

**PRAHEALTHSCIENCES**

## **Clinical Considerations for the Statistical Evaluation of Abuse Potential Studies**

Michael Smith, PharmD



# 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

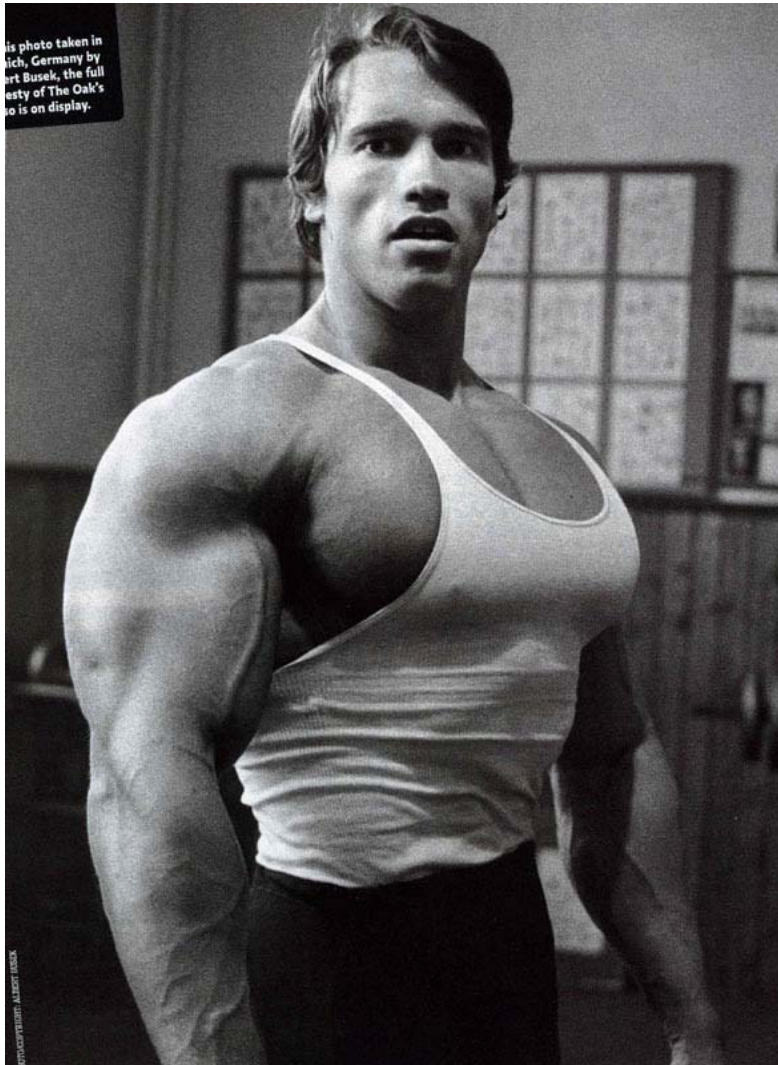
- Proc Mixed
  - Assumes residuals are normally distributed
    - Shapiro-Wilk
  - Multiplicity
    - Benjamini-Hochberg

## Non-parametric

- Wilcoxon signed rank
  - Symmetrical distribution of differences
- Sign test



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### The Dose Matters whole5life.com





# 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<sub>1/2</sub>



# PK / PD

- Pharmacodynamics

- Psychoactive Effects

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

- Pharmacokinetics

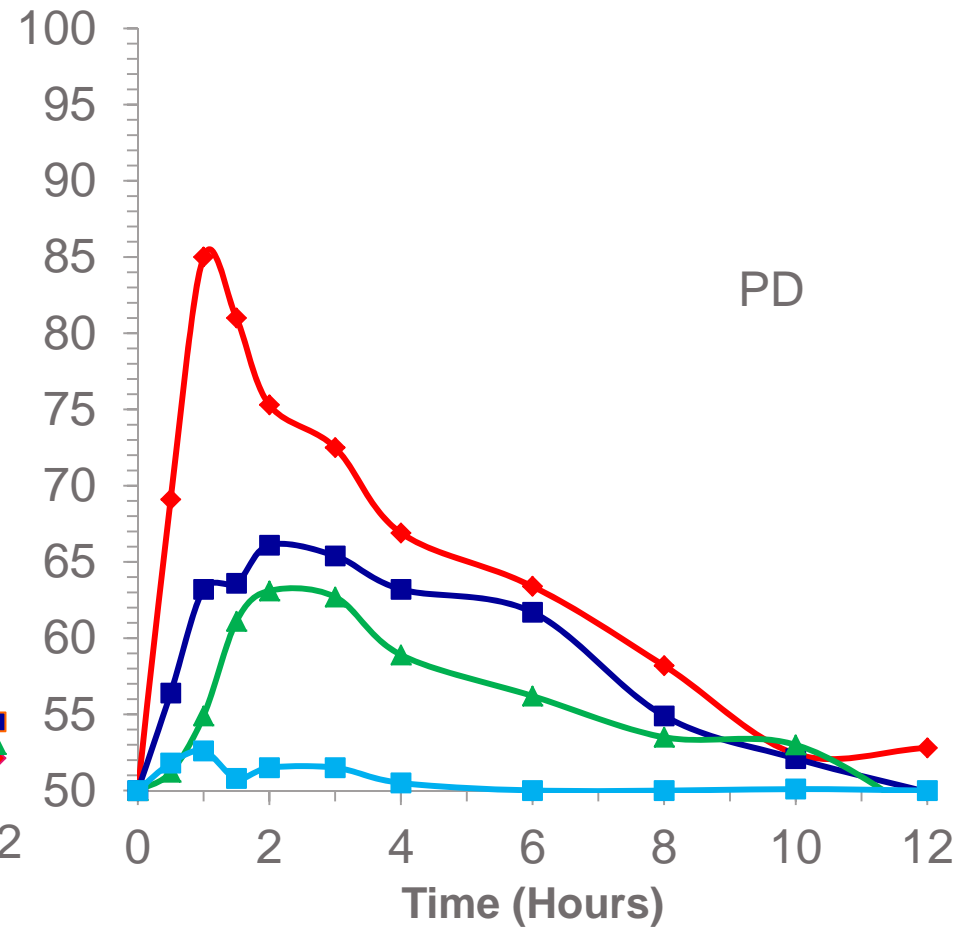
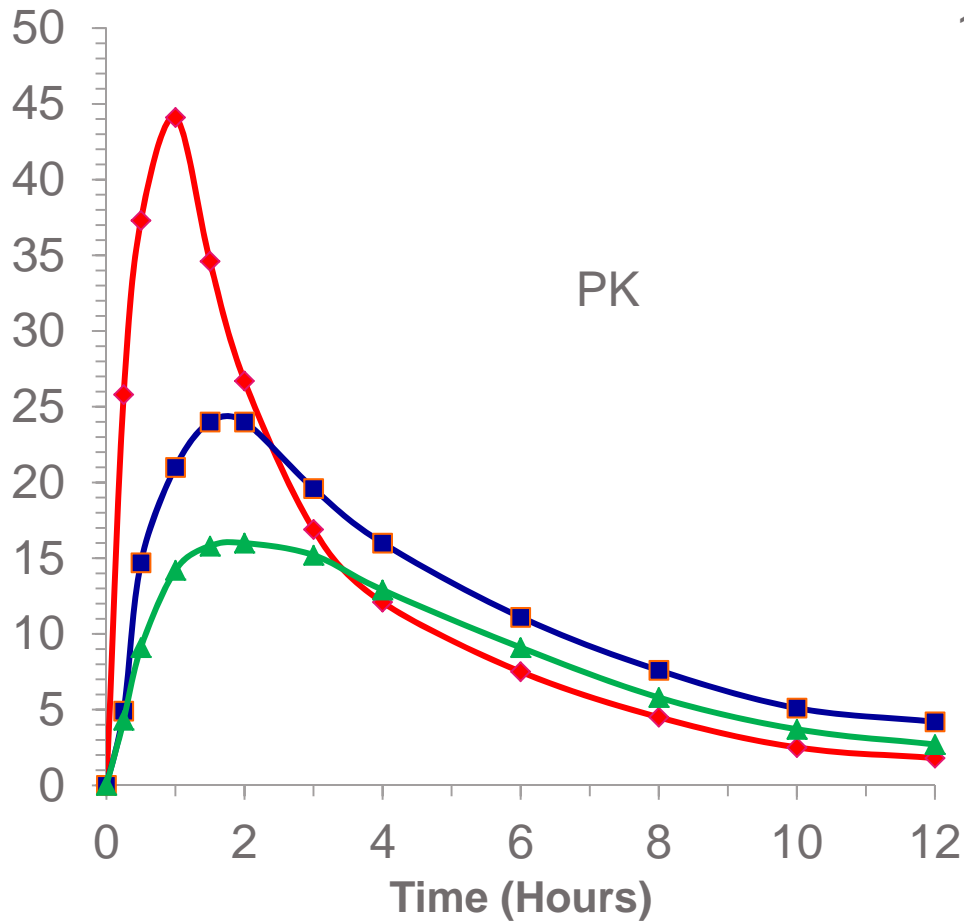
- $C_{\max}$
- Time to onset
- $T_{\max}$
- $AUC_{0-\infty}$ 
  - Partial AUC
- $T_{1/2}$
- Abuse quotient

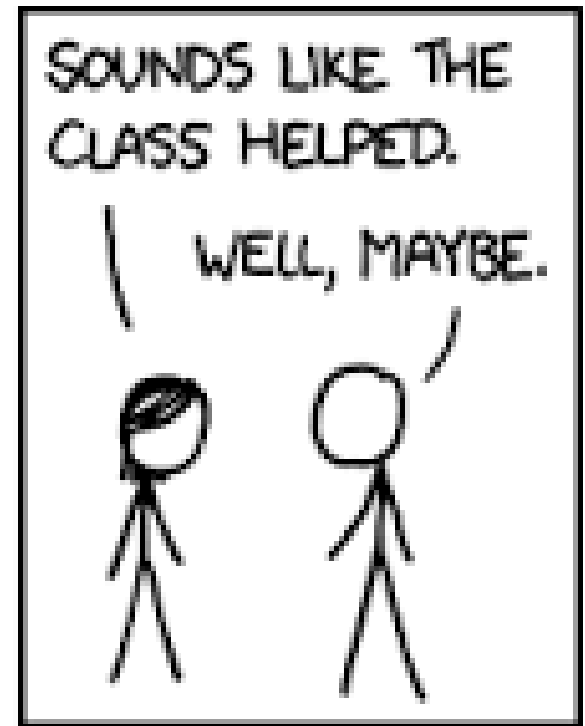
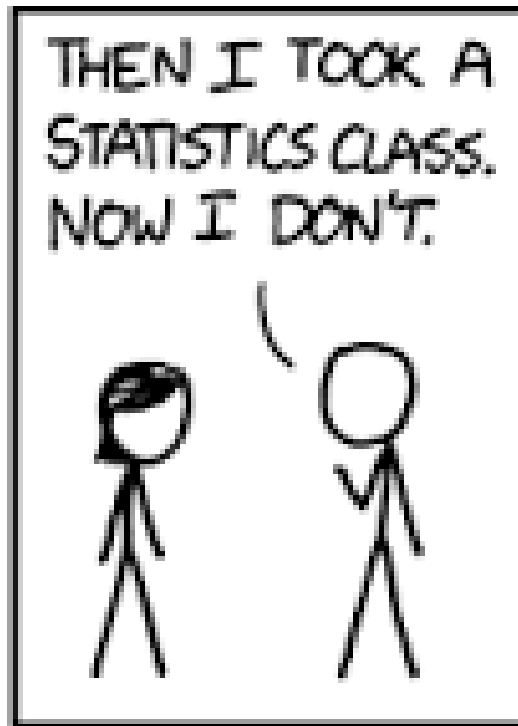
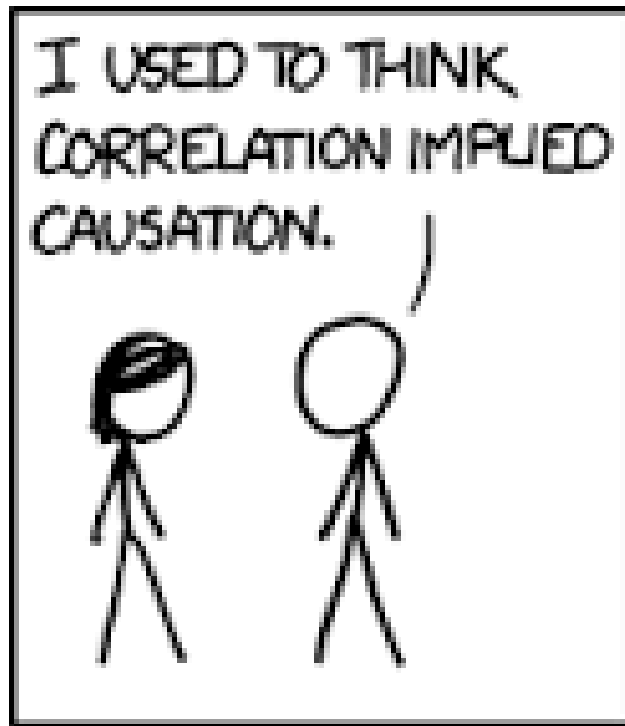
“...[PD] will be of value because it can help to correlate psychoactive drug effects with achieved plasma concentrations.”





# PK / PD







# What is Clinically Relevant?

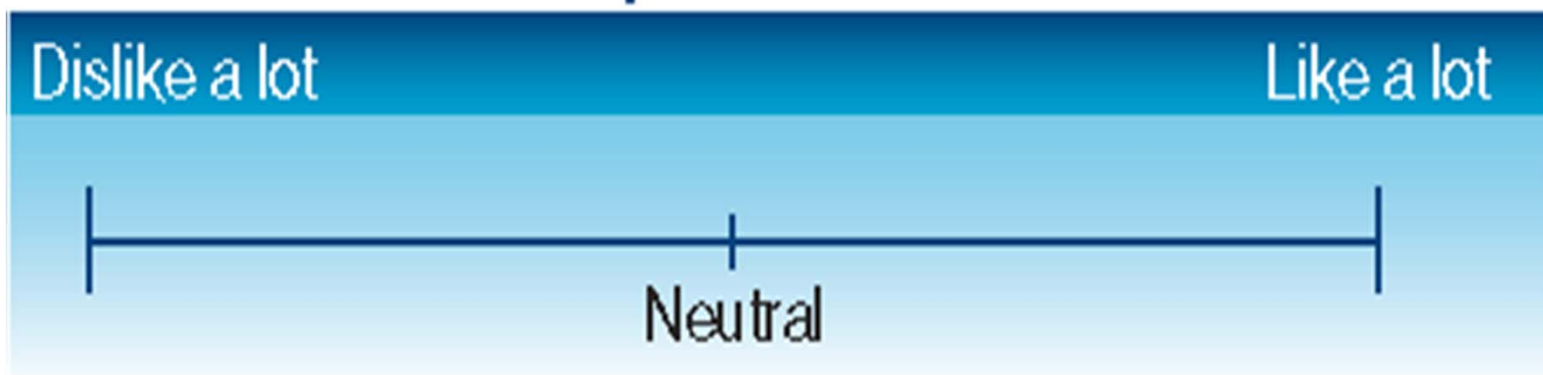
- The objectives of [HAP] studies are to provide information on the relative abuse potential of a new drug in humans and contribute to predicting the likelihood of abuse when drugs become available
  - Statistically significant → clinically meaningful
- Can we model our approach after others?
  - Meaningful reduction in pain (0-10 NRS)
  - Predictability of CSSRS / other psychiatric rating scales



## Unipolar VAS



## Bipolar VAS





# 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