Evolving Statistical Methodology to Assess HAP Studies

Selecting Margins for Different Positive Controls (*vs*. Placebo) – Does a One Size Fits All Approach Work?

Denise Milovan, PhD, CPsych

Cross Company Abuse Liability Council Member

Altasciences Consulting Senior Neuroscientist, Neuropsychologist

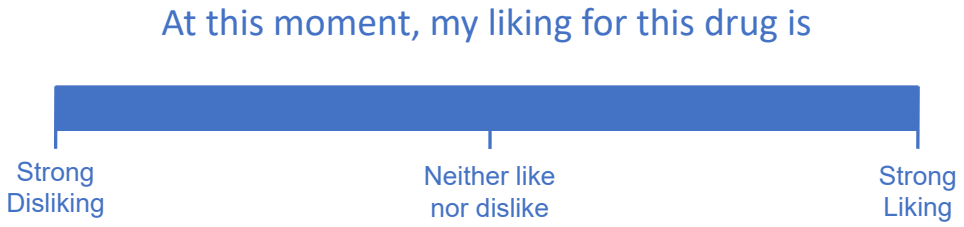
Outline

- FDA Guidance on Assessment of AP: Statistical Challenges
- Application of the AP Guidance to Psychedelics

Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry: Assessment of Abuse Potential of Drugs. 2017.

HAP Study Design: Power to Detect Differences

- Cross-over Design – Subjects serve as their own control thus, augmenting the ability to detect treatment differences
- Enriched Population – Subjects are selected for prior recreational use of drugs in the same or similar drug class as the investigational product
  - It is not recommended that drug-naïve subjects be used in HAP studies because this population has not been validated scientifically as being able to provide accurate information on the abuse potential of a drug
- Qualified Enriched Population – Subjects with recreational experience are further selected for their ability to identify, tolerate, and indicate liking of the psychoactive effects of the drug class



Qualification Criteria

≥ 40 Drug Liking E_{max} (P) ≤ 60

Drug Liking E_{max} (C) > **75**

Drug Liking E_{max} (C) - E_{max} (P) ≥ 15

Qualification *vs*. Treatment: Is the Drug Liking 15-Point Difference the Same?

- Qualification Phase
  - A subject who does not feel drug effects following intake of an active comparator has a 50% chance of guessing. They can respond as if they had received an active comparator and select strong drug liking (ie, scores above 50 points on DL VAS)
  - Qualification of appropriate subjects requires understanding of subjective effects patterns associated with different drug classes as well as of subject behaviours and motivations

- Treatment Phase
  - Typically, 4- or more study arms
  - The same 50 DL VAS points (ie, scores ranging from 51-100) must be distributed amongst 4 not 2 conditions
  - Subjective liking responses must be recalibrated to afford accurate discrimination between 4 conditions

➢ The increased complexity of the treatment phase is generally associated with increased subjective response variability and smaller C-P differences.

➢ A 15-Point C-P Qualification difference may correspond to a smaller numerical difference during Treatment.

HAP Studies 1st Principle: Establish Study Validity

- Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)?

$$H_0: \mu_C - \mu_P \leq \delta 1 \quad \underline{vs} \quad H_A: \mu_C - \mu_P > \delta 1$$

  - *The actual value of δ1 will vary according to such factors as subjective measures, drug class, and route of drug administration.*
  - *All the margins should be pre-specified and justified in the protocol*

- In practice, **δ1 = 15**

  Irrespective of measures, drug class, route of administration, or scientific justification for a δ1 ≠ 15

Uniformity in Statistical Decisions

- Uniform statistical requirements presuppose substance use of different classes of drugs is a unitary phenomenon

What we know

- Different drug classes (eg, stimulants vs depressants) are associated with different response profiles to subjective measures including Drug Liking VAS – opioids tend to have more pronounced effects, particularly when administered intranasally, relative to other drugs of abuse and routes of administration
- Different drug classes are associated with different inter-subject variability – stimulants show large individual response variation to subjective measures[1, 2, 3, 4]
- Addictions to different classes of drugs, such as stimulants and opiates, are reflected in salient cognitive and neurobiological differences
  - Stimulants produce arousing and activating effects
  - Opiates produce mixed inhibitory and excitatory effects[5]
- Rewarding effects of stimulant self-administrations are greater in new and arousing environments than in familiar and safe environments (eg, clinical trial environment)
- The opposite is observed with the sedative effects of opiates[6, 7]

Adaptive Statistical Decisions

What we may conclude

- One size may not fit all
- Workarounds to 'manage' regulatory recommended statistical margins have included:
  - Blinded outlier analysis conducted for each Drug Liking VAS E_{max} paired difference in the completer population.

    Outlier identified using Tukey fences
    Lower Fence = Q1 – (1.5 x IQR) Upper Fence = Q3 + (1.5 x IQR) Q1=1st quartile, Q3=3rd quartile and IQR=interquartile range

    Lower and upper fences calculated for each paired difference. The completers population would exclude subjects with at least n-1 of the n paired differences outside the respective lower or upper fence

  - Defining an additional study population, modified completer population (in collaboration with FDA)

    All subjects in the Completer population, excluding problematic subjects with unreliable responses which can alter study results. For the Drug Liking VAS scale, elimination criteria used to define the modified completer population include:
    1) Similar E_{max} scores (within a 5-point difference) for a subject across all study treatments (including placebo) OR
    2) E_{max} for placebo > 60 AND the E_{max}(placebo) – E_{max}(positive control) ≥ 5
- Margin determination (δ1) relying on a scientifically sound rationale accounting for subjective measures, drug class, and route of drug administration can limit the need for identifying and applying workarounds

Dynamic Nature of HAP Investigations

- Controlling response variability and improving subject selection remain important goals for HAP studies
- Some considerations include:
  - Adaptive informed consent strategies targeting minimization of placebo effects in Qualification and Treatment Phases
    eg, "You may receive one or more placebo doses and one or more active drug doses up to a maximum dose of __ for Drug1 and a maximum dose of __ for Drug2"
  - Qualification Phase with the same number of arms as the Treatment Phase or, at a minimum, 2 placebo and 1 active control conditions
  - Confirming language comprehension and minimum level of education required for completion of all selected measures (eg, not including subjects with weak comprehension of the English language for PD measures administered in English)
  - Incorporating sensitivity analysis to identify, and potentially exclude, subjects who qualified very well (ie, showed a large difference between placebo and the active control) but failed to demonstrate drug liking for the active control or showed drug liking for placebo during the Treatment Phase
    Sensitivity analyses may be especially relevant for drugs with novel mechanisms of action

Application of the AP Guidance to Psychedelics

- The 3-month-old Psychedelic Drugs Draft Guidance highlights the importance of applying robust evidentiary standards to identify signals of abuse.

- Psychedelics seem particularly well-situated to shine a bright light on the intricate nature of human behaviour and the challenges of studies aiming to adequately predict abuse potential in the real world.

References

1. Brown WA, Corriveau DP, Ebert MH. Acute psychologic and neuroendocrine effects of dextroamphetamine and methylphenidate. Psychopharmacology (Berl) 1978;58:189–195.
2. de Wit H, Uhlenhuth E, Johanson C. Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. Drug Alcohol Depend. 1986;16:341–360.
3. Holdstock L, de Wit H. Individual differences in responses to ethanol and d-amphetamine: a within-subject study. Alcohol Clin Exp Res. 2001;25:540–548.
4. Huskinson SL, Naylor JE, Rowlett JK, Freeman KB. Predicting abuse potential of stimulants and other dopaminergic drugs: overview and recommendations. Neuropharmacology 2014;87:66–80.
5. Stewart J, De Wit H, Eikelboom R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychol. Rev. 1984;91:251–268.
6. Caprioli D, Celentano M, Paolone G, Lucantonio F, Bari A, Nencini P, et al. Opposite environmental regulation of heroin and amphetamine self-administration in the rat. Psychopharmacology (Berl) 2008;198:395–404.
7. Badiani A. Substance-specific environmental influences on drug use and drug preference in animals and humans. Curr Opin Neurobiol. 2013;23(4):588–96.