of interest
- **Retrospective analysis** of data is used to assess
  - Dropouts, study discontinuations, misuse, abuse, addiction, aberrant behaviors, diversion, etc.)
  - Compare different pain patient populations for qualitative and quantitative differences in occurrence of aberrant behaviors

See various papers by S. Passik et al., 2006-9

Clinical trial outcomes raise concerns for the safe use of the drug in the general outpatient setting

- Unintentional fatal overdose
- Significant risks of overdose, misuse, abuse, and diversion
- Aberrant drug use behavior

Patients in Study

- Pain patients (cancer or non-cancer)
- High risk patients are excluded
  - Recent hx (within 5 years) or current evidence of alcohol or substance abuse might be at higher risk of abuse or addiction
  - Psychiatric condition that could compromise their safety if in study
  - Using an illicit substance or a medication for which there was no legitimate medical reason or need (UDS is conducted initially and randomly throughout study)

High Risk Behaviors

- Evidence for occurrence in clinical trials
- Can be as high as 20% patient population
  - Abuse/dependence
  - Overdose
  - Overuse
  - Positive UDS
- Possible Signals
  - Lack of drug accountability
  - Lost to follow-up
  - Identified as administrative reasons
  - Not known

See various papers by S. Passik et al., 2006-9

Study Dropouts/Discontinuations

- Subject was found to meet study exclusion criteria during the study
- Perhaps, the subject should not have been included in study in the first place
- But we do not always know individuals' histories
- Subjects can be very skillful in acquiring drugs for abuse and diversion, while keeping hidden their individual histories.

Reasons for Subject Dropout/ Discontinuations

- Lack of efficacy
- Adverse event
- Noncompliance to study protocol
  - Study visits
  - Study drug use
- Subject choice (convenience, other)
- PI choice

Diversion in Clinical Trials

- Patients withdrawn
  - Drug thefts related to patient actions
- Study centers report thefts of study drug
  - Taken from locked cabinets and involved forced entry
  - Lost in transit between pharmacy and study center
- Tabulate drug thefts
  - Tabulate by number (%) of patients
  - Tabulate by number (%) of study centers

Diversion

- Difficult to study prospectively
- Site investigators need to be trained so that each site is reporting events consistently.
- Training needs to occur before the start of the trial.
- “Diversion” is often not well defined
- Patterns of diversion heterogeneous
  - Example: Drugs used by family members

Limitations

- All protocol violations may not be aberrant behaviors
  - Noncompliance is not necessarily indicative of aberrant behaviors (abuse and diversion)
  - Aberrant behavior analysis does not serve as a formal assessment of abuse liability or as a diagnosis of abuse and addiction
- However, the legislative history of the CSA considers diversion and overuse as indicators of abuse potential.

General Problem of Drug Safety

- Even after subject drops out or is discontinued, we want the detailed information of reasons for the event
- All data on dropouts should be submitted for review
- Missing data can change interpretation of study results
- The protocol should define the terms of dropping out and discontinuations
  - Specific descriptions and reasons for the event need to be incorporated prospectively into the protocol
  - Site investigators need to be aware of signs and signals of abuse and diversion

Analyses can be useful

- Assessing abuse potential and abuse deterrence of new products designed to be less likely to be abused needs to be analyzed
- Providing new information in support of a REMS
- Providing information that can be useful in the development of the drug, directions for use, and precautions
- Assessing relative risks of the product compared to other drug products with same indication
- Relevant to determining effectiveness and safe use of the new drug

Analyses of dropouts/discontinuations

There is no good solution for the analysis

- The rates of dropout and discontinuation between the test drug and placebo can be compared
  - If significantly different (much higher), validity of study results is questionable
- Often times, there is a lack of adequate documentation of reason for the dropout
  - Include time to dropout or discontinuation
  - Recommend follow-up on the dropout subject to the end of the trial time
- All reasons for dropouts are important

Analyses, continued

- Presence or lack of a treatment effect should be identified
- Some individuals might continue on the drug because it is abuseable, as opposed to being effective
- If dropout rate is too high, fileability of the NDA may be an issue
- If too much missing data, study results for efficacy may not be interpretable
  - Should the dropout be replaced? The dropout rate depends upon the drug, its indication, and patient population

Additional Relevant Information

- Narratives of relevant CRF's for all patients who dropout or discontinue should be included
- Overall profile of these patients by reason for dropping out (e.g. AEs, treatment failures, lost to follow up, etc.) should be provided
- For more common events associated with dropouts, the incidence of these AEs should be provided
- For rarer events of *important* (serious, unexpected) AEs, the sponsor should critically assess whether any of these may represent treatment-associated injury

Summary - Retrospective Analysis

- Has limitations, but can convey important information
- Includes a compilation of events related to dropouts, discontinuations, and diversion and their evaluation
  - Patient information including CRFs and all available data on noncompliance and protocol violations
- Needs to include a description of training for all site investigators on assessing high risk behaviors, aberrant drug behaviors and diversion
  - Criteria for determining a “high risk” behavior
- Should describe the methodology and a proposal for analysis of data
  - Denominator recalculation (number of patients exposed to drug in trials) should be included

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