The Role of Human Models of Disease State in Accelerating Early Clinical Development for CNS Active Drugs

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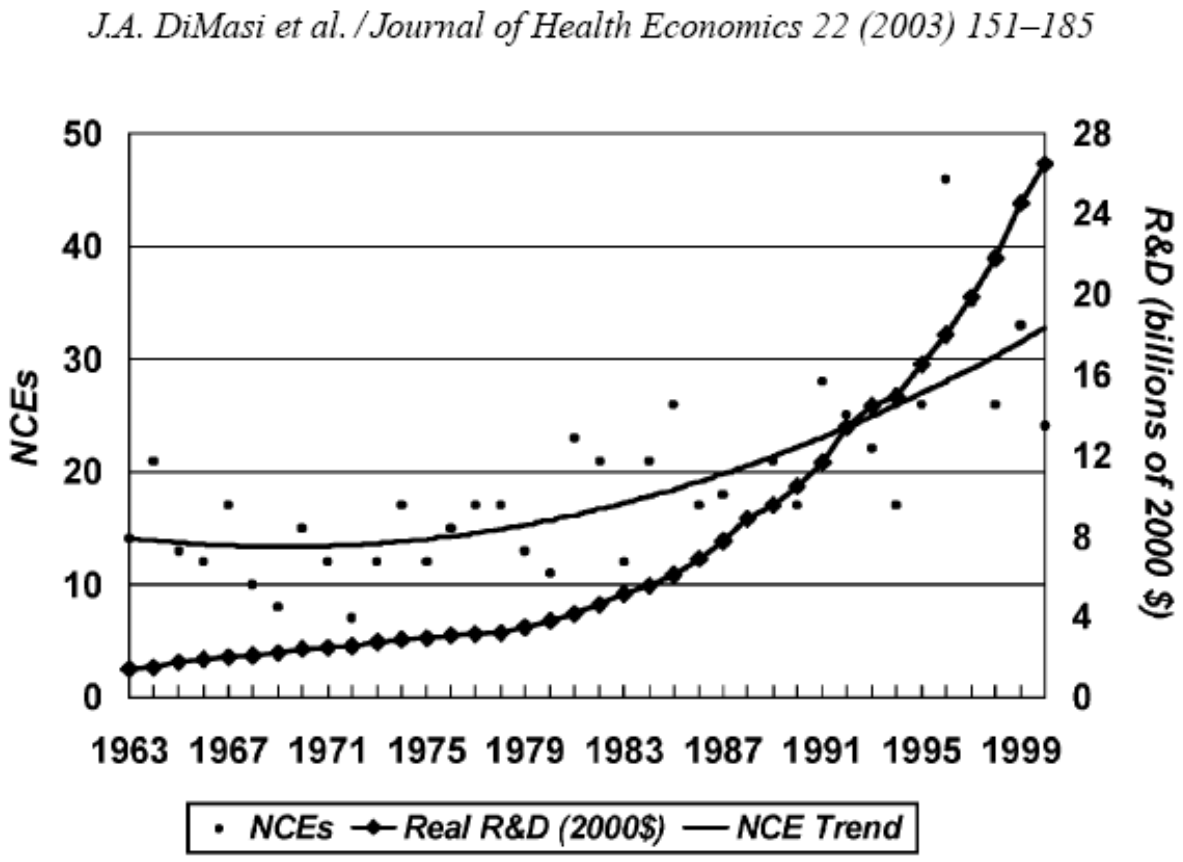
Presentation Overview

- What is a pharmacodynamic model?
- What CNS disease states can be modelled in a clinical setting?
- How can models be integrated into early clinical development programs?
- Assessment of the contribution they make to sensible drug development packages
  - Financial
  - Time
- “Academic interest” vs “valuable science”

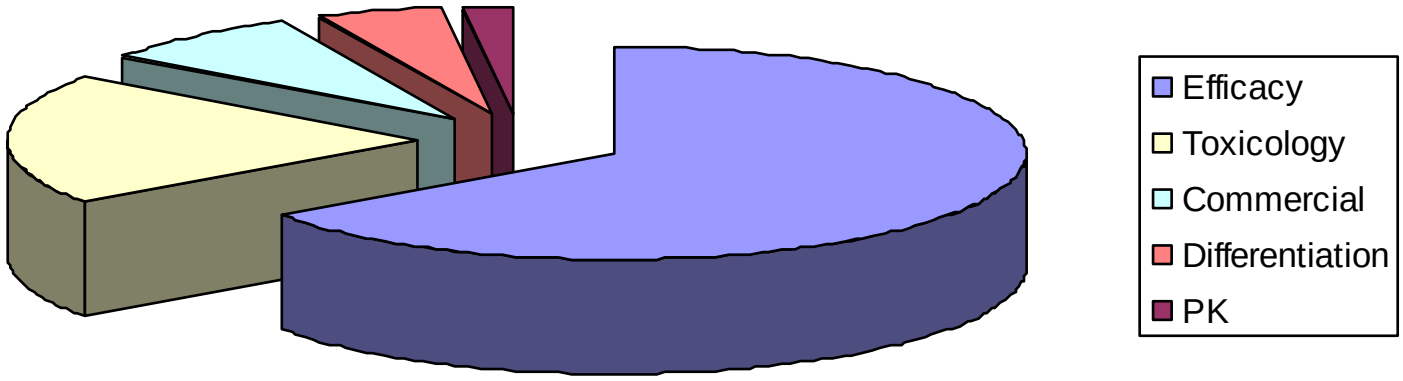
Phase 1 Approach in the 90s

- Primary focus of Phase I volunteer studies was safety, tolerability and pharmacokinetics
  - Single ascending dose
  - Multiple ascending dose
  - Food effect & drug-drug interaction studies
  - Patient trials

Cost of Drug Development



Drug Failures (2005)



Westbrook et al, 2005

Phase 1 Approach in the 90s

- Lost opportunities and development delays due to:
  - Molecules taken into patient trials lacking efficacy or appropriate dosing regimen not determined
  - Unnecessary patient exposures
  - Wasted opportunity of high concentration exposures seen in ascending dose trials
  - Huge cost in time and money

Phase 1 Current Approach

- Focus of development has changed to leveraging maximum information from early clinical trials
- Strong interest application of biomarkers and surrogate end points in this phase to provide pivotal information on efficacy, dose-response and time-course of effects
- This drive is pressured by:
  - Need of industry to recognise and develop marketable drugs as rapidly and cost-effectively as possible
  - Need to ‘kill’ non-viable compounds as early in the development process as possible
  - Desire for a signal of efficacy to promote further investment (financial and scientific)

What are Clinical Pharmacodynamic Models?

- Pharmacodynamic models are simulations of naturally occurring disease states
- Symptoms are brought under laboratory control
- Possible to investigate how compounds can modulate the elicited symptoms
- Can be applied in both patient and healthy volunteer populations

R&D Challenges

- Many existing pre-clinical models of disease do not predict human efficacy
  - Particularly the case as we move into new targets
- Need to kill non-viable compounds as quickly and cheaply as possible
- Need to be able to predict human efficacy
- Moving to Phase II knowing that the compound hits the target and produces desired response

Range of Pharmacodynamic Model Targets

- Well-validated pharmacodynamic models are available for a wide range of clinical conditions
- Clinical areas include:
  - Pain
  - Anxiety
  - Diabetes
  - Appetite control
  - Sexual dysfunction
  - Cognitive impairment
  - Depression
  - Sleep

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ANXIETY

Models of Anxiety

- Psychological
  - Aversive Conditioning
  - Simulated Public Speaking
  - Mood Induction
- Pharmacological
  - Yohimbine
  - mCPP
  - Lactate
  - Carbon Dioxide

Deakin and Graeff (1991)

Journal of Psychopharmacology 5(4) (1991) 305–315

CRITIQUE

5-HT and mechanisms of defence

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5-HT and Anxiety

- 5-HT potentiates conditioned anxiety via activation of DRN, amygdala
- Positive effects in conditioned anxiety paradigm

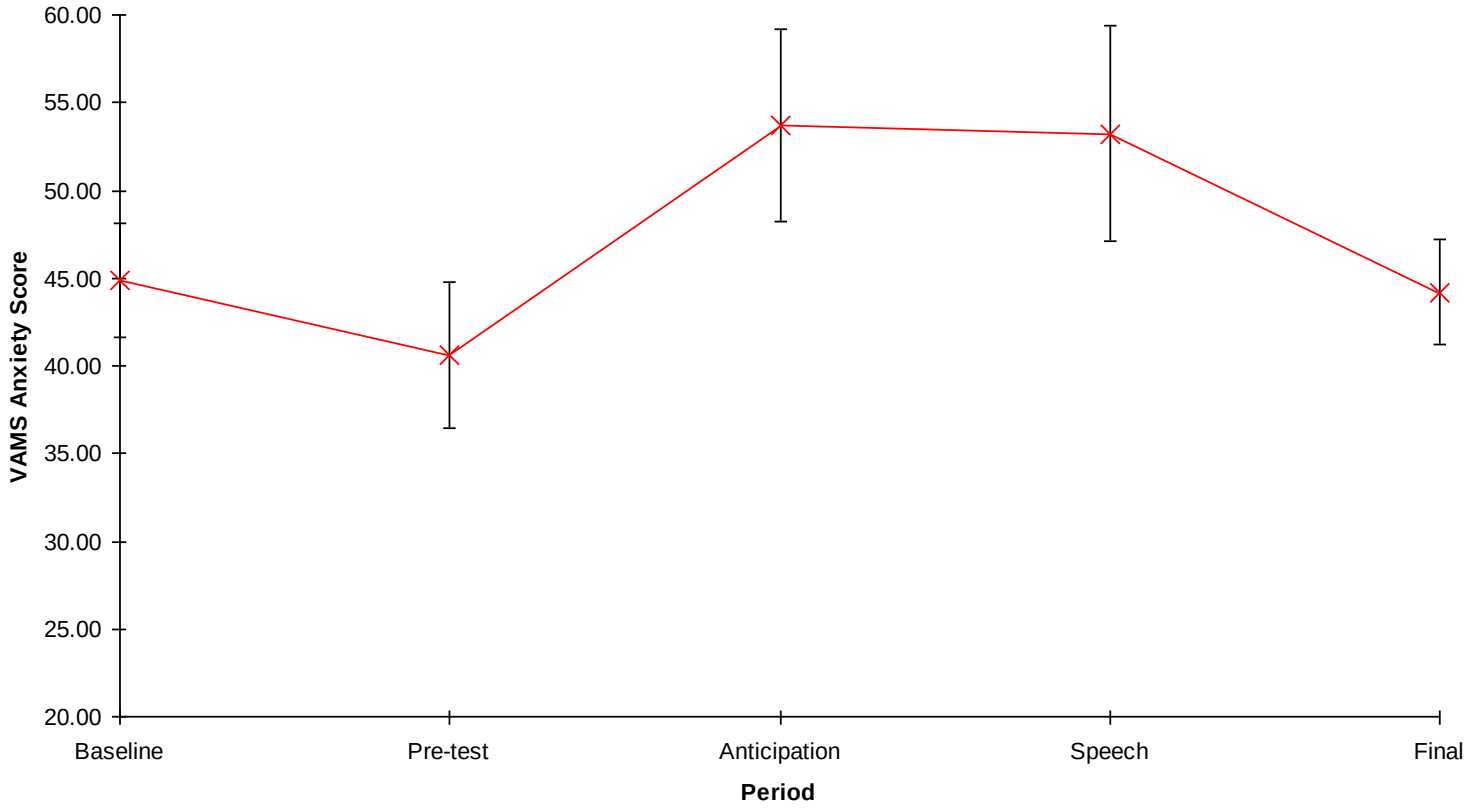
BUT

- Can 5-HT restrain some forms of anxiety?

Simulated Public Speaking Model

- Relaxed baseline measurements taken
  - Physiological measurement (skin conductance level)
  - Subjective rating scales (VAMS, SSAI, BSS)
- Subject given 2 minutes to prepare 4 minute talk on anxiety- provoking moments
- Speech videotaped and subject told it will be rated by a panel of psychologists
- Further measurements at various points during preparation period and speech

Simulated Public Speaking – Placebo Data



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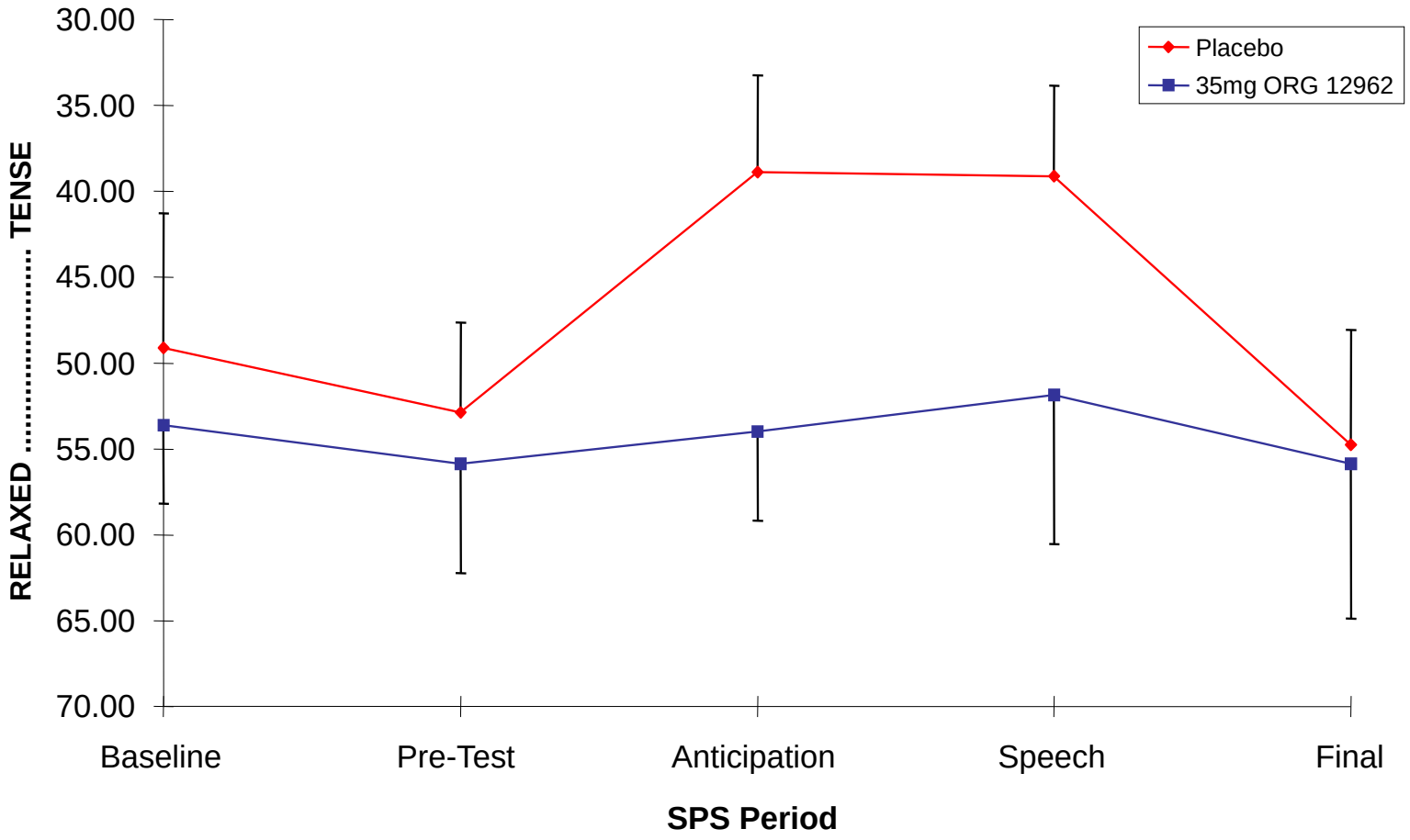
Simulated Public Speaking – 5-HT2C agonist



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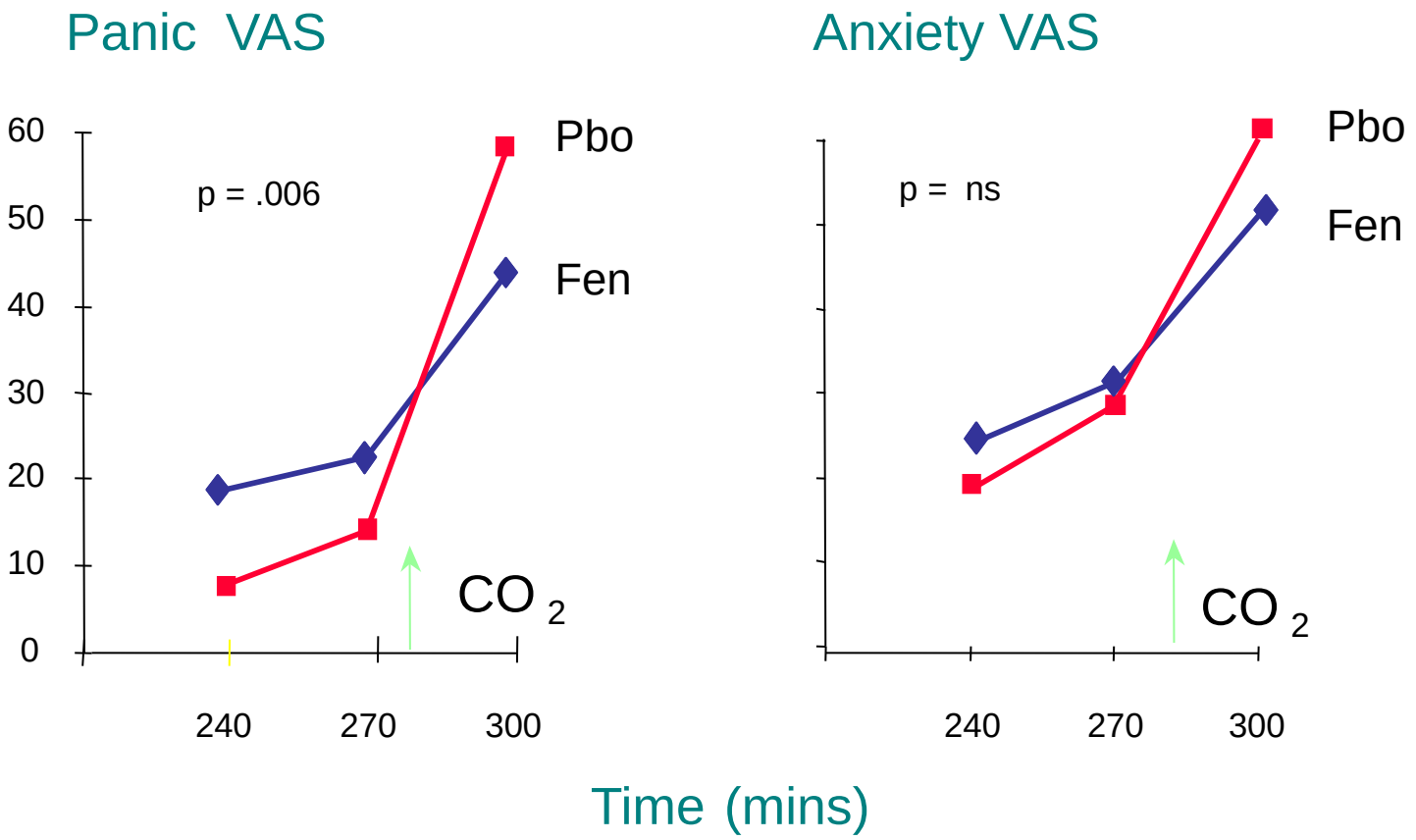
Carbon Dioxide – Effect of Fenfluramine (15mg)



Validity of Anxiety Models

- Face Validity
  - “Measureable” anxiety turned on and off by models
- Construct Validity
  - Successfully used in testing anxiety mechanisms
- Predictive Validity
  - Correctly identify molecules that work in anxiety
  - Molecules that fail in patients, fail in model e.g. CI-988

APPETITE CONTROL

Appetite Control Methodology

- Within subject, placebo controlled studies
- Fasted subjects dosed with test compound or placebo prior to food intake challenge
- Subjects given set ‘test-meal’ and asked to eat until comfortably full
- Visual analogue scales used to rate subjective feelings of hunger, satiety, prospective food consumption and palatability of test meal
- Objective outcome is weight/energy intake of food consumed

Appetite Control Methodology

- Balance concealed within table and connected to PC in adjacent room
- Subject eats test meal on top of balance
- Weight of food remaining sampled every 3 seconds for duration of meal
- Data analysis allows determination of total energy intake and rate of eating in early and late phase of meal

Appetite Control Methodology

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Appetite Control – Method Development Study

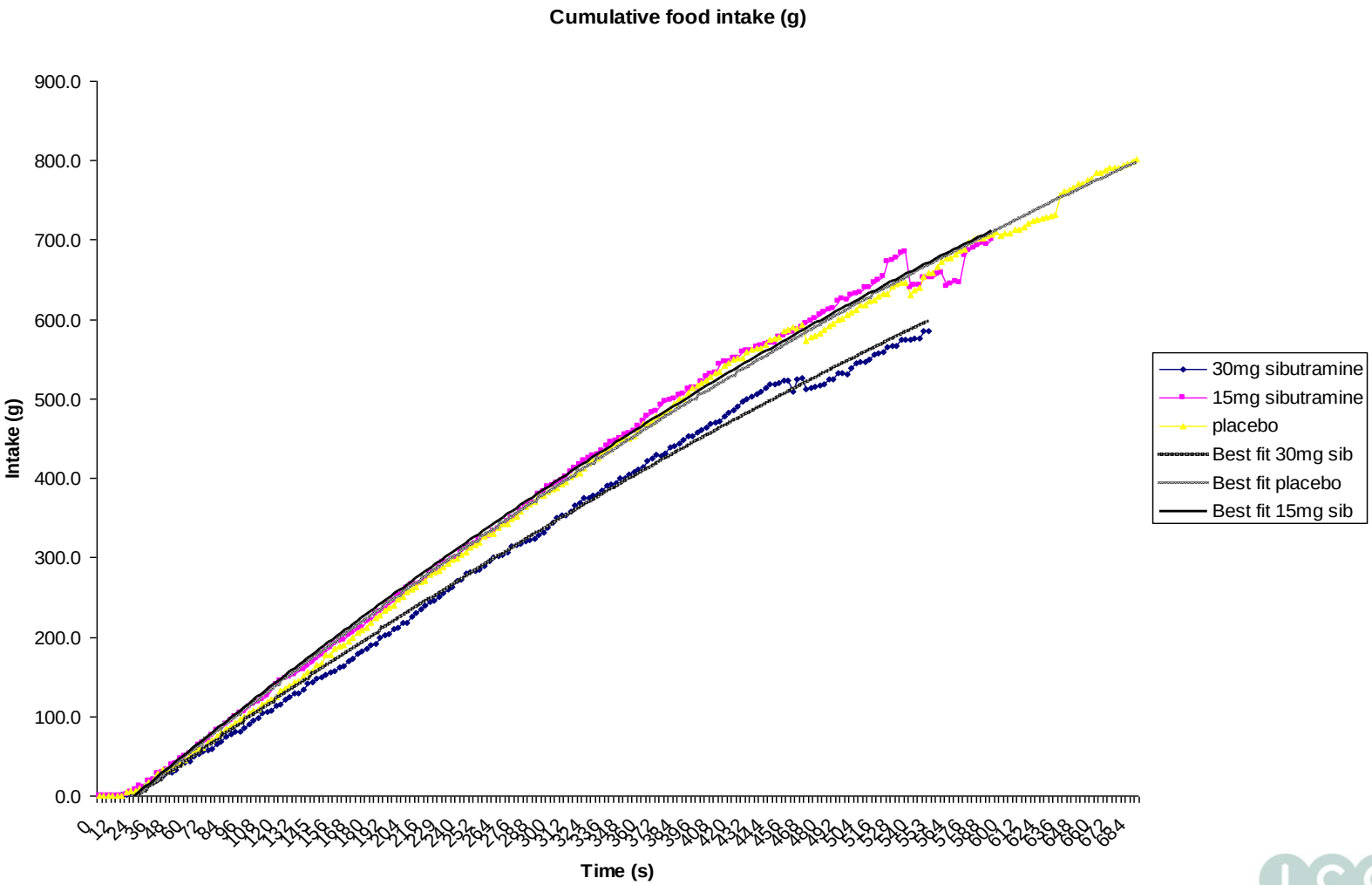
- Three-way cross-over study in 12 overweight (BMI 24.5-29.4 kg/m^2, Waist circumference >94cm) male volunteers

- Treatments
  - Placebo
  - 15mg sibutramine
  - 30mg sibutramine

Appetite Control – Headline Data

- 30mg sibutramine reduced energy intake by 27% compared to placebo (p=0.004)
- 15mg sibutramine reduced energy intake by 13% compared to placebo (p=0.037)
- Significant difference between doses of sibutramine (p=0.001)

Appetite Control – Headline Data



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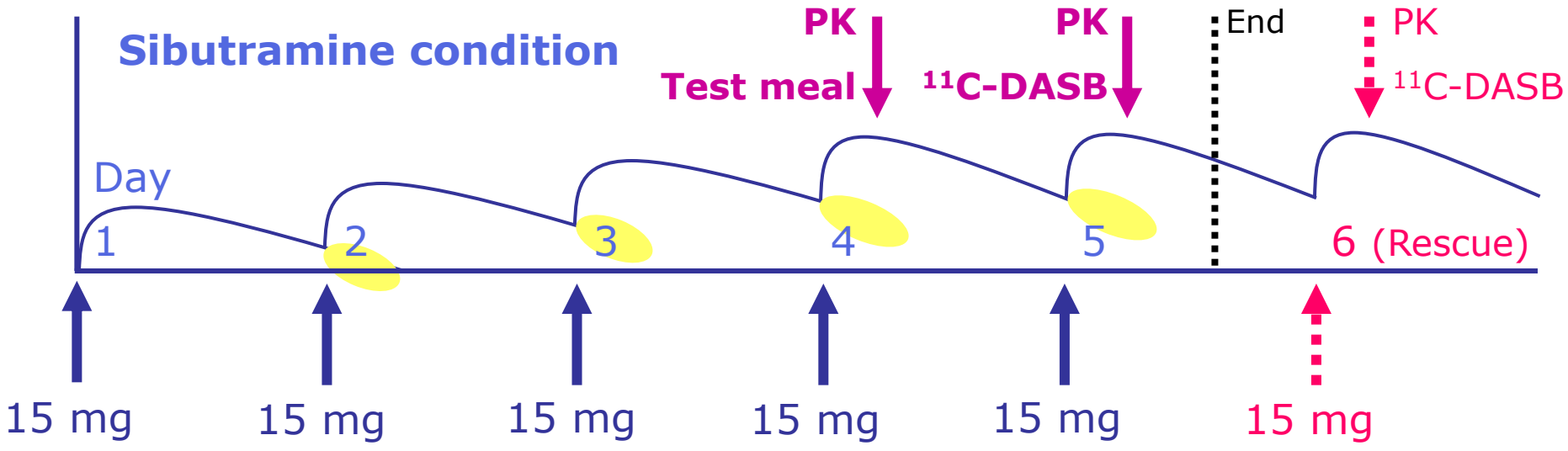
Appetite Control – Summary

- Changes in food intake can be elicited in volunteers by pharmacological manipulation
- Model can be used to show both increase and decrease in food consumption
- Model can be used to predict how drugs will work in a clinical setting e.g.
  - FIM Single Ascending Dose
  - Part B “dose of interest”

Sibutramine – testing DASB

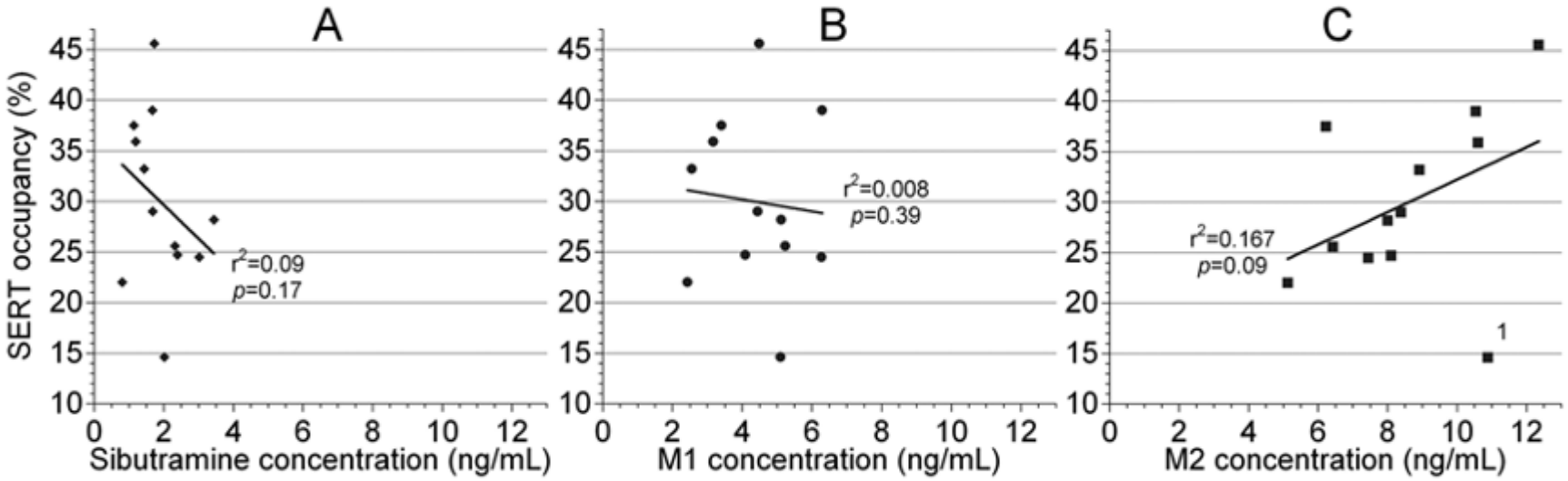
- Subjects: 12 normal-weight, non-smoking, drug-free, healthy males
- Design: double-blind, placebo-controlled, balanced-order, within-subject crossover
- 2 separate residential study periods of 5 days:
  - Period 1: sibutramine 15 mg/day to steady state over 5 days
  - Period 2: identical schedule, dosed with placebo

Sibutramine – testing DASB



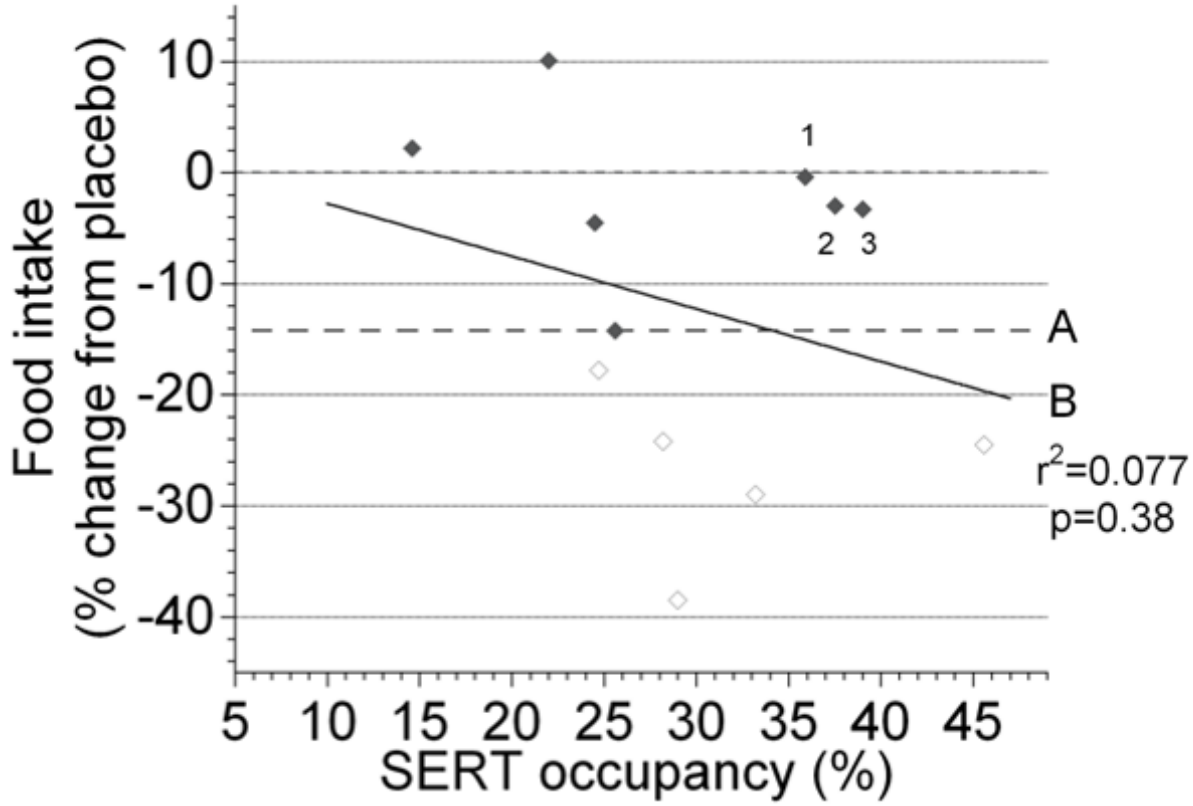
Talbot et al (2009)

Occupancy v Concentration



Talbot et al (2009)

Occupancy v Food Consumption



Talbot et al (2009)

Sibutramine – testing DASB

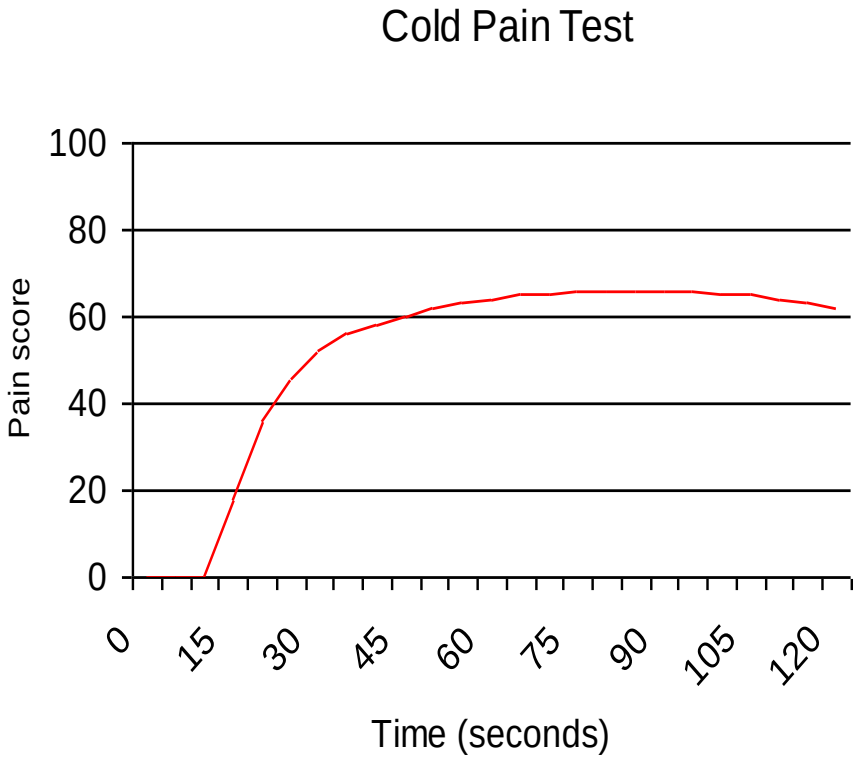
- Study demonstrated association between serotonin transporter protein (SERT) and sibutramine in healthy volunteers
- Degree of occupancy significantly related to M2 metabolite concentration
- Trend for relationship between appetite suppression and SERT occupancy

CENTRALLY MEDIATED PAIN

Cold Pain Model - Methodology

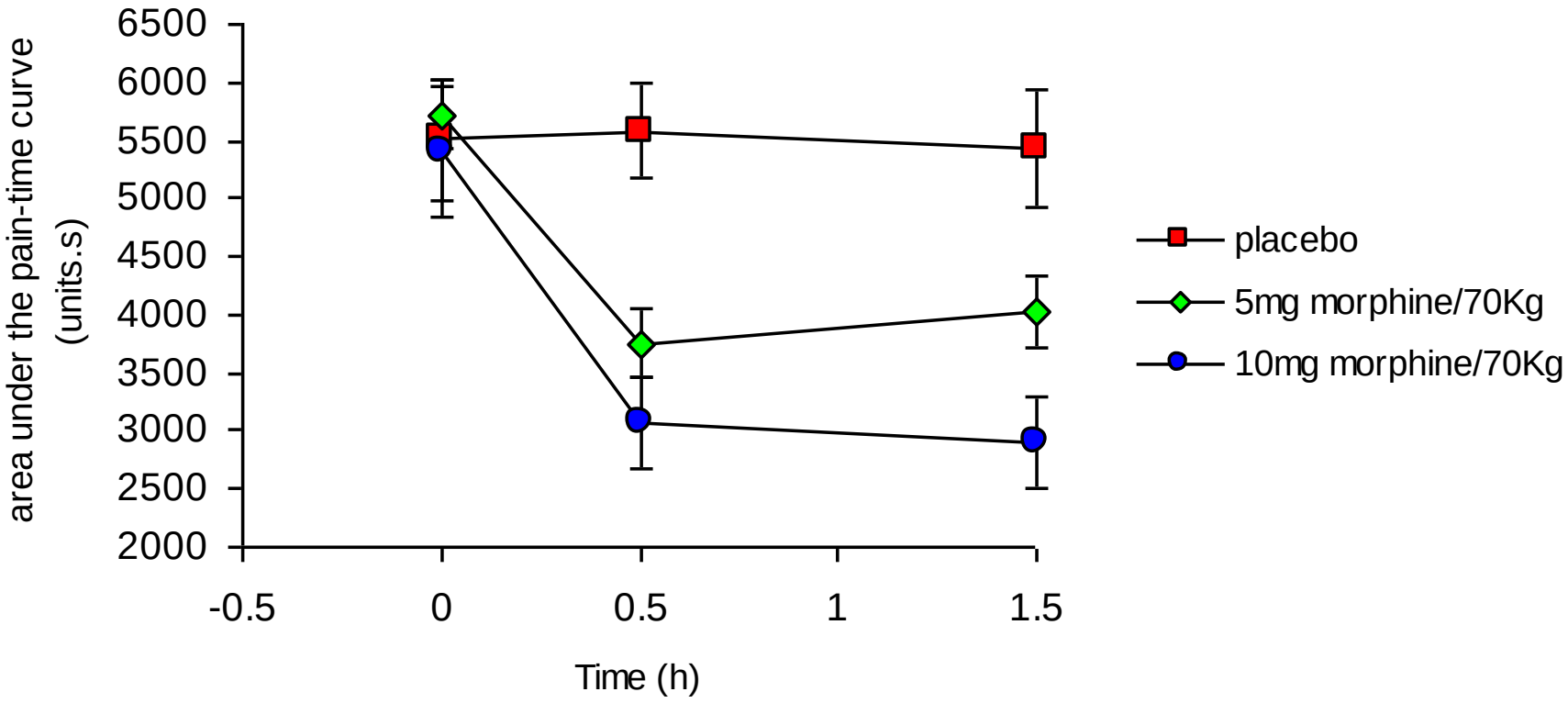
- Stirred, thermostatically-controlled water bath at 2°C
- Subject's non-dominant hand immersed in the water for 2 minutes
- Hand held open and submerged to the wrist
- Subject continually adjusts a visual analogue scale on a computer screen using other hand
- Scale from "no pain" to "maximum pain"

Cold Pain Model



Cold Pain Model – Dose Response

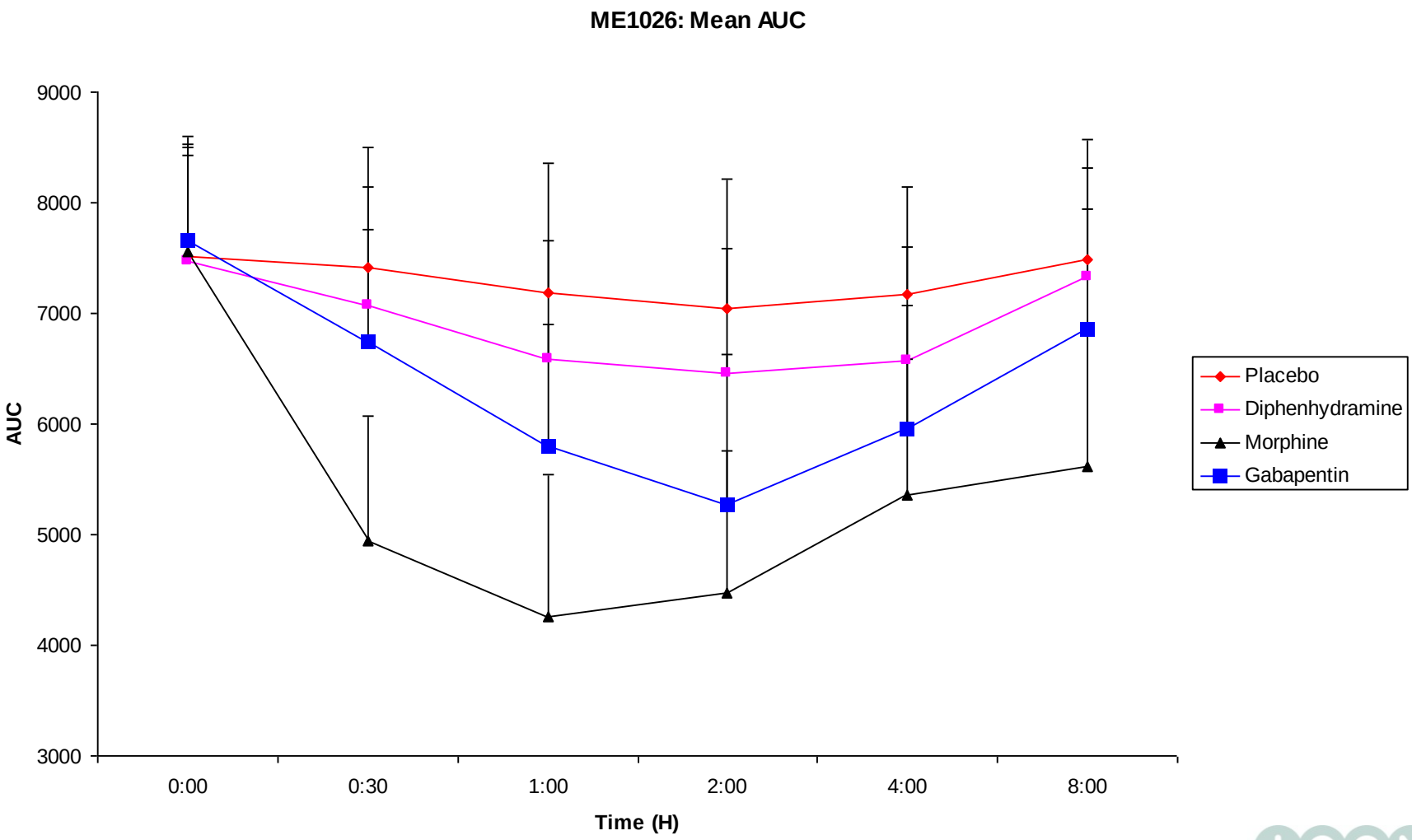
Mean (s.e.m.) AUC for placebo, 5mg and 10mg of morphine by 30 min iv infusion (n=12)



Cold Pain Model - Benchmarking

- 16 healthy male and female subjects
- 4-way crossover study
  - Morphine
  - Gabapentin
  - Diphenhydramine
  - Placebo
- Double-blind, double dummy design used and dosing timed so C_{max} the same for all treatments
- Cold Pain tests performed pre-dose and at 1h, 1h30, 2h, 4h and 8h post-dose
- Active placebo (diphenhydramine) included to control for adverse effects

Cold Pain Model – Benchmarking



Pharmacodynamic Models - Summary

- Simple, standardised methodology key to reliable, reproducible model development
- Allows assessment of efficacy potential of novel centrally-acting compounds, as well as time course of effects and comparison to market leading compounds
- Enables rapid go/no go decisions to be taken
- R&D resources can be directed to most promising candidates

Question & Answer

Thank you!

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