Clinical Considerations for the Statistical Evaluation of Abuse Potential Studies

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Outline

• General study design & statistical tests

• Endpoints and parameters

• PK / PD

• Meaningful results
Guidance: Interpretable Study

- Discriminate positive control versus placebo
- Must reliably report drug liking
- Ratings of drug experiences related to the drug’s subjective effects
- Similarity to specific classes of known drugs of abuse
- Other factors that influence the significance of study results include:
  - Demographics: age, sex, race, drug of choice, frequency of participation in drug studies, duration of drug abuse, variety of drugs used, and duration of drug abstinence
Study Design

• Double-blind, double-dummy, placebo and positive control, crossover studies
  – Critical comparisons
    ▪ C v P (validity)
    ▪ T v P
    ▪ T v C
    ▪ Slopes of the dose effect functions across different measures should be determined
  – Repeated Williams Square
  – Outcomes/endpoints
  – Sample size
    ▪ Co-primary endpoints
    ▪ Multiplicity adjustment
    ▪ Parametric v Nonparametric
Statistical Tests

Parametric

• Proc Mixed
  – Assumes residuals are normally distributed
    ▪ Shapiro-Wilk
  – Multiplicity
    ▪ Benjamini-Hochberg

Non-parametric

• Wilcoxon signed rank
  – Symmetrical distribution of differences

• Sign test
The Dose Matters

- sweet spot
- diminishing returns
- harmful dose

benefit

amount of stressor
Endpoints & Parameters

• Most directly related to likelihood of abuse
  – Liking
    ▪ At the moment, Overall
  – TDAA
  – Drug similarity
  – Drug effects
    ▪ Specific (eg, Good, Bad, Any, High, Spacey, Sleepy, Dizzy
    ▪ Series (eg, DEQ, Bowdle, Leeds, Bond-Lader)

• Drug effect typical of drug class
  – Strength of drug effect
  – Behavioral and cognitive performance
    ▪ Hallucinations, psychomotor, memory, perception, attention, language ability,
      consciousness, executive function
  – Physiological effects
    ▪ Sedation, cardiac, miosis
  – Mood state changes
    ▪ ARCI, POMS

• PK profile
  • Emax / Emin
  • Max change from baseline
  • TEmax / TEmin
  • Full/Partial AUE
  • Cmax
  • Tmax
  • Full/Partial AUC
  • AQ
  • $T_{1/2}$
Pharmacodynamics

- Psychoactive Effects
  - Sedation
  - Euphoria
  - Perceptual distortion
  - Cognitive distortion
  - Hallucinations
  - Mood changes

Pharmacokinetics

- $C_{\text{max}}$
- Time to onset
- $T_{\text{max}}$
- $\text{AUC}_{0-\text{inf}}$
  - Partial AUC
- $T_{1/2}$
- Abuse quotient

“…[PD] will be of value because it can help to correlate psychoactive drug effects with achieved plasma concentrations.”
PK / PD

**PK**

**PD**

Time (Hours)
I used to think correlation implied causation.

Then I took a statistics class. Now I don't.

Sounds like the class helped.

Well, maybe.
What is Clinically Relevant?

• The objectives of [HAP] studies are to provide information on the relative abuse potential of a new drug in humans and contribute to predicting the likelihood of abuse when drugs become available
  – Statistically significant → clinically meaningful

• Can we model our approach after others?
  – Meaningful reduction in pain (0-10 NRS)
  – Predictability of CSSRS / other psychiatric rating scales
Conclusions

• …to identify subtle differences in drug effects that are relevant to abuse assessment
  – Maximize data collection, minimize impact
    ▪ Pilot studies; robust PK
  – Clinical and statistical groups work closely to identify, evaluate, and improve confidence in data collection, study design, and statistical models
    ▪ Modeling PK / PD
    ▪ Active comparators with demonstrated reduction in abuse potential
  – Determine clinically meaningful reductions in abuse potential
    ▪ ADF guidance