Panel Discussion: Best Practice in Physical Dependence/Withdrawal Assessments

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Factors to consider: nonclinical withdrawal assessments

• Profile of the NCE
  • Pharmacology
  • Behavioral profile (e.g. stimulant/depressant)
  • Chemistry

• Justification for comparator

• Dose and duration of treatment
  • Pharmacokinetic goals (ie. AUC vs Cmax)

• Duration of observation

• Species of test subject

• Route of administration

• Dependent measures
  • Sensitivity?
  • Representative of safety concern?
  • Translation to clinic?
Factors to consider: clinical withdrawal assessments

• Spontaneous AE capture or structured questionnaire?

• Common versus unique withdrawal symptoms for drugs of different classes
  • Best study design for drug with novel MOA?

• Learnings from/translation of effects seen in nonclinical studies

• Relapse of disorders
  • Potential for differences in sensitivity to withdrawal
FAQ’s
Parameters to measure in a withdrawal study?

- What are appropriate endpoints to consider measuring in a withdrawal study?
- Are there/should there be standard measurements (or a minimal required set) for withdrawal studies for CNS active drugs? Are there examples of endpoints that are widely applicable?
- Can I use an FOB as a standard physiology measure in a nonclinical withdrawal study?
- What is the appropriate length of the observation periods?
- Which parameters translate well from animal assessments to the clinic? Is it known if this translation is specific to a certain drug class?
- What outcomes are considered safety concerns?

Withdrawal assessments for all drugs?

- Is a withdrawal assessment routinely required for a non-CNS active drug, or a CNS active drug with low abuse potential?
- Would a non-CNS withdrawal syndrome have different implications for drug safety relative to a CNS withdrawal syndrome?
- How do I design a study for a non-CNS active drug – what are the withdrawal effects of interest (safety concerns)?
Comparators for nonclinical withdrawal studies?

- How should I select a comparator for an NME with a novel MOA?
- Is a positive control required in all studies?
- Which drug classes are well-characterized for withdrawal effects?
- What is necessary to validate a new positive control in a physical dependence/withdrawal study?

Data analysis in withdrawal studies?

- What analysis methods are appropriate; within group (pre-post) or between group comparisons?

Withdrawal assessments in repeat dose toxicology studies?

- Can I assess dependence and/or withdrawal in the context of a repeat dose tox study?
- If so, are any non-standard groups/data required to underwrite the study as an assessment of withdrawal?