Background

- Dimebon is a mitochondrial stabilizing drug with great expectations for treatment of Alzheimer’s disease.
- Phase II study suggested robust clinical effect (Dooody 2008).
- Subsequent Phase III studies failed to confirm this effect.
- Objective 1: Identify possible causes of Dimebon clinical failure.
- Objective 2: Explore differences between Phase II and Phase III outcomes in terms of genotypes.

Methods

- Use Quantitative Systems Pharmacology model for cognition in Alzheimer’s Disease (Fig 1) - [Roberts, submitted]
- Biophysically realistic computer model of AD cortical neuronal network
- Implement cholinergic, DA, NE and 5-HT pharmacology (in total 29 CNS targets)
- AD pathology is implemented as loss of synapses and neurons and reduced cholinergic tone
- Calibrated with retrospective clinical data on ADAS-Cog (Fig 2)
- Simulate symptomatic functional dose-response for Dimebon using full human neuropharmacological pharmacology (Okun et al. 2010)
- Explore effect of COMT Val158Met genotype from simulation of imaging studies with NMC-112 (Best et al. 2008) [Spiros 2012] and 5-HTTLPR 1/1 vs 1/2 genotype [Best et al. 2010]

Cortical Biophysical Model of Memory Trace Representation

- The biophysically realistic network with with biophysical models of pyramidal and interneurons related to cholinergic, dopaminergic, noradrenergic and serotonergic innervation of pyramidal cells and inhibitory interneurons, shown as a directed graph with directed edges between nodes.
- A background noise input characterizes the level of noise at the interface of the network with the rest of the brain. The network consists of 100 neurons, 50 pyramidal units, 50 interneurons, excitatory and inhibitory synapses, cholinergic, dopaminergic, noradrenergic and serotoninergic inputs, shown as directed edges between nodes.
- The network is organized into distinct layers of the brain, shown as a directed graph with directed edges between nodes.

Calibration of the Network with Clinical Alzheimer Data

- ADAS-Cog Calibration All Data Points

Dimebon Pharmacology

- Dimebon is in vivo functional concentration is in 100-150 nM range (Okun et al. 2010)
- Dimebon’s in vivo functional concentration affects domain-specific functions such as memory and executive function and improves cognitive outcomes (Okun et al. 2010).
- Dimebon’s D1R antagonism is vitalized in a significant liability for cognitive performance.

Results

- Pharmacology of Dimebon
  - Anti-histaminic compound used in Russia
  - Has mitochondrial stabilizing properties, neuroprotective in Alzheimer’s disease (Dooody 2008)
  - First Phase II study in Alzheimer’s disease was successful (Dooody 2008)
  - Complex human pharmacology (Okun et al. 2010) (Fig 6). Symptomatic effect driven by weak AChE inhibition and 5-HT1A antagonism.

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Effect of COMT Gene

- Dimebon’s in vivo functional concentration is in 100-250 nM range
- COMT Val158Met genotype affects breakdown of dopamine and noradrenaline
- COMT Val158Met modulates effect of Dimebon

Effect of 5-HT LPR Genotype

- Dimebon’s in vivo functional concentration is in 100-250 nM range
- 5-HT LPR short vs long variants affects 5-HT expression, basal 5-HT levels and modulation of 5-HT, 5-HT1A, 5-HT2A by Dimebon
- The dose response for Dimebon’s 5-HT1A antagonism is different for different genotypes of the 5-HTT LPR genotype. This suggests that there could be a genetic substrate for Dimebon’s 5-HT1A antagonism.

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Anticipated ADAS-Cog at 26 Weeks Stand-Alone

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Anticipated ADAS-Cog at 26 Weeks with Donepezil 10 mg

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Anticipated ADAS-Cog at 26 Weeks with Dimebon 10 mg

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Conclusion

- It is crucial to include symptomatic off-target pharmacology of disease-modifying drug in candidate selection to reduce failure.
- Conversely, dialing in a symptomatic improvement pharmacology in a disease-modifying drug can substantially de-risk drug discovery project and accelerate clinical development.

References