Clinical Trial Designs to Evaluate Drug Withdrawal

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Disclosure

Altreos Research Partners Inc. provides consulting services to the pharmaceutical industry on abuse liability and clinical pharmacology

DL Global Partners Inc. provides consulting services to the pharmaceutical and device industry concerning development of products for brain disorders and abuse liability.

“Drug Withdrawal”

Old concept and terminology

- Physical dependence as a ***cause*** of drug addiction (1950s and 60’s)
- International Conventions (1961, 1971)/CSA (1971)/FD&C Act

Physical dependence as a cause was supplanted by behavioral construct of positive and negative reinforcement, and ‘psychological dependence’

Most of time we are not looking at diagnostic category of ‘drug withdrawal’ but simply emergent AEs

Terminology clarified to be “neuroadaptation” and discontinuation signs and symptoms

- Many drugs can do this e.g., beta blockers, antiepileptic drugs
- Value free with respect to being a reason for continued harmful drug use

Why Assess Withdrawal/Neuroadaptation and Physical Dependence?

1. Data are required

Under Section 812 of the CSA, the controlled substances are divided into five schedules. Each controlled substances is placed under Schedule I, II, III, IV, or V based on its potential for abuse, accepted medical treatment and safety within the United States, and its likelihood of causing physical and psychological dependence.

2. Safety
3. Label
4. Guidance to prescribers as to how to discontinue

Populations of Interest

Patients (primary or secondary indications)

Special populations

Healthy volunteers?

Design Considerations in Patients

Double-blind placebo-controlled discontinuation in long-term Phase II or III studies

- All or subset of subjects transferred to placebo
- Naturalistic pre- and post-discontinuation design
  - Collection of AEs with added time points/questioning
- Structured pre-post design
  - Pre-specified measures and data collection strategy and analysis

Placebo-Controlled Pre-Post Design

All subjects switched to placebo
On-treatment vs. off-treatment
Placebo vs. active

Dorian et al. 1983; Busto et al., 1998

Placebo Controlled Subset

Some subjects on active drug remain on drug, some are switched to placebo
On-treatment vs. off-treatment
But, on-treatment effects may “mask” withdrawal effects

Special Patient Populations and Contexts - Switching

- Clinical context of trials where patients
  - Are being switched to alternate/new therapy with titration to establish equivalent efficacy (e.g., AEDs, and others, e.g., antipsychotics, etc.)

In these contexts the switching, titrating and stabilization phase may be associated with AEs reflecting un-masked neuroadaptation

But, may be difficult to distinguish from AEs associated with new drug/regimen

Assessing Tolerance in Patients

Tolerance – a frequent aspect of neuroadaptation

- Effect size diminishes over trial
- Higher doses are needed to maintain or achieve same or adequate response

Approaches

- Within-patient time series analysis of differences in frequent and sensitive efficacy measures and TEAEs longitudinally within a trial
- Rarely done
  - Biases of clinical trial design and need to generate dosing recommendations that can accompany approved indication label
  - Most trials are proscribed to be fixed dose from beginning to end
  - Trials not very sensitive with focus on between group comparisons "response was maintained"

Designs: Healthy Volunteers

PROS

May test intrinsic neuro-adaptive potential of a drug

"Clean" subject pool

Designs seem straight forward and easily controlled

Good for drug classes for which antagonists are available

May need smaller sample sizes because of more frequent and sensitive measures

'Healthy' volunteers, but e.g., opioid dependent? (e.g. Tomkins et al.)

CONS

Not a group at risk, except maybe in naturalistic world of healthy abusers

Too clean? – Who cares and what do we learn of clinical importance for label or clinical practice?

What does a signal mean? Many drugs will give a signal

What doses? Can a wide dose range be given? How long to treat?

Ethical and safety issues?

Evaluation of Zopiclone Physical Dependence Liability in Normal Volunteers

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Pharmacology *27:* suppl. 2, pp. 228–234 (1983) /
Int. Pharmacopsychiat. *17:* suppl. 2, pp. 228–234 (1982)

Healthy male volunteers (N=9)

56 day randomized crossover with PBO 21 nights + 7 nights PBO or ZOL 7.5mg 21 nights + 7 nights of PBO

Endpoints:

- Heart rate, BP, auditory evoked EEG (all n.s.),
- sleep duration (ZOL > PBO 28 min $p < 0.013$,
- sleep soundness, (ZOL < PBO disc day 2 and 4; $p>0.0001$);
- state anxiety (ZOL > PBO disc day 2 and 4; $p>0.0021$)

What did we learn?

- Studies need to be long, complex and require a supportive environment
  - Compliance and retention
- Measures need to be sensitive and done frequently
  - Inclusion of objective measures important
- Ethics and risks of exposing healthy volunteers to medication they don't need
  - Role of payment as inducement to take unknown risk
- Found a small 'signal' but don't know what it means (clinical relevance)

Challenges in Design and Interpretation

- In clinical trials, doses are therapeutic and dose range is limited
  - Drug abusers take high doses for a long time
- Selection of measures and scales
  - For NCEs, can only guess at potential discontinuation signs and symptoms
  - Usually have no idea about true clinical importance of small differences
- Half life assumption is a huge over-simplification
  - Onset and offset of neuroadaptive changes may or may not map to PK
- Proper designs are costly and add complexity to clinical trials
  - Bias that clinical trials end with last dose and safety follow up visit

Challenges in Design, Analysis and Interpretation II

- Placebo-control
  - Beware Pseudo-withdrawal - patient reports vague symptoms when warned that discontinuation is imminent
  - Many of the 'validated' scales, contain…vague symptoms…
  - Blinded discontinuation is essential
- Abrupt or tapered discontinuation?
- Frequency and timing of data gathering
  - Pre-discontinuation baseline
  - Post-discontinuation
  - Observations by phone, clinic visit or some combination?

Data collection strategy

- Intense follow up on AEs
- Open-ended probe questions
- Semi-structured probe question set
- Detailed question set or use of proscribed scales
- Narratives

Consultation with FDA-CSS

- Life is better with prospective planning and strategy
  - Pre-clinical and clinical strategy to collect data concerning discontinuation should be discussed with FDA-CSS (generally as early as possible – EOP2 or Type C meeting)
  - Late add-ons and modifications of trials that are underway is very upsetting to trial conduct, sites and finance and often involves too many compromises and rationalizations
  - Salvaging data from trials that are underway or worse completed are rarely adequate
- These data are required (per CSA) – but extend to label/clinical practice

Conclusions

- Prospective inclusion of blinded washout periods in existing trials provide **required** data on discontinuation phenomena and inform labeling and clinical practice
- May be difficult for some indications, *but*…
  - Consider if risks to HNV (not already 'voluntarily' dependent) are justified
    - Studies in HNV don't inform patient risks/clinical management
    - Gives some idea of "physical dependence" but this is neither *necessary nor sufficient* to induce abuse and "addiction"
    - What can we learn?
      - Severe syndromes likely to emerge from animal & patient evaluations
      - Clinical relevance to abuse/'addiction' of a few mild emergent signs?
    - Does it pass the "cringe test"? Ethics approval likely to be a challenge

Definition of a healthy patient?

… one who hasn't been tested enough

Definition of a drug without neuroadaptation?

… one that hasn't been tested enough

Thank-you

QUESTIONS??