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**Abuse-related outcomes:**

**Prospective evaluation in clinical trials of analgesic drugs**

Deborah B. Leiderman, M.D., M.A., FAAN  
CNS Drug Consulting LLC  
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**Challenge in Drug Development:  
to better characterize safety  
during development**

- Clinical Trials in general: highly selected patient populations; patients with co-morbid conditions excluded (e.g. cardiotoxicity—low detection rate in healthy young adults with low CV risks..)
- Specific challenge in analgesic domain: how to capture non-medical use and better characterize safety/ risk variables

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**Safety Issues - Risks of  
high dose opioid therapy**

- Overdose – non-fatal or fatal
- Misuse, abuse, and diversion
- Aberrant drug use behavior

Particularly challenging to capture in clinical trials

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### Risks /Safety Issues of (high dose) Opioid Products

- Use by non-tolerant individuals
- Misuse, abuse and diversion
- Unintended exposure
- Abuse/Addiction

Can these adverse outcomes be identified and characterized in clinical trials?

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### Signals of Interest in Clinical Trials – Retrospective Analyses

Per Mike Klein's presentation:

- Abuse/dependence
- Overdose
- Positive UDS
- Unreliability
- Using non-prescribed medication(s)
- Study drug theft
- Lost study drug
- Overuse or misuse of study drug (not taking as prescribed)
- Unapproved use of a medication used for another problem
- Acquiring opioids from other sources (medical or nonmedical)

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### Clinical Trial Drop-Outs & Discontinuations

- Drop-outs= missing data.....often important safety-related
- Misuse (including overdose, non-medical use, errors), non-adherence, diversion may be "hidden"

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**Chronic Opioid Treatment and Risk of drug abuse**

- Prevalence of active substance abuse in patients on opioid therapy for chronic pain – estimated at 20-40%; higher in some populations

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**Predictors of Opioid Misuse- Ives et al – UNC study 2006**

- Prospective cohort study
- 1 year incidence and predictors of misuse among patients enrolled in chronic pain disease management program within academic internal med practice
- N= 196

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**Ives - II**

- Referral Clinic- multidisciplinary team with PCP, clinical pharmacist, internist, psychiatrist, nurse
- Encouraged referral of difficult to manage patients
- Seen monthly until stable
- Medication agreement

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### Ives III - Opioid Misuse Study Definition

- Negative urine tox (UTS) for prescribed opioids
- UTS positive for opioids or CS NOT prescribed by practice
- Multiple providers, Diversion, Forgery
- Stimulants on UTS

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### Ives - IV

- Mean patient age 52, 55% male, high depression rate
- 62/ 193= 32% exhibited opioid misuse /15 pts negative UTS for Rx opioid
- Multivariate analysis- age (younger), history of cocaine abuse, drug or DUI, past alcohol abuse predicted misuse
- NOT predictive: race, SES, depression score, disability or pain scores

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### American Pain Society 2009\* Review of Current Evidence on Utility of Risk Assessment Tools

- Use of opioids for chronic NCP (non cancer pain) controversial –inconclusive and/or limited data
- Significant potential harms - how to minimize risks?
- Core elements of best clinical practice – risk stratification, monitoring for aberrant behaviors
- Evidence for validity/utility of tools limited

\*Dow et al  
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### APS 2009—Evidence Base

- 44 studies retrieved: 4 studies of risk prediction instruments; 9 studies of monitoring instruments; 2 studies on effects of UDS or adherence monitoring
- SOAPP and SOAPP-R and ORT (OPIOID Risk Tool) identified
- "No study evaluated the utility of formal risk stratification instruments compared with informal clinical assessments alone, or compared ..."

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### APS 2009 - Monitoring Instruments

- Current opioid Misuse Measure (COMM) – one study showed weak prediction of current aberrant drug related behaviors
- Other monitoring studies – methodological shortcomings
- Overall conclusions- need external validation, standardized definitions, clinical outcomes assessment

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### Where do we go from here?

- Trial design
- Patient populations
- Outcome measures
- Instruments/ tools

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### Recommendations: Methods and Variables

- Trial Design Innovations: Include prospective and systematic assessment of non-medical use (patients) or by others (abuse/diversion within family household— a challenge!!) Capture rather than lose the data..

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### Recommendations: Patient Variables

- Include high risk patients with comorbidity: history of pain and substance abuse disorder (alcohol, substance abuse – broadly define or consider prescription drug abuse history)
- Study Analysis plans can stratify and adjust for risk

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### Explore Assessment Measures

- Characterize study patients - SOAPP, COMM, ?
- Family-household members – Obtain history at a minimum!
- Adherence - Routine UDS; Explore electronic recording of dose/ tablet administration

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### Other Trial Design Thoughts

- Formal characterization of household risk-analyze as a variable
- Incorporate electronic monitoring of clinical try drug supply
- Routine UDS- only useful if systematic as is routinely done in addiction trials
- Measurement of "aberrant behaviors"/ non-adherence can be formally analyzed, even early protocol-specified terminations= DATA  
Example- patient discontinued due to repeated UDS results

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### FDA Abuse-Misuse Related AE list - prospective assessment in clinical trials

- Abuse/dependence - Big basket of behaviors
- Overdose - ?Capture through AEs
- Positive UDS -Yes
- Unreliability -Yes
- Using non-prescribed medication(s) - Query and UDS- yes
- Study drug theft -Yes- ?perpetrator
- Lost study drug -Yes- electronic monitoring of supply
- Overuse or misuse of study drug (not taking as prescribed)
- Unapproved use of a medication used for another problem- UDS
- Acquiring opioids from other sources (medical or nonmedical)- UDS, PDMP

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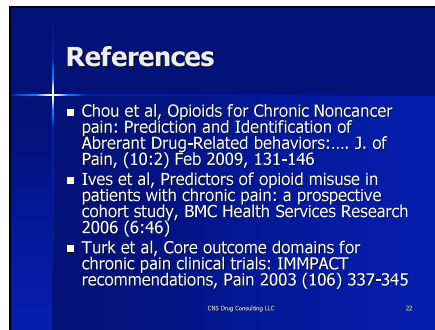
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### Systematic assessment of risk outcomes

- Consider comparative trials, particularly if investigational medication hypothesized to be "lower risk" than standard, comparator opioid analgesic product
- Potential to differentiate product from class—new products putative characteristics
- Implications for label and for REMS

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### References

- Chou et al, Opioids for Chronic Noncancer pain: Prediction and Identification of Aberrant Drug-Related behaviors:.... J. of Pain, (10:2) Feb 2009, 131-146
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