

# The Use of Clinical PD Models to Accelerate the Development of CNS Drugs Through Phase 1



Dr John Connell  
Vice President, Clinical Pharmacodynamics  
ICON Development Solutions

# Presentation overview

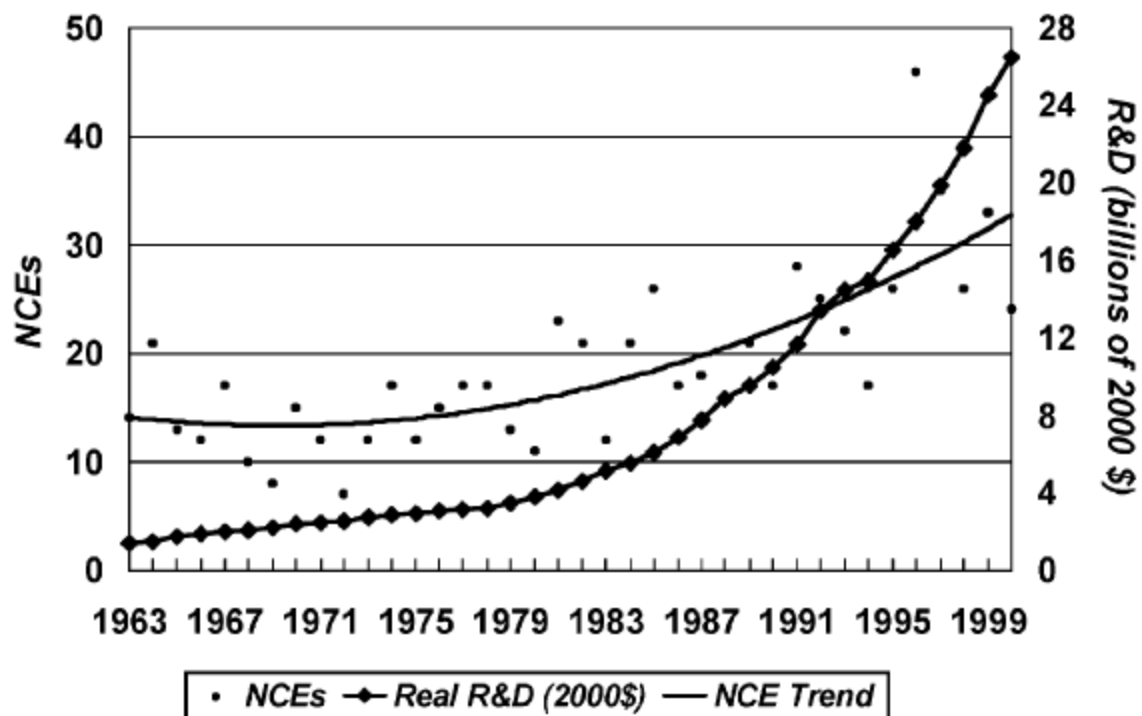
- What is a pharmacodynamic model?
- What CNS disease states can be modelled in a clinical setting?
- How can models be integrated into early clinical development programs?
- What benefits do models bring to development plans?

# Phase 1 Traditional Approach

- Traditionally primary focus of Phase I volunteer studies has been safety, tolerability and pharmacokinetics
  - Single ascending dose
  - Multiple ascending dose
  - Food effect & DDI
  - Patient trial

# Cost of Drug Development

*J.A. DiMasi et al. / Journal of Health Economics 22 (2003) 151–185*



# 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-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
- It is 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 quickly and cheaply
- Need to be able to predict human efficacy
- Moving to Phase II knowing that the compound hits the target and does something

# 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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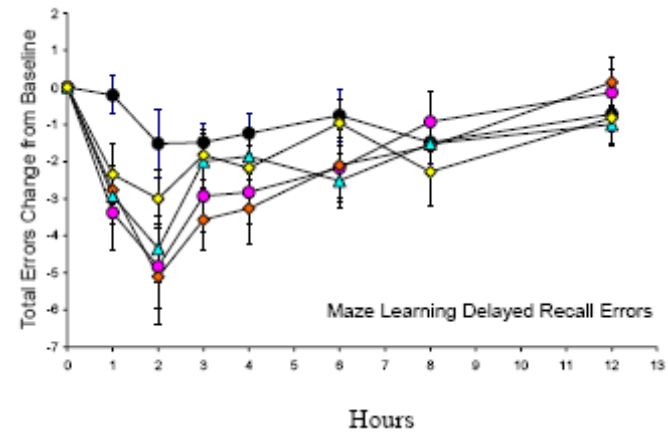
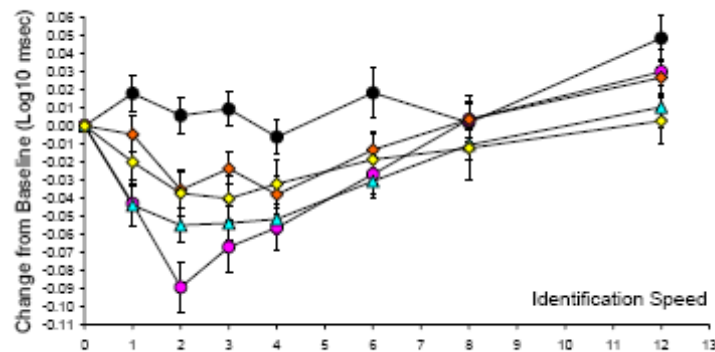
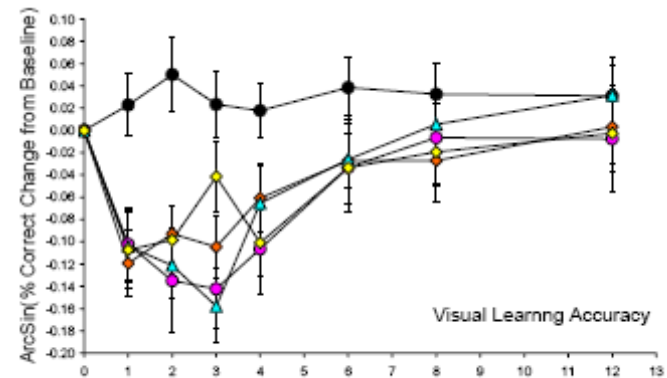
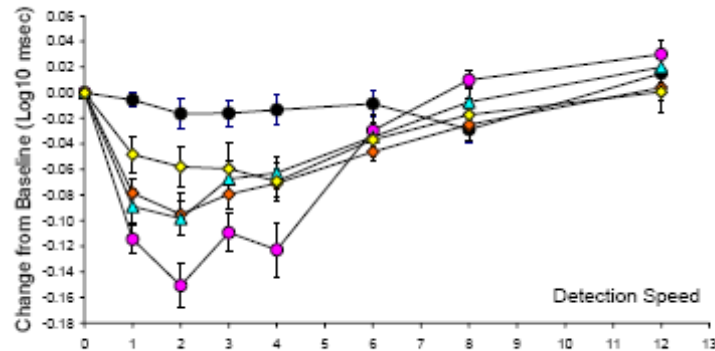
# Scopolamine Model

- Scopolamine widely used as a model of cognitive impairment
- Non-specific muscarinic antagonist producing temporary & reversible impairments of attention and memory in healthy subjects
- Cognitive impairments similar to those seen in elderly subjects and in mild Alzheimers disease
- We have repeatedly demonstrated reversal of scopolamine induced cognitive impairment using Donepezil in this model.

# Scopolamine Model

- Study Design
  - 28 healthy male volunteers
  - 5-way crossover
    - Placebo
    - 0.5mg Scopolamine (iv)
    - 0.5mg Scopolamine + 10mg Donepezil (oral)
    - 0.5mg Scopolamine + drug X (oral)
    - 0.5mg Scopolamine + 10mg Donepezil (oral) + drug X (oral)
- Main outcome measures
  - CogState Early Phase computerized test battery
    - Groton maze learning test
    - One card learning
    - Simple reaction time
    - Choice reaction time

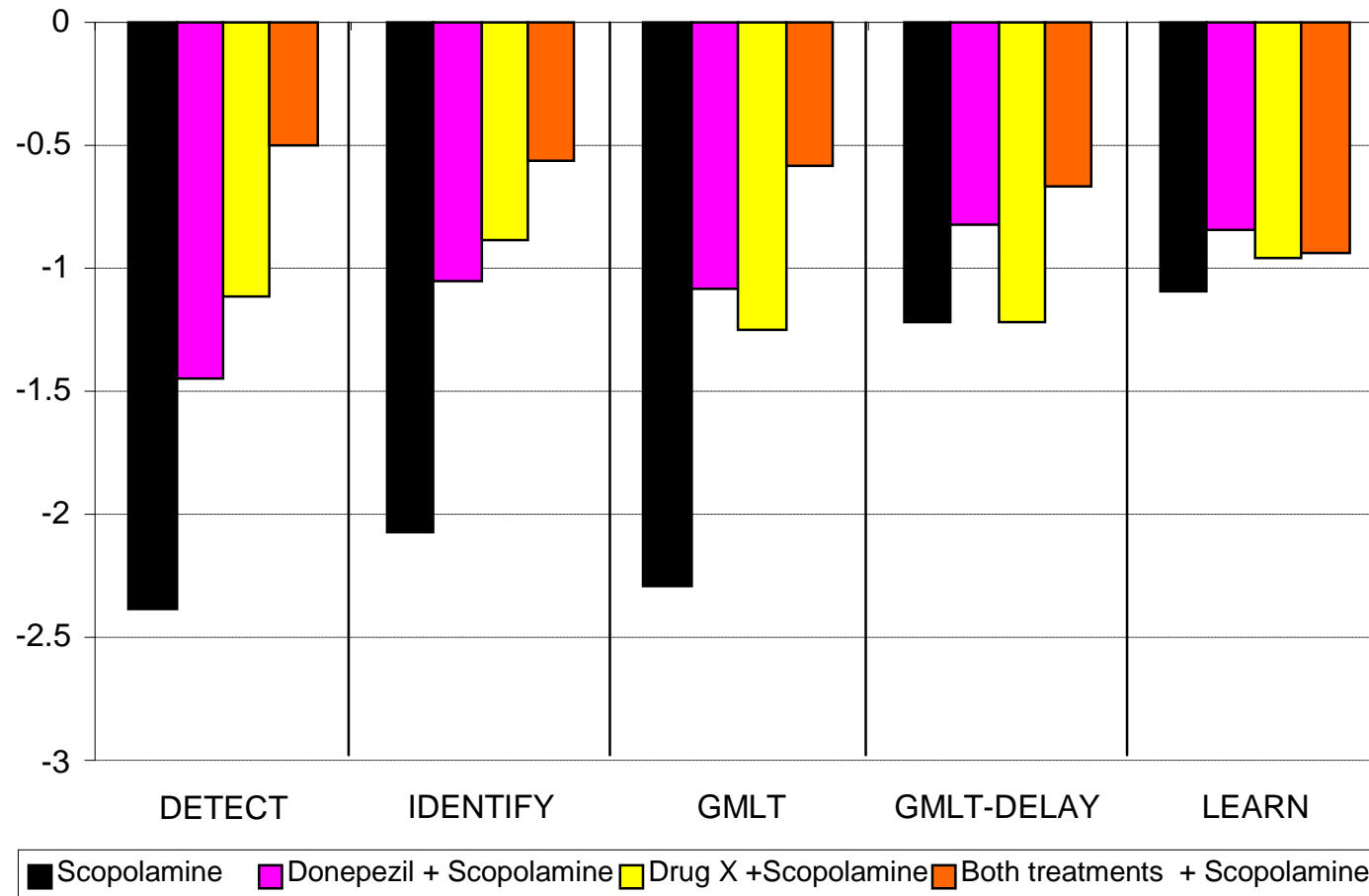
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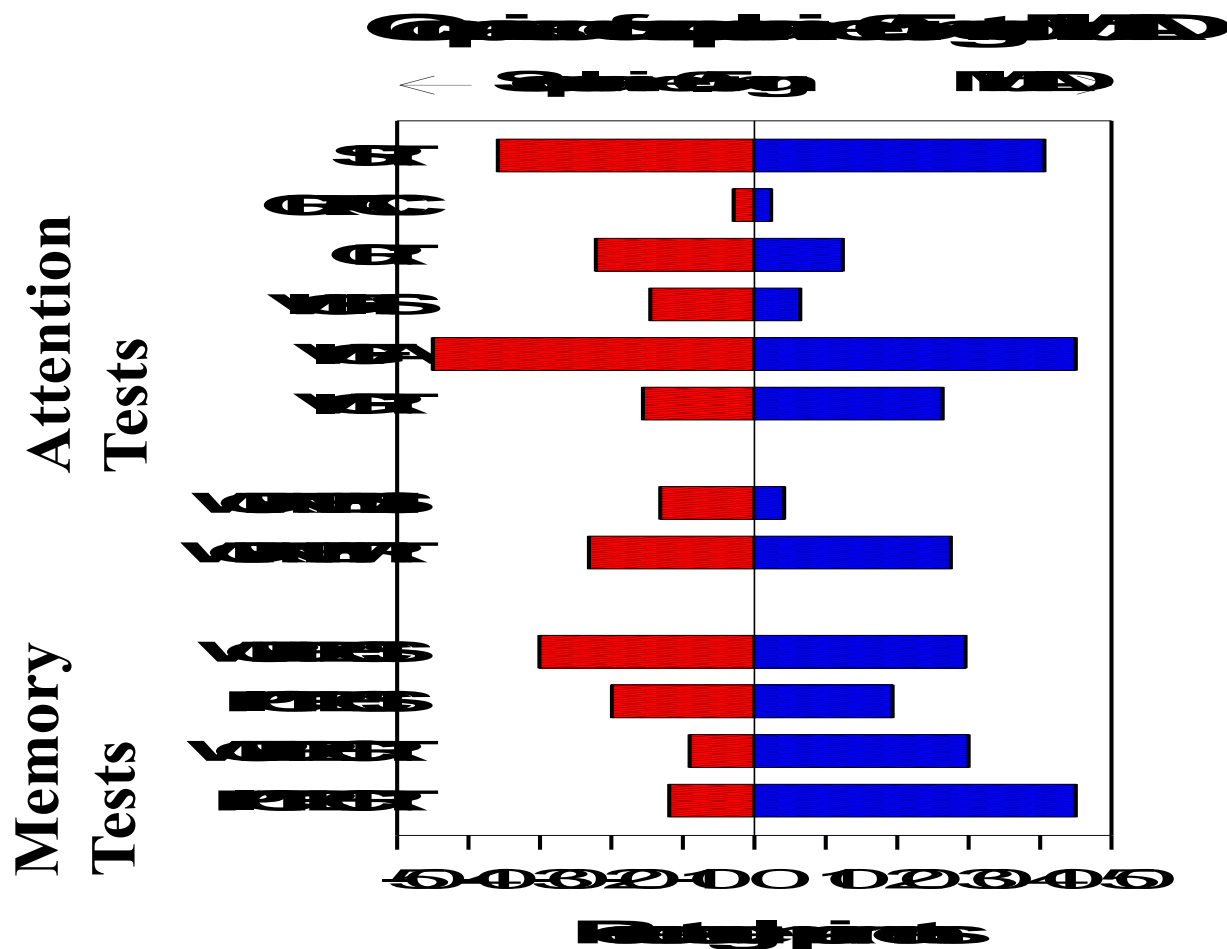
- Placebo
- Scopolamine
- Donepezil plus scopolamine
- Drug X plus scopolamine
- Both treatments plus scopolamine

# Scopolamine Model

Magnitude of effect size compared to placebo



# Scopolamine Model – Patient Translation



# Summary

- Quantitative pharmacodynamic assessments with a high degree of validation and quality control can play a pivotal role in accelerating early drug development
- Techniques can help support go/no go decisions
- Information relating to dose and putative efficacy can be obtained
- Pharmacodynamic models can contribute to a sensible and cost-effective drug development package

# Question & Answer

Thank you!

Request a Copy: [john.connell@iconplc.com](mailto:john.connell@iconplc.com)