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Outcome Measures: The Role of Objective, Physiologic and Safety Data

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Framing the Topic

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- Topic definition somewhat arbitrary
  - Physiologic versus non-physiologic??
  - Subjective versus objective
  - Measured by the brain versus a machine
- Measurements that don't relate to the likely reinforcing properties of a drug or behaviors related to taking drug
  - Many physiologic adverse events can be punishing and decrease likelihood of repeated drug taking
  - Many physiologic events can teach as to similarity to known drugs of abuse
- Some physiologic or behavioral adverse events e.g. perceptual change with opioids with kappa or sigma activity suggest different types of abuse

Defining Topic Areas

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1. Safety measures
   - Human experimental studies
     - Physiologic measures
     - Adverse event reports
   - Clinical trials
     - Adverse events reports
2. Pharmacologic effects
   - Human experimental studies
   - Clinical trials
3. Pharmacokinetics

Analgesic Development

- Historically full agonist opioids
- Varying degrees of mu selectivity and specificity
- Novel receptor systems – prototypic pharmacologic framework won't work very well
- Peripheral and central actions
- Adjunct therapies

Human Experimental Studies

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- Single dose cross over with 2-3 dose levels of active drug
- **Some doses will be high doses often near the MTD**
  - Prior exposure in limited number of subjects (i.e., SAD / MAD studies with 6-8 subjects)
  - Margin of safety of the drugs determines the form and intensity of the monitoring
  - The margin of safety often becomes apparent during the study
- Subjects are “healthy” volunteers / drug users, screened for risk factors and often screened for ability to tolerate doses (pre-study “qualification”)
  - Almost 50% will fail medical screening
  - The less stringent the study inclusion/exclusion criteria or the less robust the screening process the greater the risk?
- Comments may not apply necessarily to drug discrimination studies or low dose self administration studies

Standard Safety Monitoring

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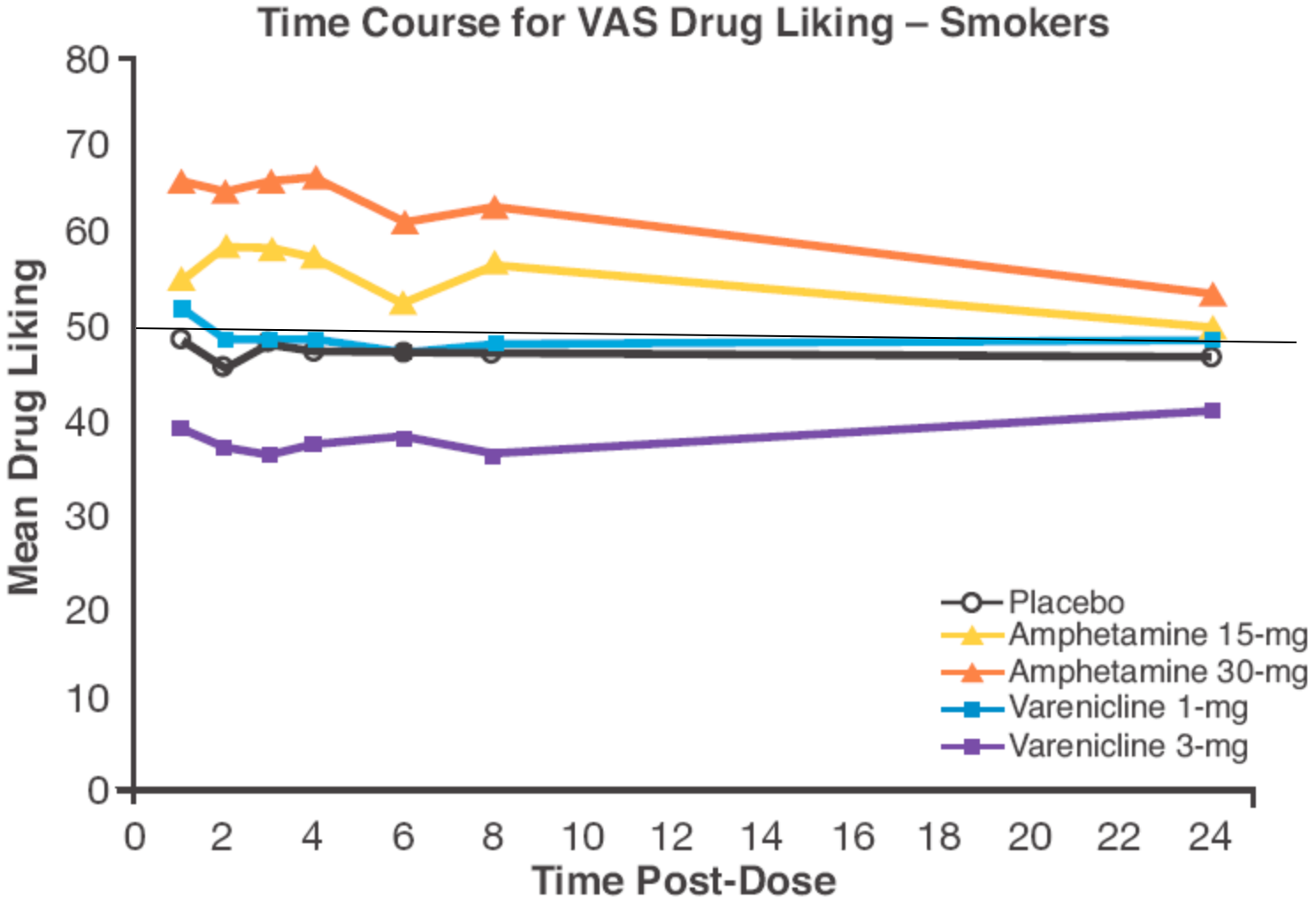
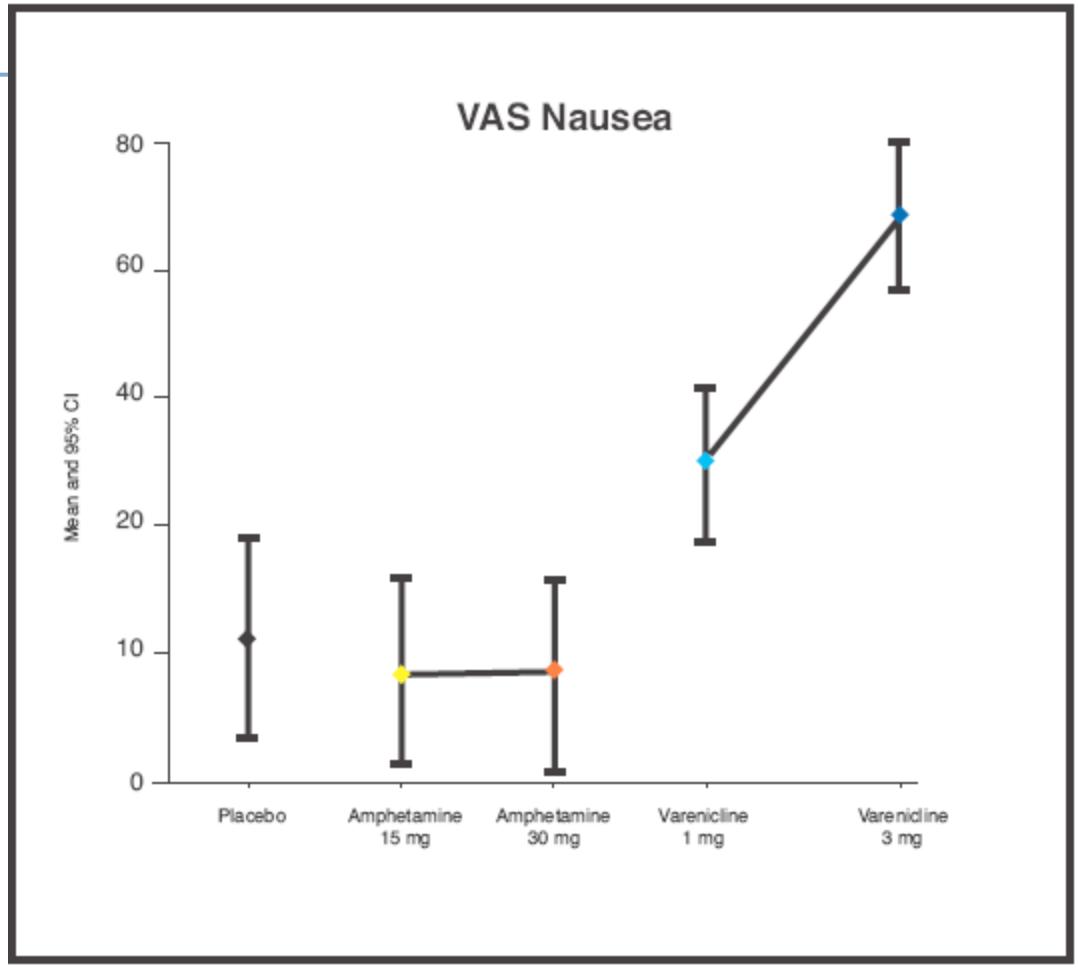
- Type, frequency and timing matched to PK and risk
- Adverse events
  - Spontaneous
  - Elicited
- Types of monitoring
  - Cardiovascular
  - Respiratory
  - Laboratory
  - Urine drug testing

Varenicline: VAS Liking Bipolar Scale – Liking Disliking



Varenicline: Nausea

Nonsmokers

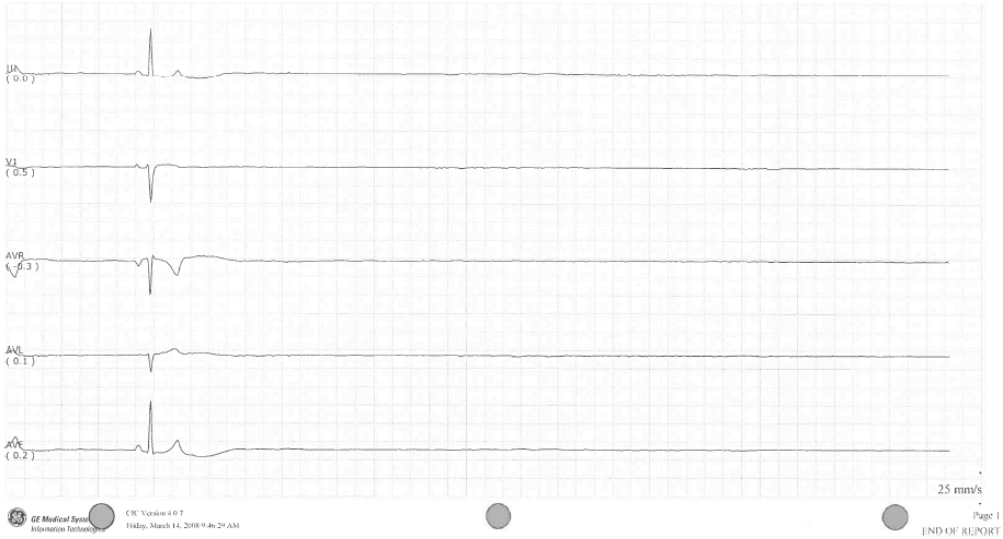


Cardiovascular Monitoring

- Blood pressure and heart rate
  - Observer driven
  - Automatic
  - Electronic data transfer
- Intermittent electrocardiograms
- Cardiac Telemetry –
  - Intermittent
  - Continuous
  - 12-72 h full disclosure

Examples of Cardiac Events on Telemetry

- VPB and APBs
- Bradycardia – HR <40
- Vasovagal events
- Supraventricular tachycardia
- Persistent bigeminy
- Ventricular tachycardia – 4 to 52 beats
- Asystole 30 seconds



Respiratory Monitoring

- Respiratory function
  - Respiratory rate
  - Automatic recording
  - Tidal volume
  - Minute volume
- SaO2
  - Continuous or intermittent (often part of telemetry)
  - 95%/90%
  - Late onset with CR opioids
- End tidal CO2
- CO2 sensitivity
- Arterial blood gases

Clinical Laboratory: During a Study

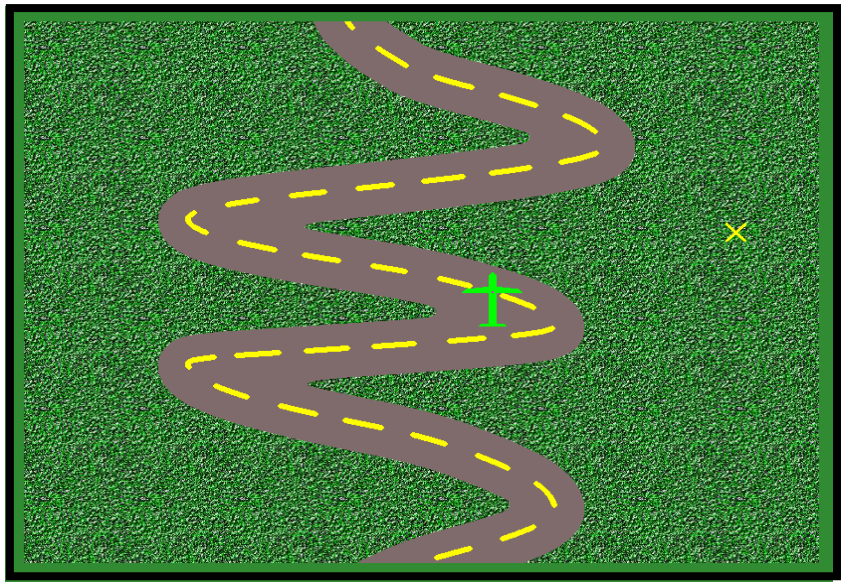
- Selection based on standard panels or targeted to actual risk?
- Very few really add value – way too many are done
- Boiler plate protocols and legacy traditions
- Regulatory tradition and expectation – measure a lot

Urine Drug Testing

- Not a safety test – is a drug use test
- Qualitative, semi-quantitative, quantitative
- Thresholds and cut offs are arbitrary
- No relationship of positive UDS and clinical effects
- No evidence that any level in the urine alters the pharmacodynamic measures in a human abuse liability study if no evidence of clinical intoxication
- Paradox – study is in drug users but they are meant to have negative UDS!!!
  - Some sponsors may not even want to see the drug that is being given in the study show in the urine eg benzodiazepines

Other Measures

- Motor tracking performance with divided attention task
- Simple and complex reaction time
- Cognitive testing - memory, executive function
- EEG
  - Internittent or continuous
  - Evoked potential
  - Sensory gating
- Pupillometry
- Lumbar puncture
  - single
  - Multiple
  - cannula
- fMRI
- PET



Pupillometry

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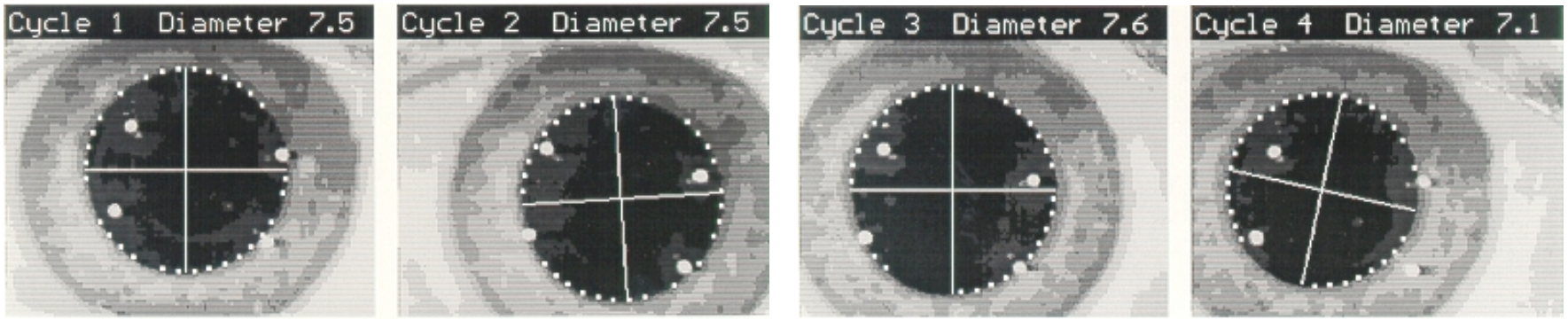
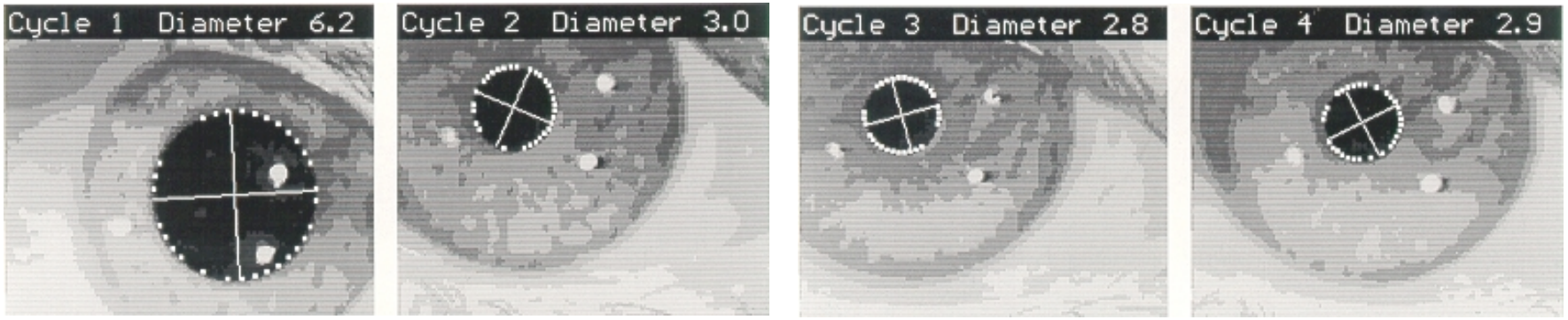
Placebo Response



Fentanyl Response



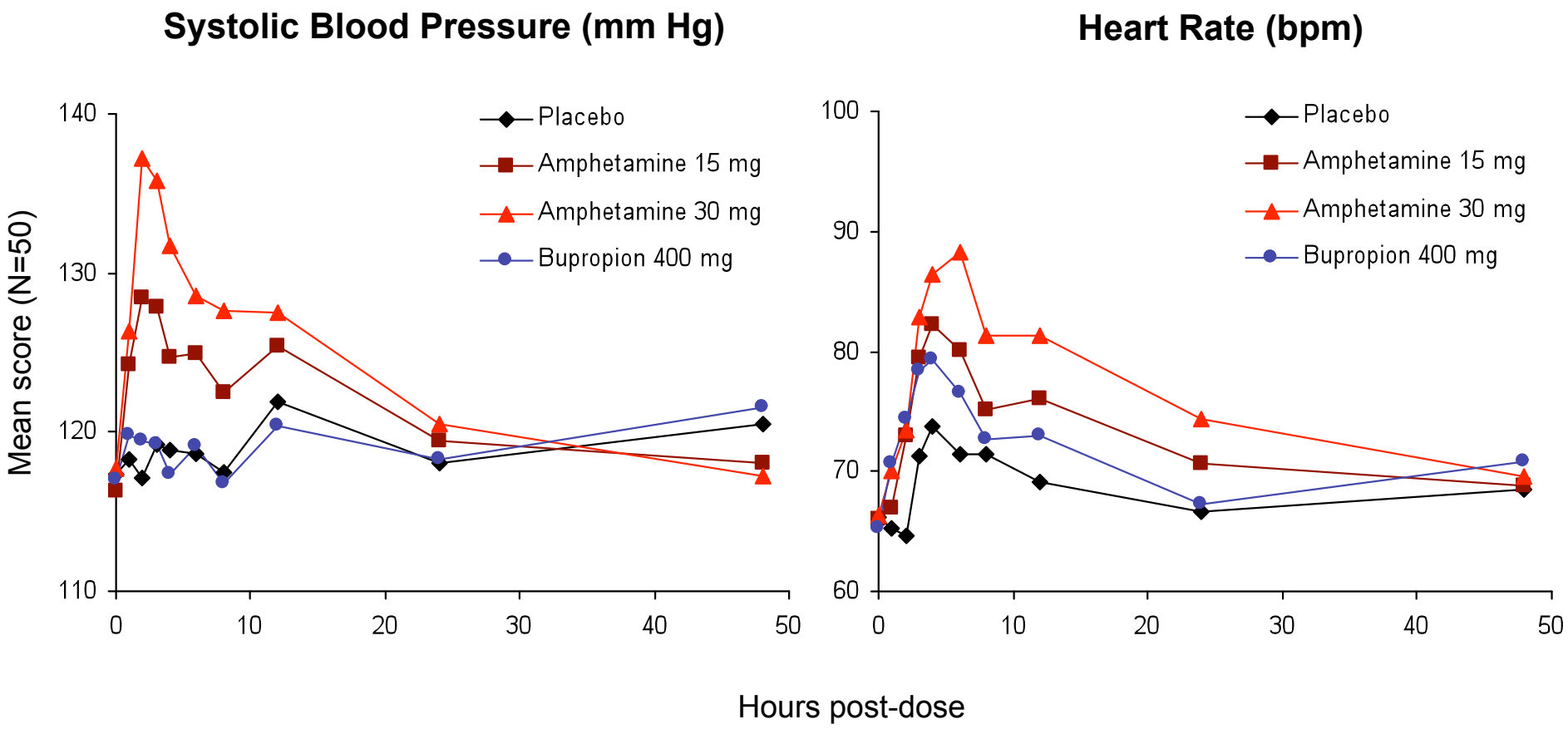
Opioid Pharmacology

- Pupilometry
- Heart rate
- Respiratory rate
- Lacrimation and salivation
- Bowel sounds
- Micturition
- Nausea and vomiting
- Postural steadiness

Stimulant Pharmacology

- Heart rate
- Blood pressure
- Tremor
- Reflexes
- Pupilometry
- Cognitive function,
- reaction time,
- motor tracking, attention (may be improved)

Stimulant-Induced Changes in Vital Signs



Sedating Agents

- Cognitive function,
- reaction time,
- motor tracking,
- attention (impaired)
- Critical flicker fusion
- Ocular pursuit
- Standing steadiness platform
- EEG
  - Evoked potentials
  - Topographic mapping

Impaired Cognition and Subjective Sedation

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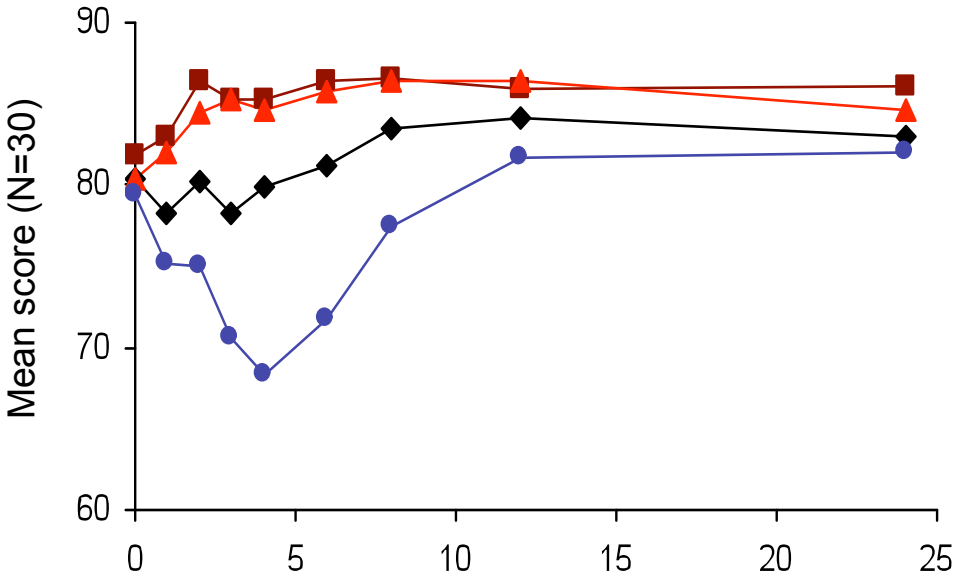
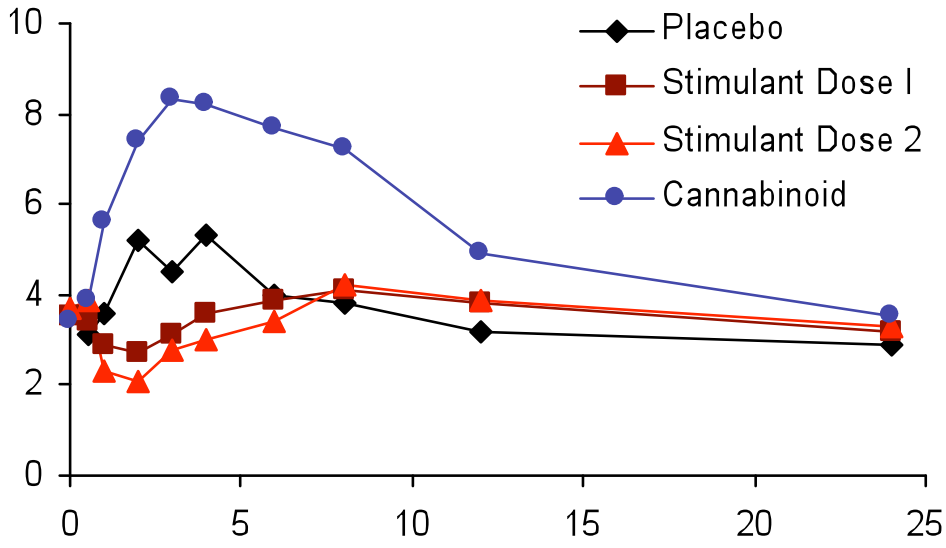
Divide Attention Test with Manual Tracking (Percentage Over Road)



Subjective "Sedation" (ARCI PCAG)

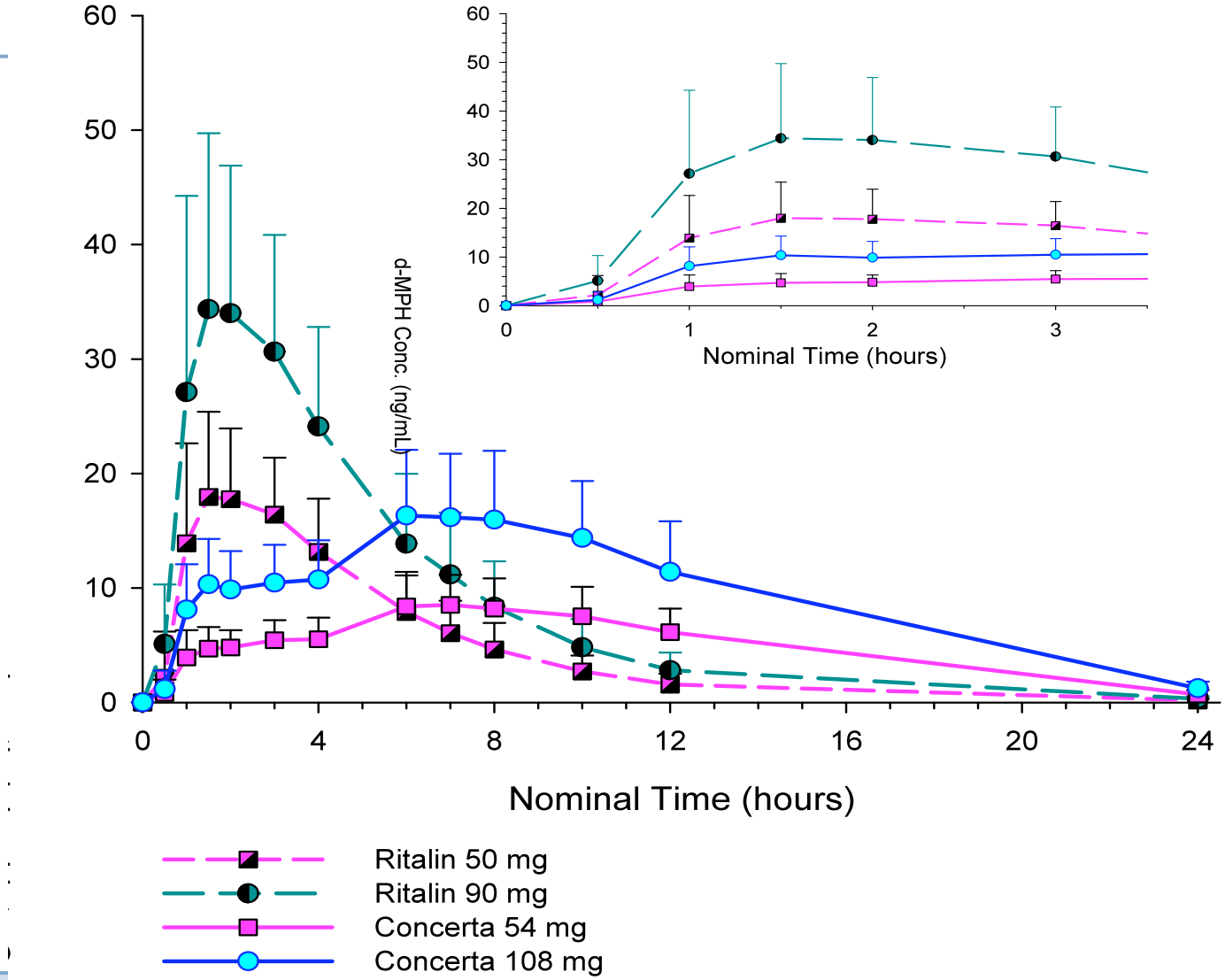


Hours post-dose

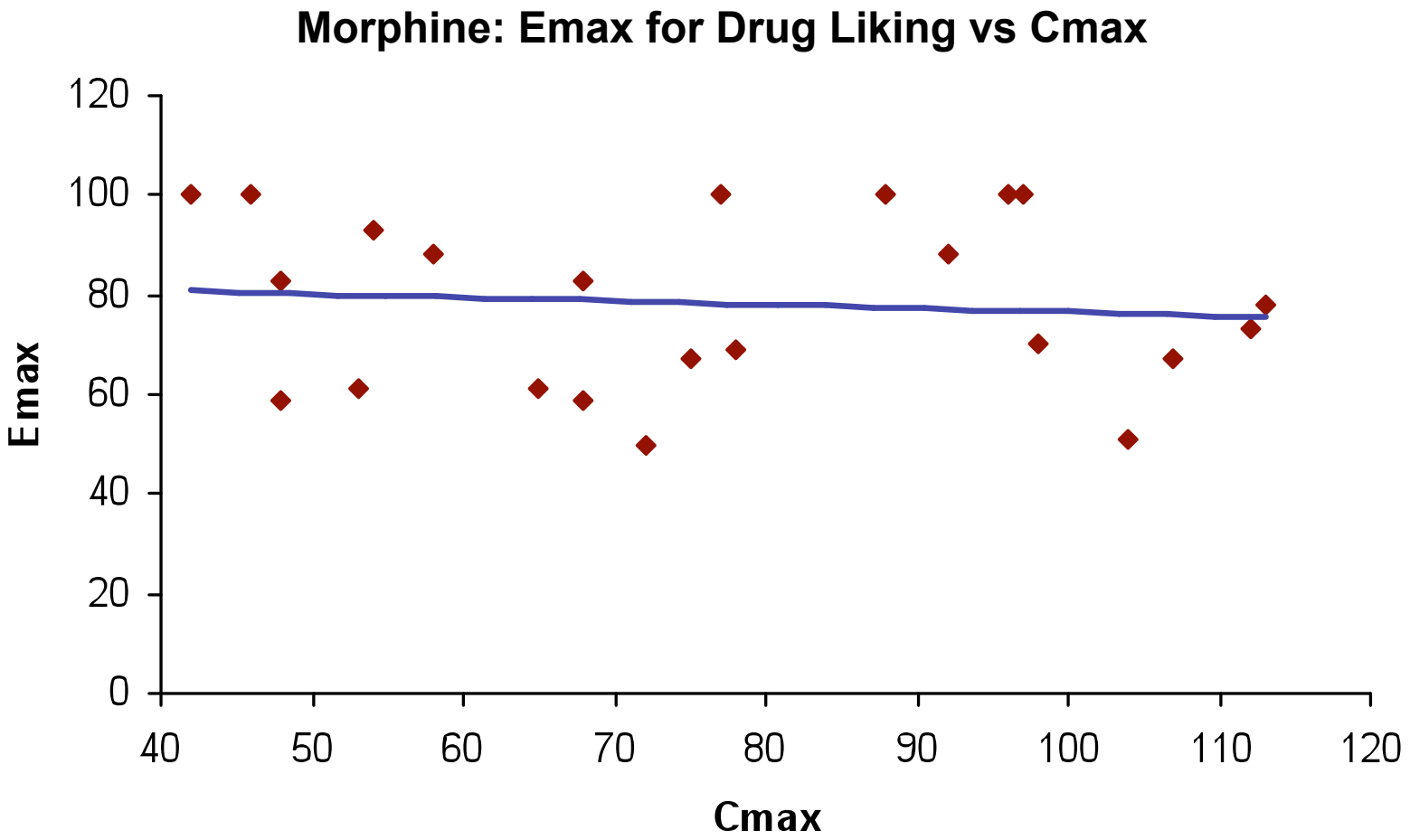
Pharmacokinetics

- Options
  - Don't do any
  - Sparse PK
  - Full PK
  - PK-PD modelling
- What is the question?
  - Drug got in?
  - Drug concentration relates to effect?
  - Variation in PK relates to variation in effects?
  - Maximum concentrations seen in animals – toxicokinetics limits permitted human exposure?

Assessing Abuse Liability: Methylphenidate Kinetics



PK-PD Relationships?



Safety Data Collection – Meeting the Standard

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- Electronic data collection, transfer and management
- 21CFR11 compliant systems
- Live QC
- Study monitoring
- Study audit

Staff Training and Supervision

- MDs, paramedics and RNs
  - All ACLS certified
- Evacuation SOP and drills
- Hospital transfer protocol
- MD present through-out or available within minutes

Clinical Trials

- Doses are “therapeutic” – risk lower
- Vital signs and AE collection at time of visits
- Safety challenge
  - AE clinical terms, coding, interpretation, presentation
  - AEs associated with treatment period and discontinuation period
  - Spontaneous and elicited
  - Fox and the chicken coop – role of independent AE review?
- Other physiologic measures
  - Not needed in most cases
  - Cardiovascular risk

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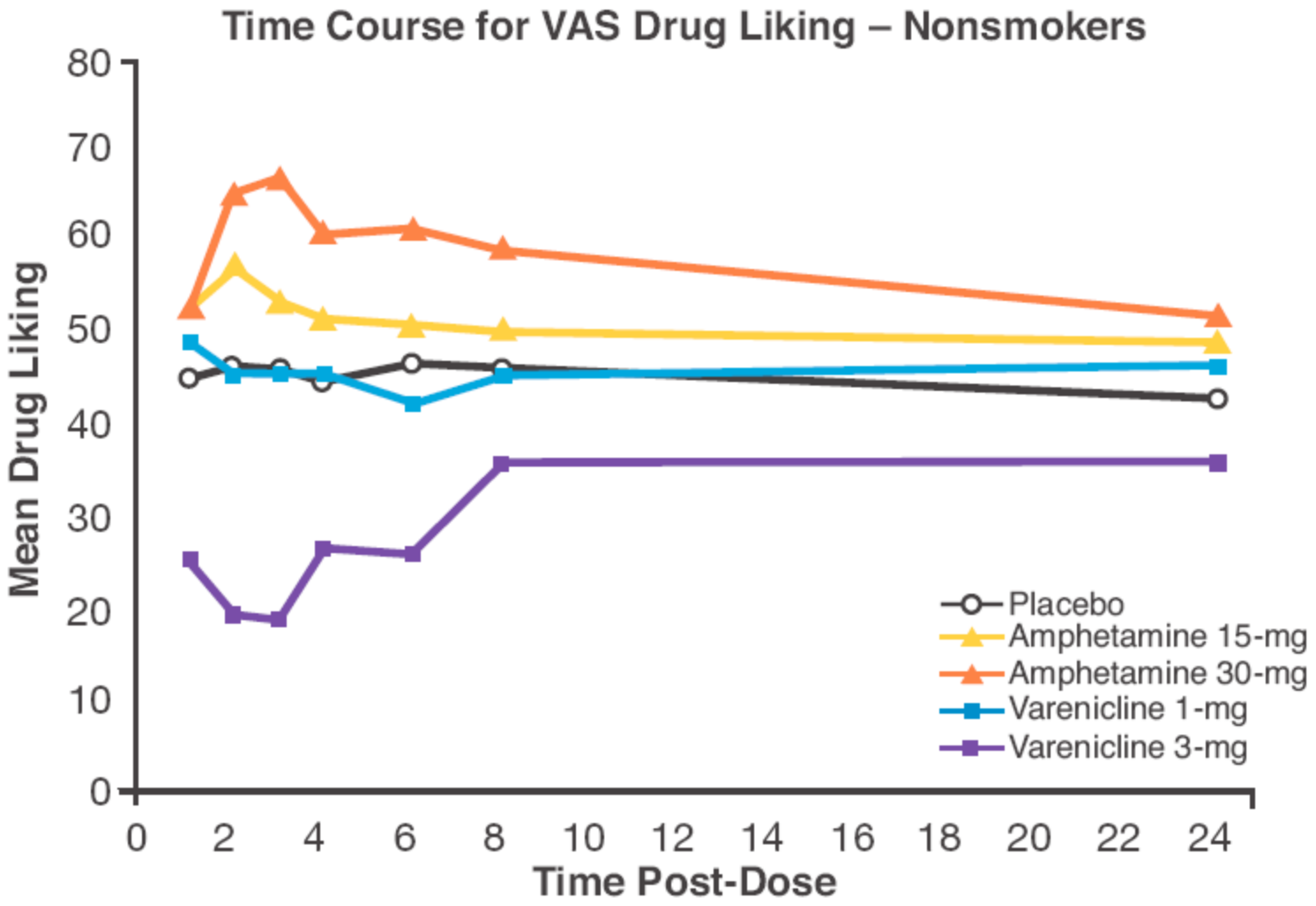

Asystole