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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