

Failure Analysis of Dimebon Using Mechanistic Disease Modeling: Lessons for Clinical Development of New AD Therapies

Hugo Geerts^{1,2}, Patrick Roberts^{1,3}, Athan Spiros¹

¹In Silico Biosciences, Lexington, MA, USA; ²University of Pennsylvania, Philadelphia, PA, USA,

³Oregon Health & Sciences University, Portland, OR, USA

Background

- ✱ Dimebon is a mitochondrial stabilizing drug with great expectations for treatment of Alzheimer’s disease
- ✱ Phase II study suggested robust clinical effect (Doody 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 neuromodulatory pharmacology [Okun et al. 2010]
- ✱ Explore effect of COMT Val158Met genotype from simulation of imaging studies with NNC-112 [Slifstein et al. 2008] [Spiros 2012] and 5-HTTLPR 1/1 vs s/s genotype [Best et al. 2010]

Cortical Biophysical Model of Memory Trace Representation

(1A) The biophysically realistic network with Glutamate and GABA synapses and diverse voltage gated ion-channels includes also the effect of different neuromodulatory receptors (5-HT1A, 5-HT2A, 5-HT3, 5-HT4, 5-HT6, D1, D2, D4, M1, M2 mAChR, α7, α4β2 nAChR and α2R) and various other targets (NMDAN1NR2A, NMDANR1NR2C, AMPA, GABA-α1, GABA-α2, Ach, COMT, DAT, NET, SERT) according to in vitro and in vivo preclinical data on the relationship between receptor modulation and membrane excitability [Roberts, submitted]. A memory trace is introduced at a certain time and the time over which this trace is maintained is a measure of trace stability. A background noise B captures the interaction of this microcircuit with the rest of the brain. (1B) The network consists of 120 neurons, 80 pyramidal cells, 40 interneurons; Alzheimer pathology is introduced using synapse and neuronal cell elimination and cholinergic deficit. (1C) state-diagram readout of the network, showing the stability of the memory trace over the working memory span

Figure 1A

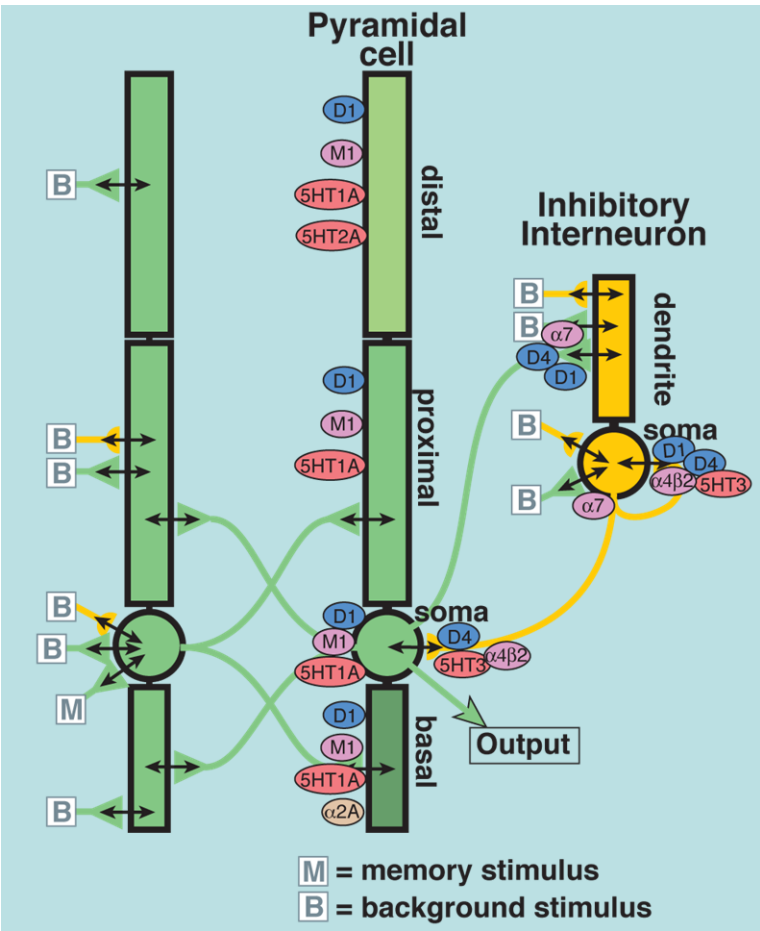


Figure 1C

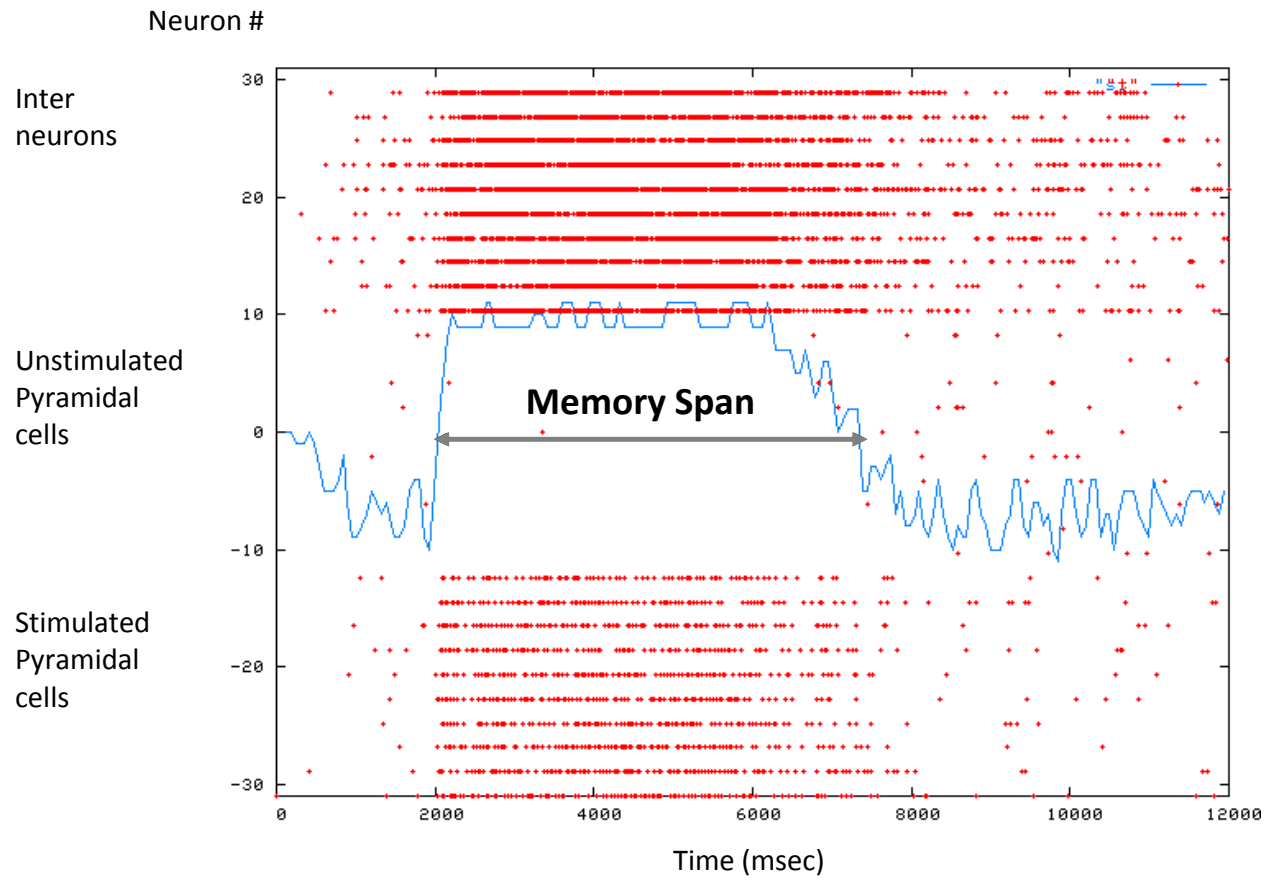
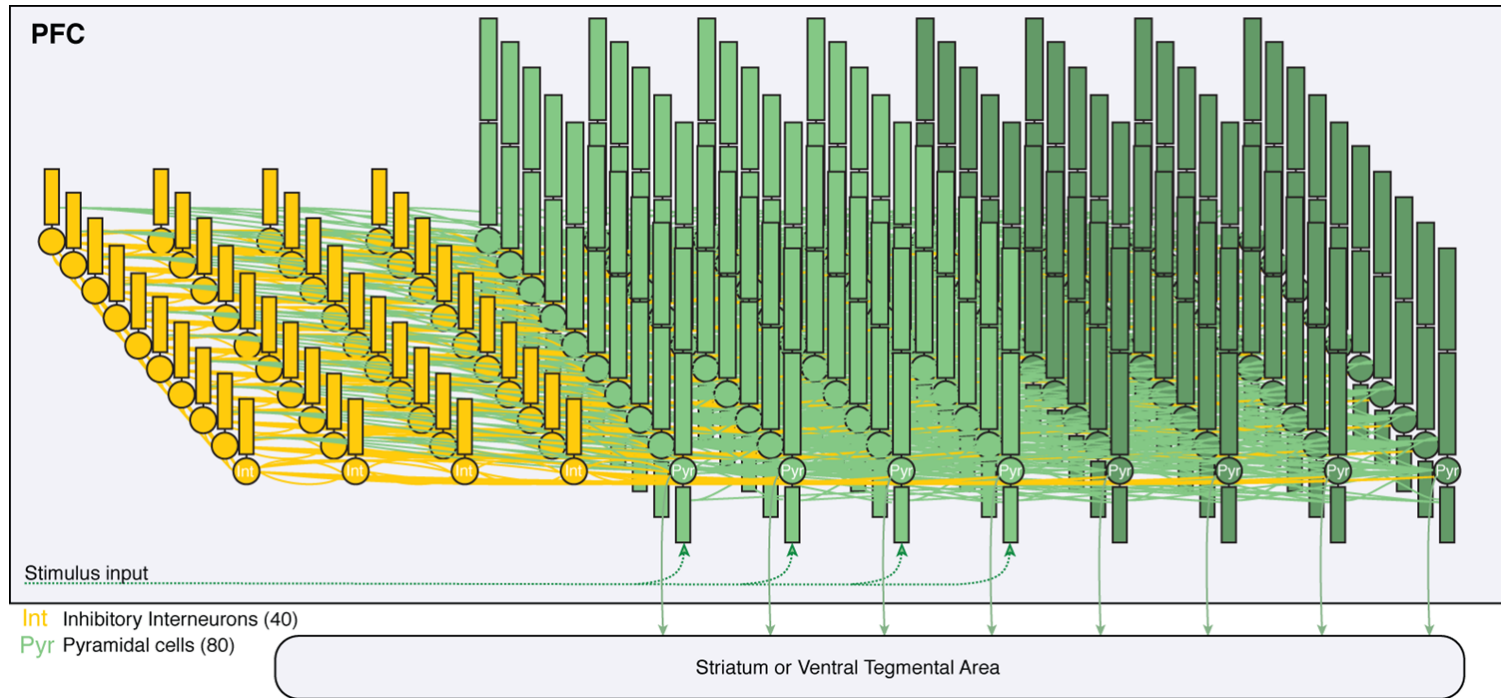


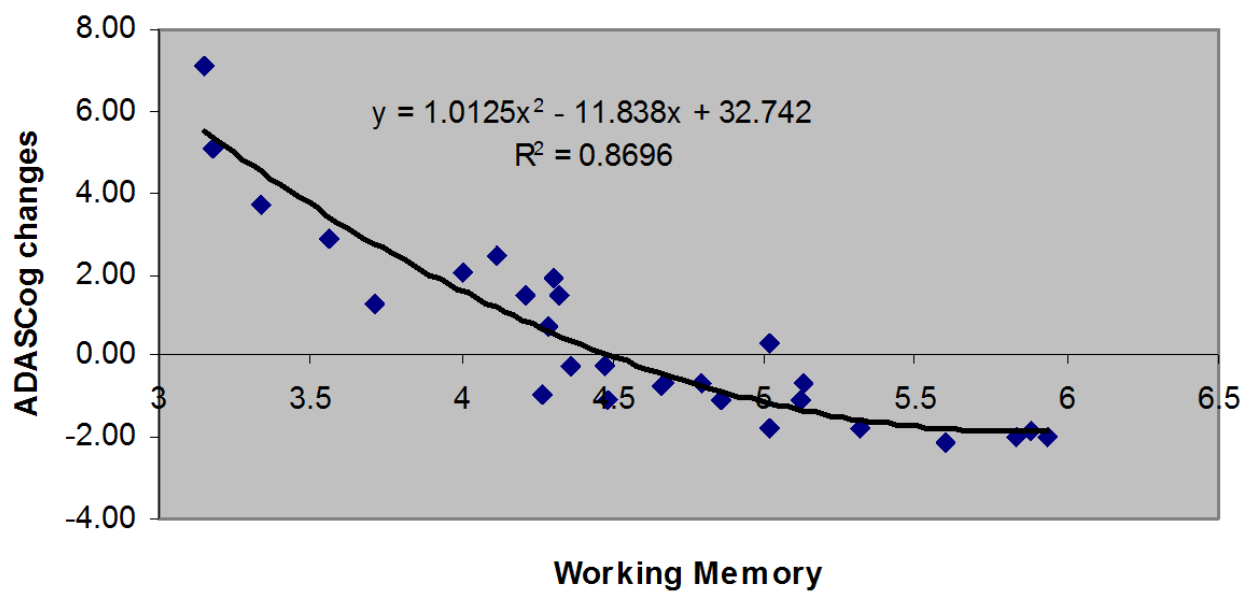
Figure 1B



Calibration of the Network with Clinical Alzheimer Data

Figure 2

ADAS COG Calibration All Data Points



Implementing the neuropharmacology of donepezil, galantamine, rivastigmine and the 5-HT6 antagonist SB742457 as a function of dose and time (28 data) and adjusting 11 biological coupling factors results in a robust correlation between the model outcome and the reported clinical ADAS-Cog data

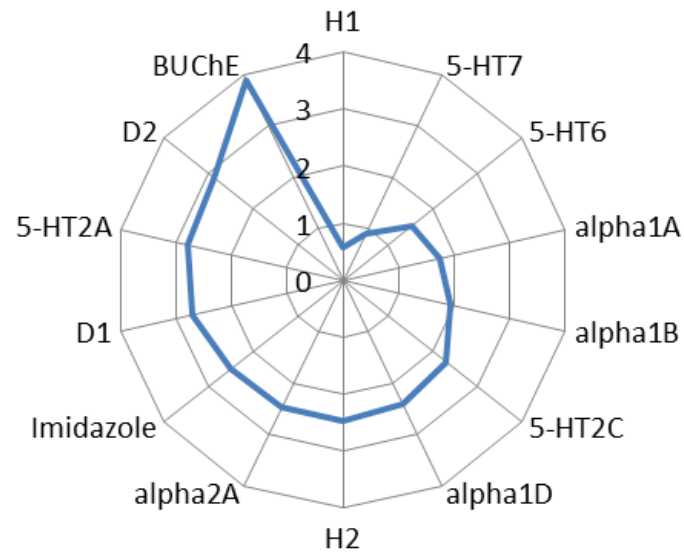
Results

A. Pharmacology of Dimebon

- ✱ Anti-histaminergic compound used in Russia
- ✱ Has mitochondrial stabilizing properties, neuroprotective in Alzheimer’s disease [Zhang 2010]
- ✱ First Phase II study in Alzheimer’s disease was successful [Doody 2008]
- ✱ Complex human pharmacology [Okun 2010] (Fig 3). Symptomatic effect driven by weak AChE-inhibition and 5-HT6 antagonism

Dimebon Pharmacology

Figure 3



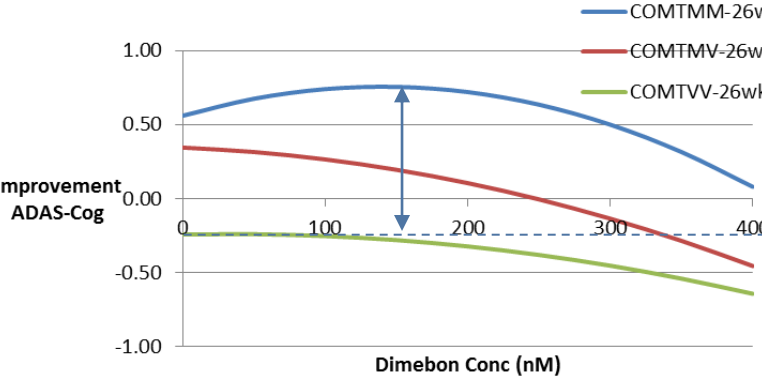
Neuropharmacology of Dimebon. Dimebon affects many human neuromodulatory receptors. This figure shows the pKa values of the most important receptors. The 5-HT6 antagonism improves cognitive outcomes through its indirect effect on Ach and Glutamate; however the D1R antagonism is substantial and is a significant liability for cognitive performance.

B. Effect of COMT Gene

- ✱ Dimebon’s in vivo functional concentration is in 100-250 nM range
- ✱ COMT Val158Met genotype affects breakdown of dopamine and norepinephrine
- ✱ COMT Val158Met modulates effect of dimebon at D1R

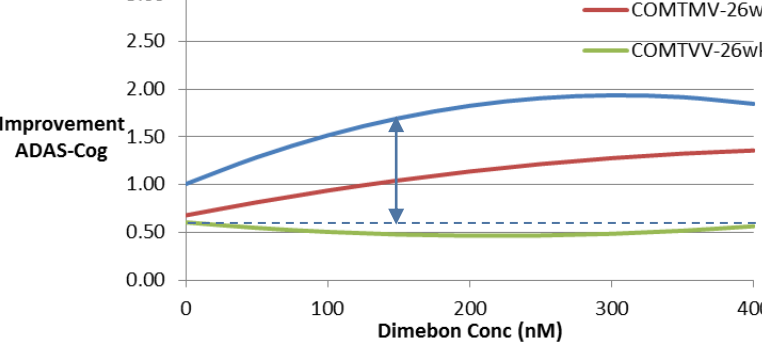
Figure 4

Anticipated ADAS-Cog at 26 Weeks Stand-Alone



Anticipated dose-response after polynomial smoothing for different genotypes of the COMTVal158Met genotype at 26 weeks as a stand-alone medication (A) and as comedication with 10 mg donepezil (B). The COMT Met-Met genotype shows a stronger dose-response, likely because the higher ambient dopamine level will attenuate dimebon’s D1R antagonism. Note that the maximal difference between a placebo COMTVV and a dimebon treated COMT MM patient can reach 1 point on the ADAS-Cog scale for a stand-alone and 1.25 points for augmentation therapy on donepezil.

Anticipated ADAS-Cog at 26 Weeks with Donepezil 10 mg

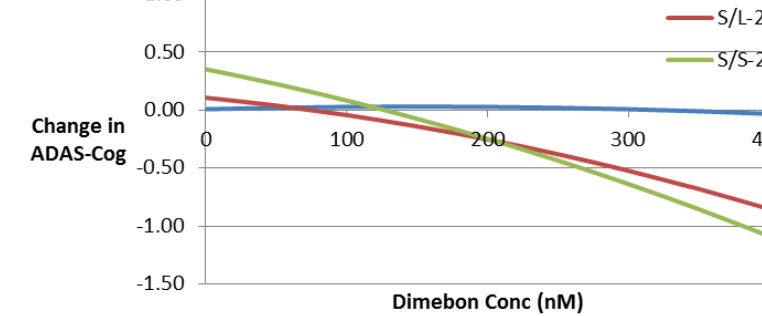


C. Effect of 5-HTT LPR Genotype

- ✱ Dimebon’s in vivo functional concentration is in 100-250 nM range
- ✱ 5-HTT LPR short vs long isoform affects 5-HTT expression, basal 5-HT levels and modulation of 5-HT7, 5-HT6, 5-HT2A by Dimebon

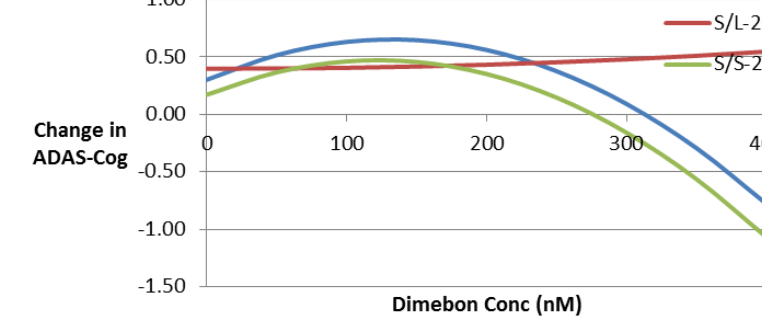
Figure 5

ADAS-Cog Changes with 5-HTT LPR at 26 Weeks Stand-Alone



Anticipated dose-response after polynomial smoothing for different genotypes of the 5-HTT LPR short vs long isoform genotype at 26 weeks as a stand-alone medication (A) and as comedication with 10 mg donepezil (B). Interestingly both the s/s and the l/l dose-responses are different from the s/l dose-response. This is likely due to a non-linear interaction between the pro-cognitive effects of increased 5-HT4R stimulation and the anti-cognitive effects of 5-HT6 on pyramidal cells and 5-HT3 stimulation on inhibitory interneurons against a background of decreasing excitatory-inhibitory tone as a consequence of the disease progression. Note that the maximal difference between a placebo s/s and a dimebon treated l/l patient can reach 0.5 point on the ADAS-Cog scale for augmentation therapy on donepezil.

ADAS-Cog Changes with 5-HTT LPR at 26 Weeks with 10 mg Donepezil



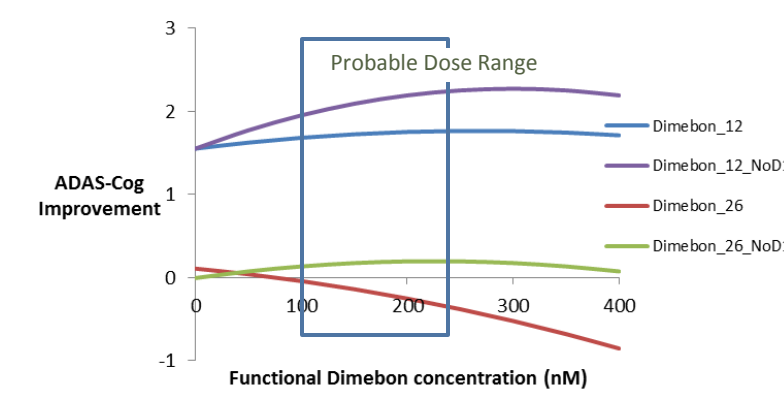
D. Improving Dimebon’s Pharmacological Profile in Alzheimer’s Disease

- ✱ Dimebon’s in vivo functional concentration is in 100-250 nM range [Giorgetti 2010]
- ✱ Dose-response is attenuated by D1R antagonism
- ✱ Eliminating D1R antagonism will help substantially cognitive improvement

Eliminating D1R Activity

Figure 6

Simulated ADAS-Cog Effect with Dimebon



Eliminating the D1R antagonism from dimebon’s pharmacology can lead to almost a point improvement on the ADAS-Cog scale for 12 and 26 weeks as a stand-alone medication. The dose-responses is simulated for the mixture of the three COMT genotypes. This suggests great care should be taken for off-target effects even for ‘disease-modifying’ drugs.

Discussion

- ✱ Assumptions:
 - Dimebon has no major metabolites; active moiety is identical to parent molecule
 - Dimebon does not affect other receptors not mentioned in screening table (Fig 3 and [Okun 2010])
 - Dimebon can reach functional brain concentrations in the 100-250 nM range [Giorgetti 2010]
 - No modeling of mitochondrial stabilization property
- ✱ D1R pharmacology (off target) is major liability for cognitive improvement (same range as the clinical relevant difference between COMT MM and COMT VV genotype); can reduce clinical outcome by 1 point on the ADAS-Cog scale.
- ✱ Effect modulated by COMT genotype and to a lesser extent by 5-HTT LPR genotype
 - Dimebon’s D1R antagonism attenuated by higher levels of DA in COMT MM subjects
- ✱ Effect modulated to a lesser extent by 5-HTT LPR genotype
 - Non-linear interaction between diverse pro-cognitive 5-HT4R stimulation on pyramidal cells) and anticognitive properties (5-HT6 stimulation on pyramidal cells and 5-HT3 stimulation on inhibitory interneurons) in background of increasing imbalance between excitatory and inhibitory tone as consequence of disease progression.
 - This effect can also be modulated by anti-depressant medication imbalance between treatment arms.
- ✱ Imbalanced representation of these genotypes between placebo and active arms can result in robust differences in ADAS-Cog outcome.
 - Imbalance in COMT genotypes (Placebo COMT-VV, active arm COMT-MM) can lead to ‘apparent’ clinical improvement.

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

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