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OFFICE OF CLINICAL PHARMACOLOGY

Application of Placebo Model in Drug Development–A Regulatory Perspective

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Disclaimer: My remarks today are my own personal views and do not represent those of the FDA

Outline

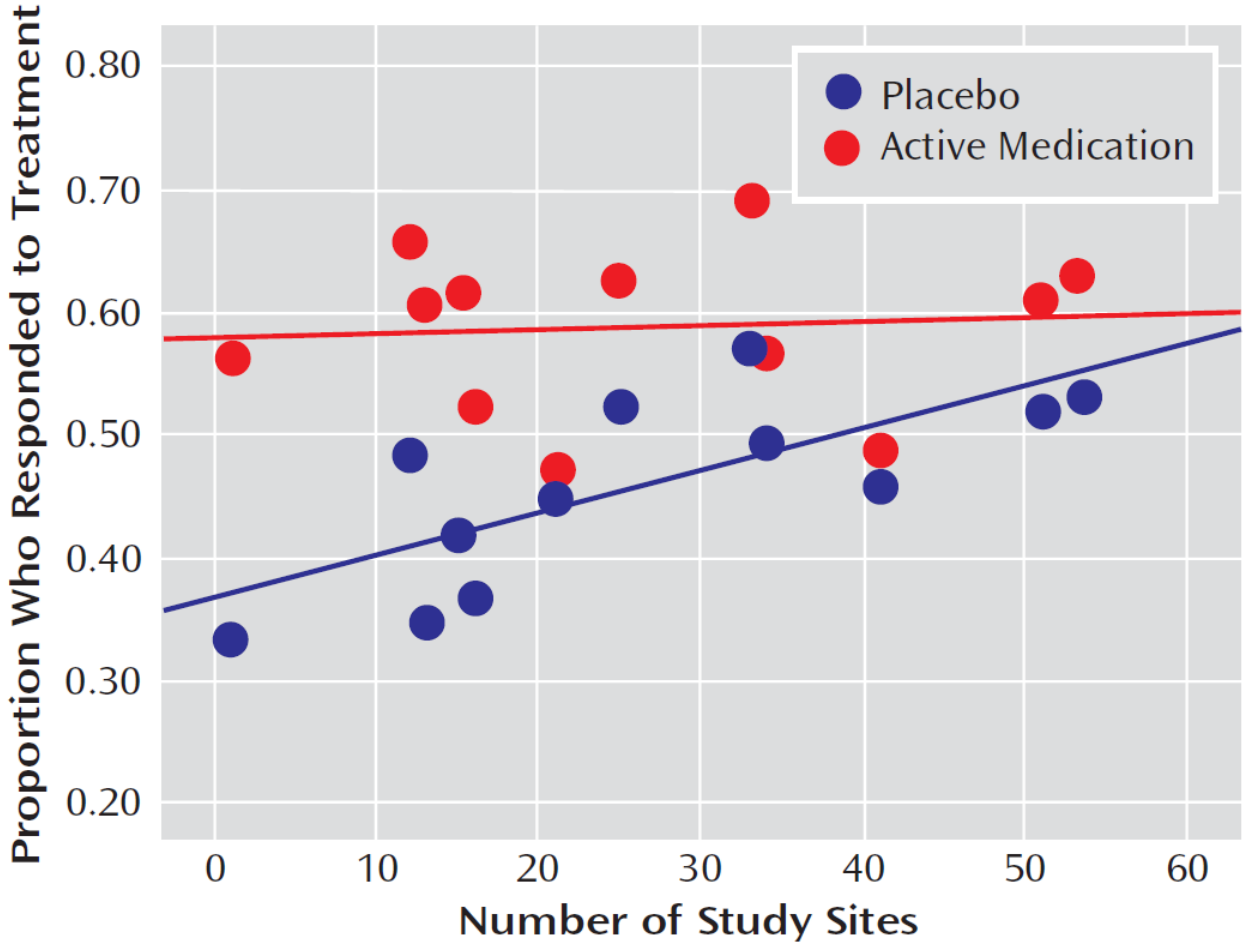
- Overview
- Case studies
  - Alzheimer's Disease (AD)
  - Attention Deficit Hyperactivity Disorder (ADHD)
- Summary

Overview

- Many therapeutic areas still rely on placebo arm as the comparator
- Placebo effect exists in almost every therapeutic area
- Many factors contribute to the placebo effect
- Different placebo response patterns could happen under the same trial design
- In 2011, German Medical Association advised physicians to give out more placebos
  - Dr. Peter Scriba, chairman of the German Medical Association's advisory board, said that "placebos could help patients with mild anxiety, depression, chronic inflammatory problems, pain and asthma."

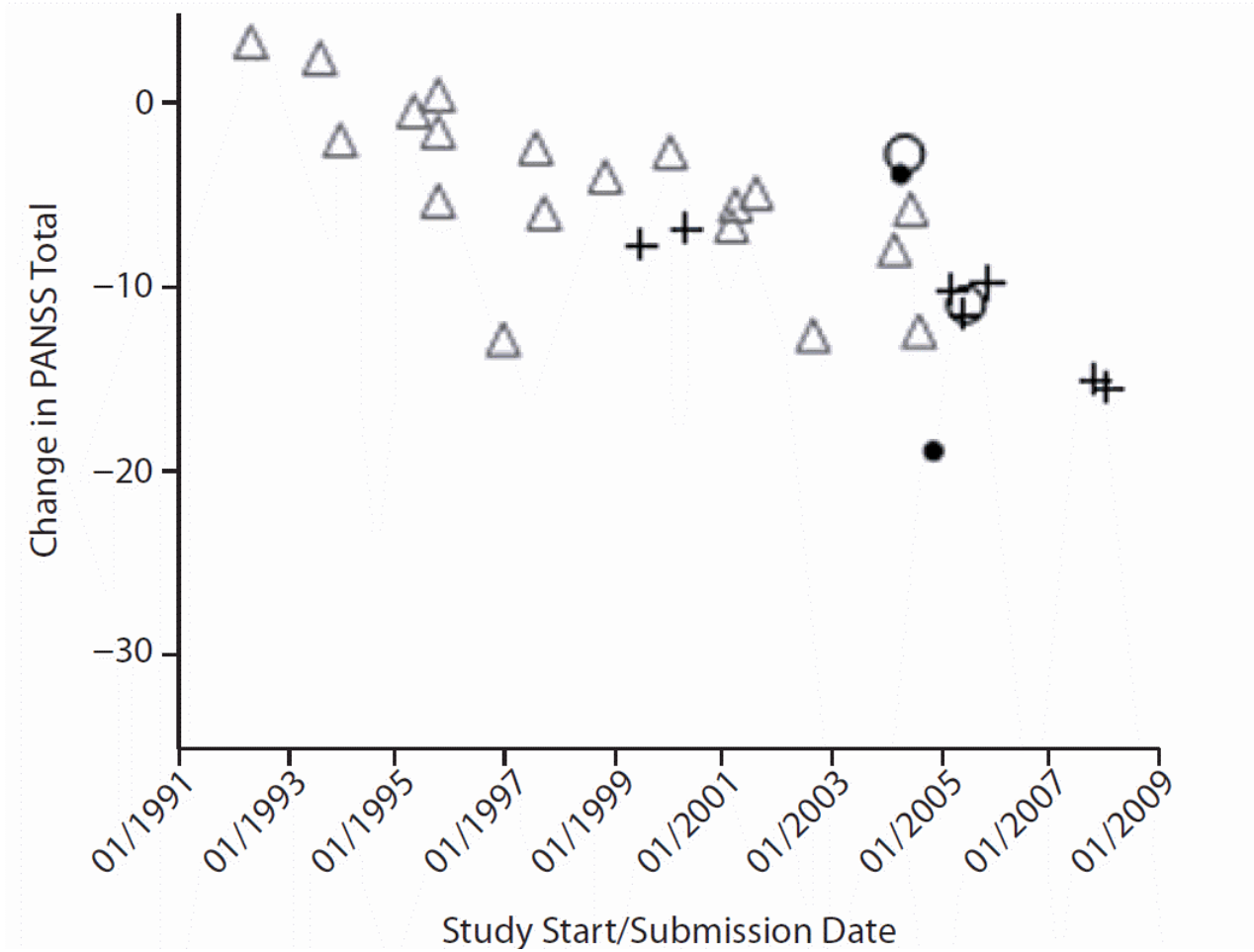
http://archive.boston.com/yourtown/cambridge/articles/2011/03/31/german_doctors_advised_to_give_out_more_placebos_1301580340/

Placebo Effect for Antidepressants



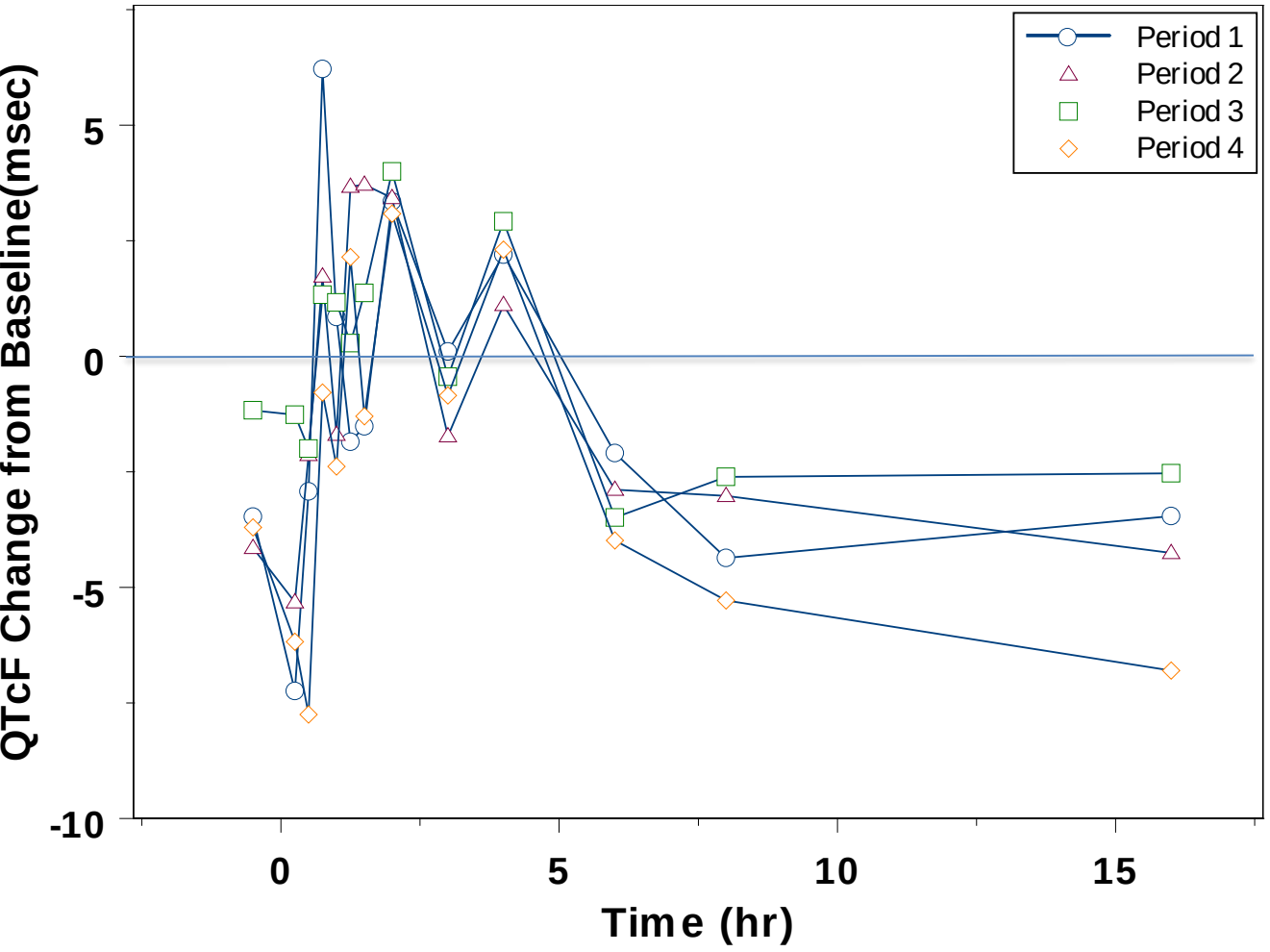
Placebo Response in Randomized Controlled Trials of Antidepressants for Pediatric Major Depressive Disorder, Jeffrey A. Bridge, et al. *Am J Psychiatry 166:1, January 2009*

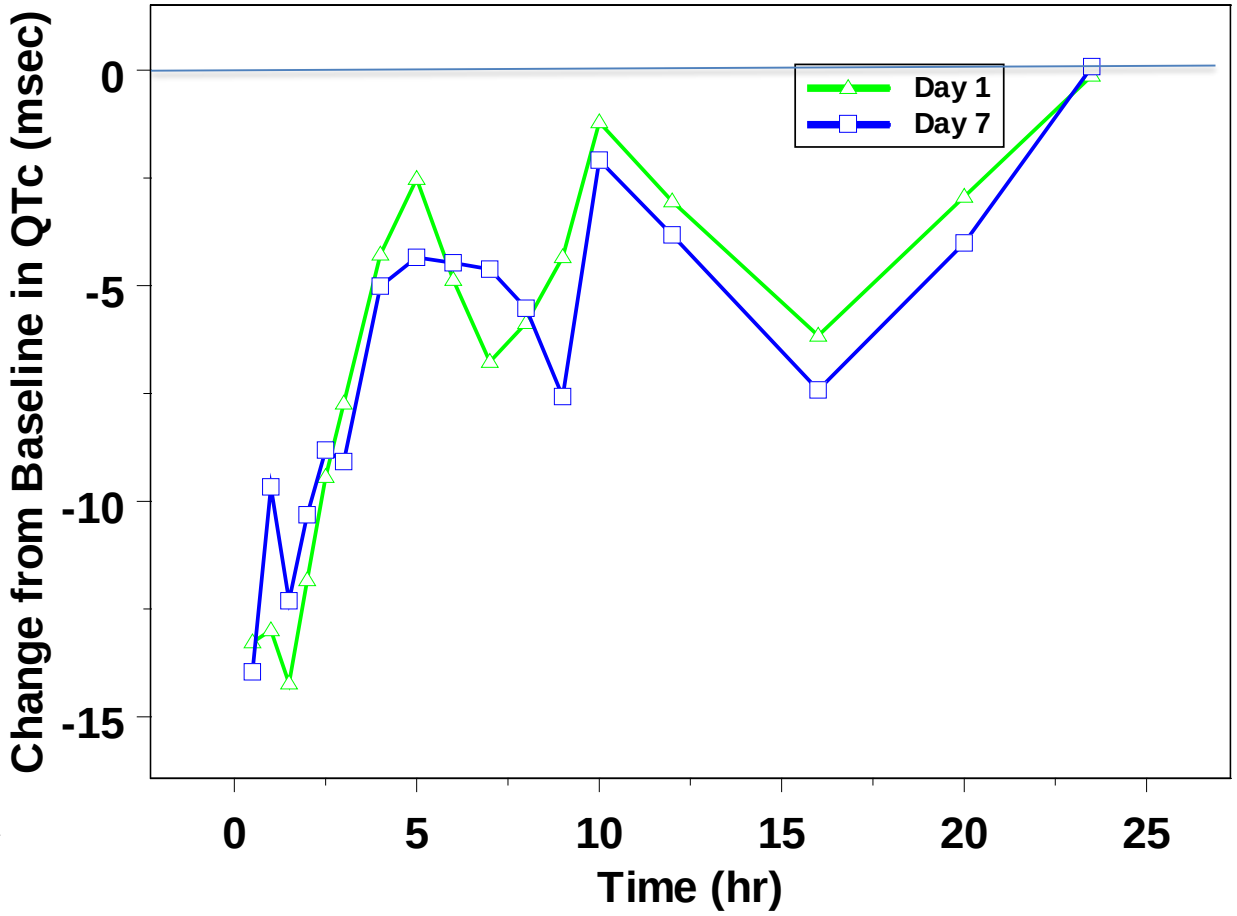
Placebo Response over Time



Exploratory Analyses of Efficacy Data From Schizophrenia Trials in Support of New Drug Applications Submitted to the US Food and Drug Administration, Ni A Khin, et al. *J Clin Psychiatry 2012; 73 (6): 856-864*

Different Placebo Response Patterns

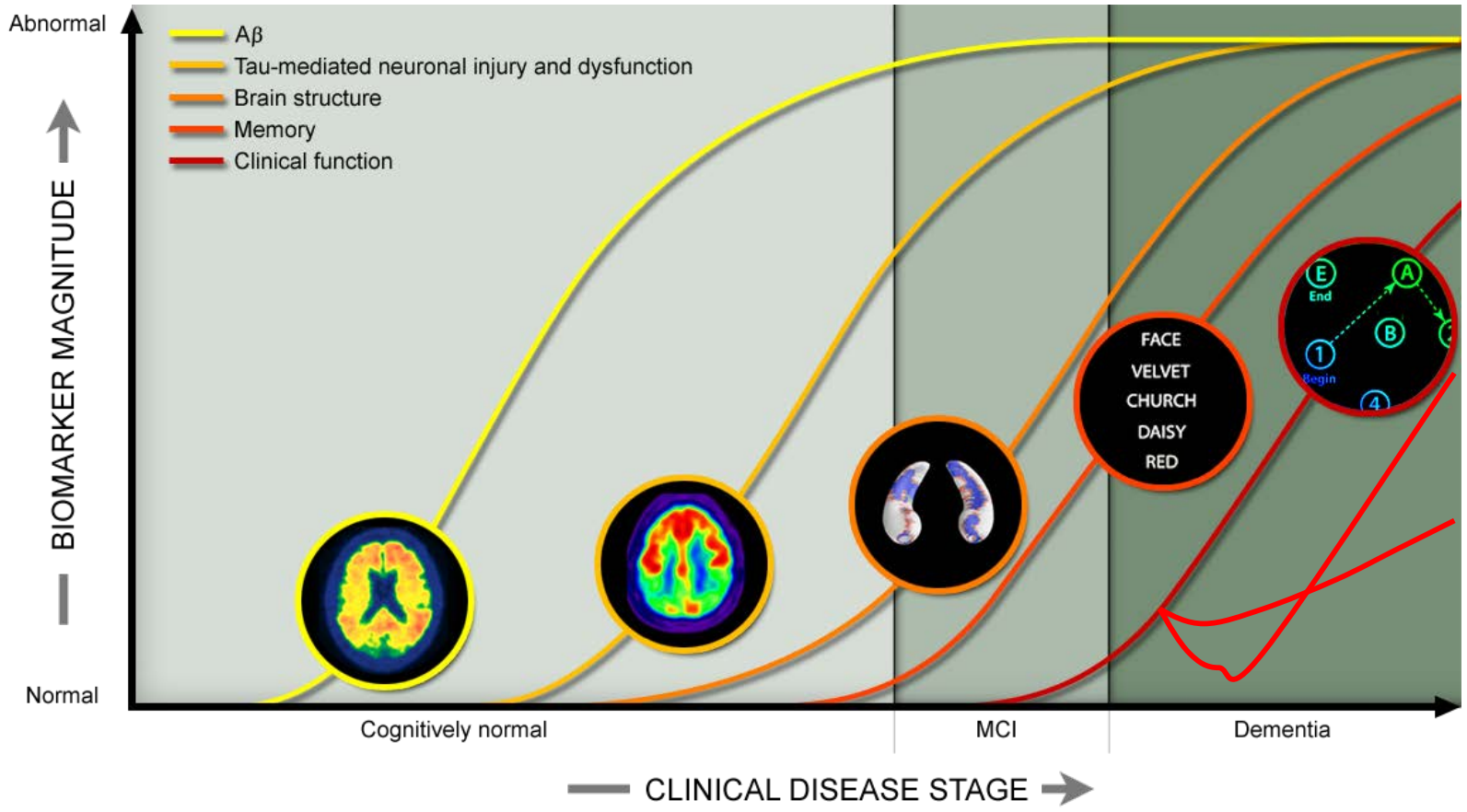




Alzheimer's Disease (AD)

- Currently available AD treatments only relieve symptoms
- New compounds targeted to prevent neuro-damages (i.e., disease-modifying) are under investigation
- More sophisticated clinical trials and alternative endpoints are needed to evaluate the disease-modification effect
- Quantifying the natural disease progression is critical for trial design

Amyloid Cascade Hypothesis

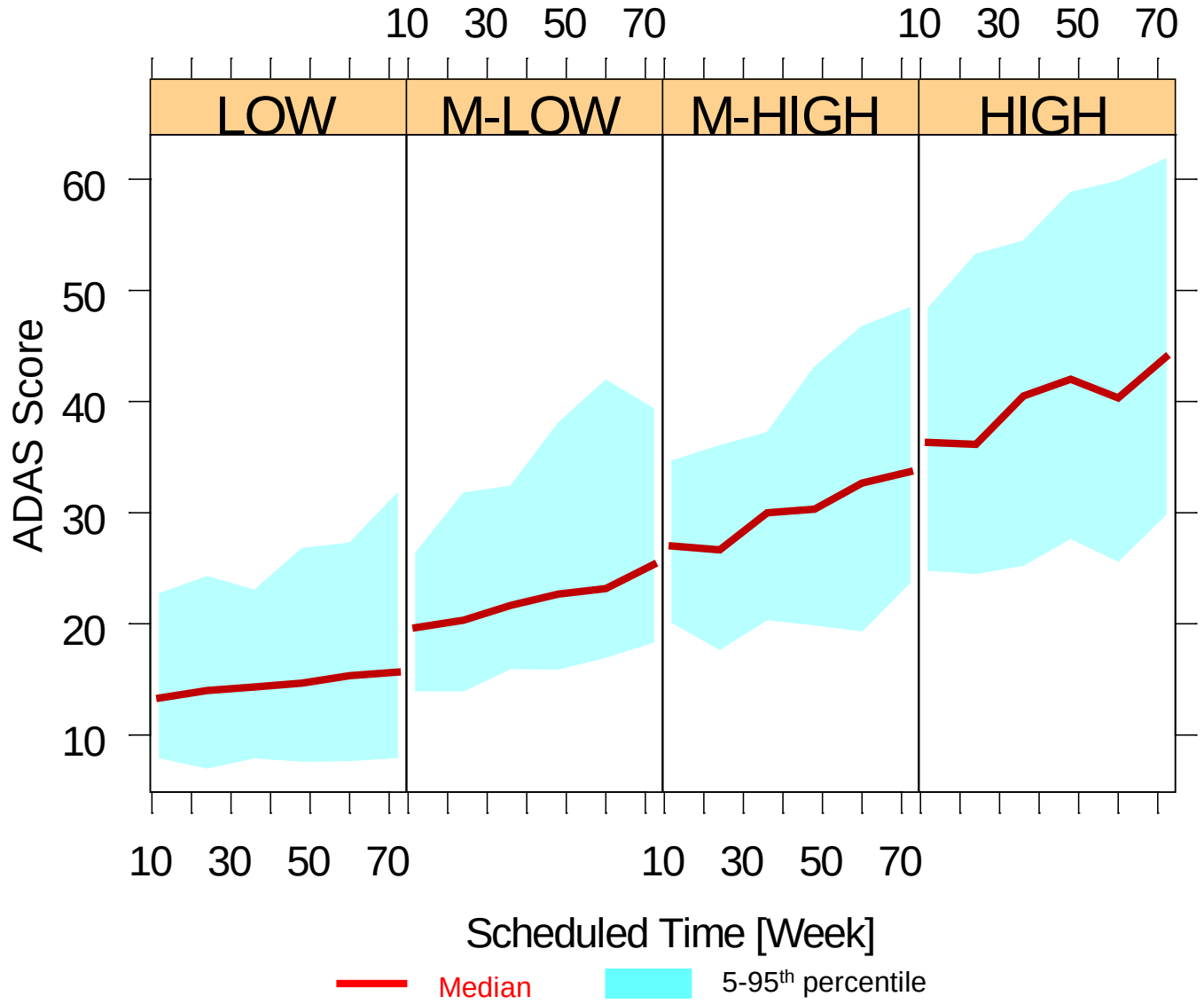


Database

- **Clinical Trials**
  - Patients: mild to moderate AD
  - Primary Endpoint: ADAS-cog
  - Duration: > 3 month
  - Observations/Subject: >2
- **Data**
  - Number of Trials: 10 (2 trials has treatment duration > 1 year).
  - Observations: 2479 patients with 6737 ADAS-cog score.
  - Baseline: median $ADAS_0$ = 24

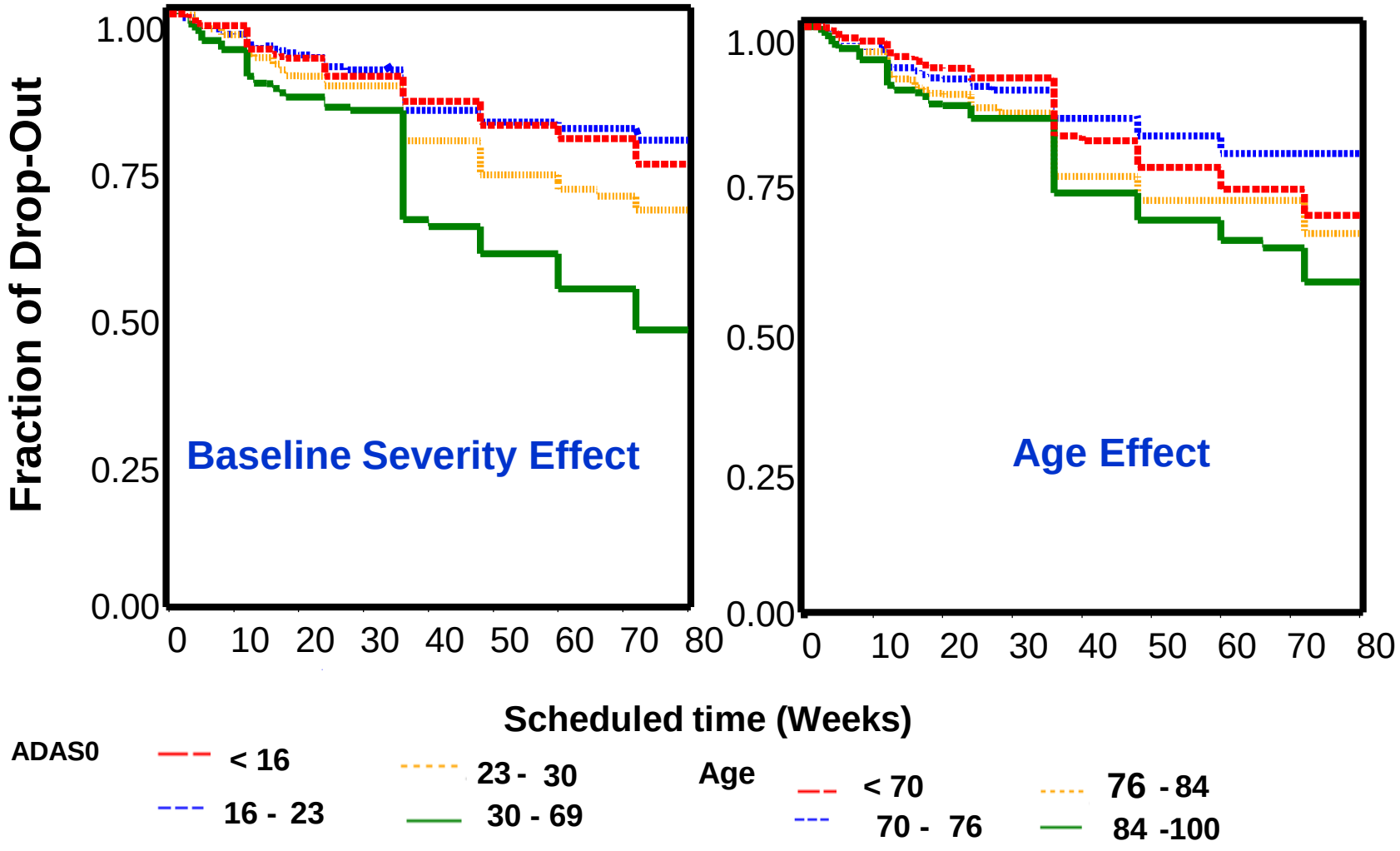
Only Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores observed from Week 10 and above from placebo group were included for AD modeling.

Non-Linear Disease Progression Under Placebo



William-Faltaos D, et al., Quantification of disease progression and dropout for Alzheimer's disease, Int J Clin Pharmacol Ther. 2013 Feb;51(2):120-31

Drop-Out Model



William-Faltaos D, et al., Quantification of disease progression and dropout for Alzheimer's disease, Int J Clin Pharmacol Ther. 2013 Feb;51(2):120-31

Joint Efforts

- **Coalition Against Major Diseases (CAMD)**
  - **Develop new tools (biomarkers and disease progression models) and methods that can be applied during the development of new treatments for neurodegenerative diseases**
- **Partners:**

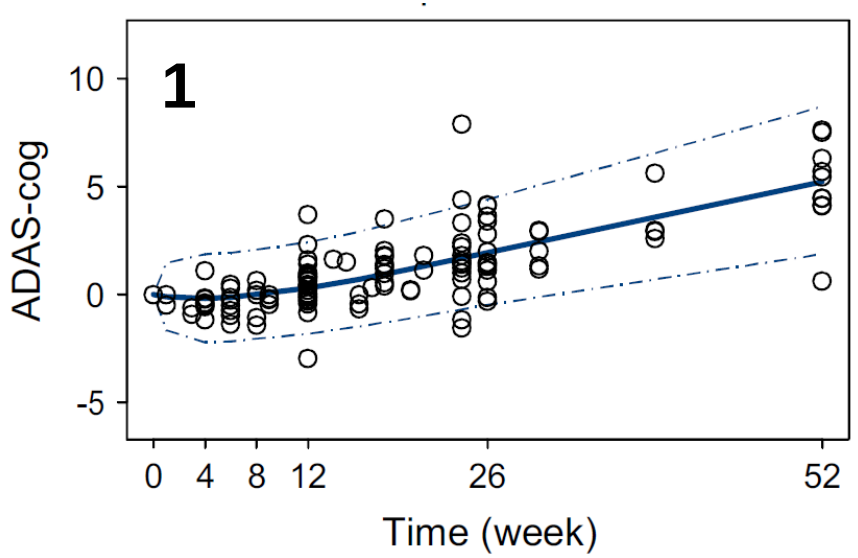
Government:
U.S. Food and Drug Administration
European Medical Agency (EMA)
Engelberg Center for Health Care Reform at the Brookings Institution
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Aging (NIA)

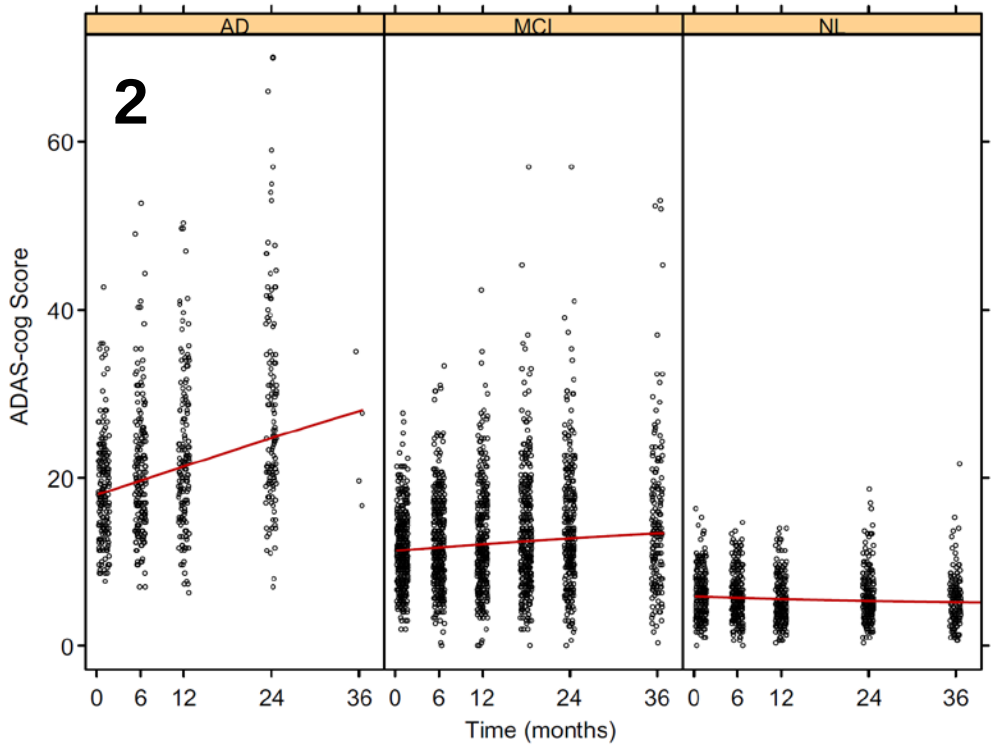
Other:
Alliance for Aging Research, Alzheimer's Association
Alzheimer's Foundation of America, CHDI Foundation, Inc.
National Health Council (NHC), Parkinson's Action Network
Parkinson's Disease Foundation

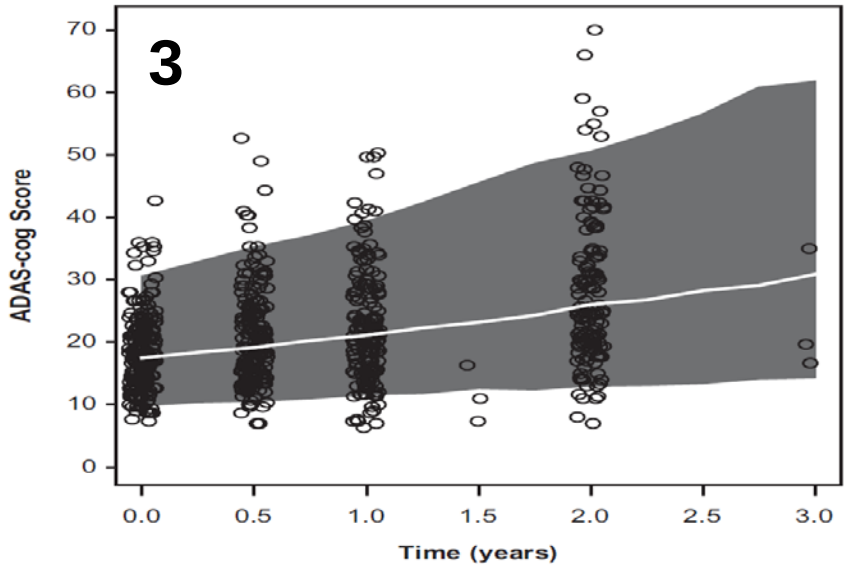
Industry:
Abbott Laboratories
AstraZeneca Pharmaceuticals LP
Bristol-Myers Squibb Company
Eli Lilly and Company
F. Hoffmann-La Roche Ltd.
Forest Research Institute
Genetech, Inc.
GlaxoSmithKline
Johnson & Johnson, LLC
Novartis Pharmaceuticals Corporation
Pfizer, Inc.
Sanofi-aventis U.S., Inc.

http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm231134.htm

Other Disease Models for AD







1. Ito, et al, Alzheimer's & Dementia, 2010
2. Ito, et al, Alzheimer's & Dementia, 2011
3. Samtani, et al, JCP 2011

Data for 2 and 3:
https://www.loni.ucla.edu/ADNI

Fit-for-Purpose Model Qualification

- First drug development tool (DDT) submitted for qualification
  - AD trial simulation Tool
- A drug-disease-trial model that describes disease progression, placebo effect, drug effects, and dropout rates
- Data: literature, clinical trials, ADNI
- Multiple collaborators
- Multiple rounds of interactions between CAMD and FDA
- Comprehensive review of the submission by an inter-disciplinary team

AD Trial Simulation Tool

- **“Regulatory agencies in the U.S. and Europe have endorsed a quantitative simulation tool that allows researchers to model clinical trials in mild to moderate Alzheimer’s disease”**
- **“The Food and Drug Administration (FDA) declared the simulator a “fit-for-purpose” drug development tool on June 12, and the European Medicines Agency (EMA) qualified it for use on July 1”**
- **“The FDA encourages these kinds of pre-competitive collaboration among multiple companies to build a shared tool,” said Yaning Wang at the FDA, who worked on the project”**

http://www.alzforum.org/new/detail.asp?id=3542

Guanfacine

- **Intuniv™ (extended-release guanfacine, SPD503), approved for QD administration for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents age 6–17 years old.**
- **Initially approved dose in 2009: 1 to 4 mg**
- **Subgroup analyses suggested a lack of efficacy for adolescents (13-17)**
- **PMR study for adolescents (13-17)**

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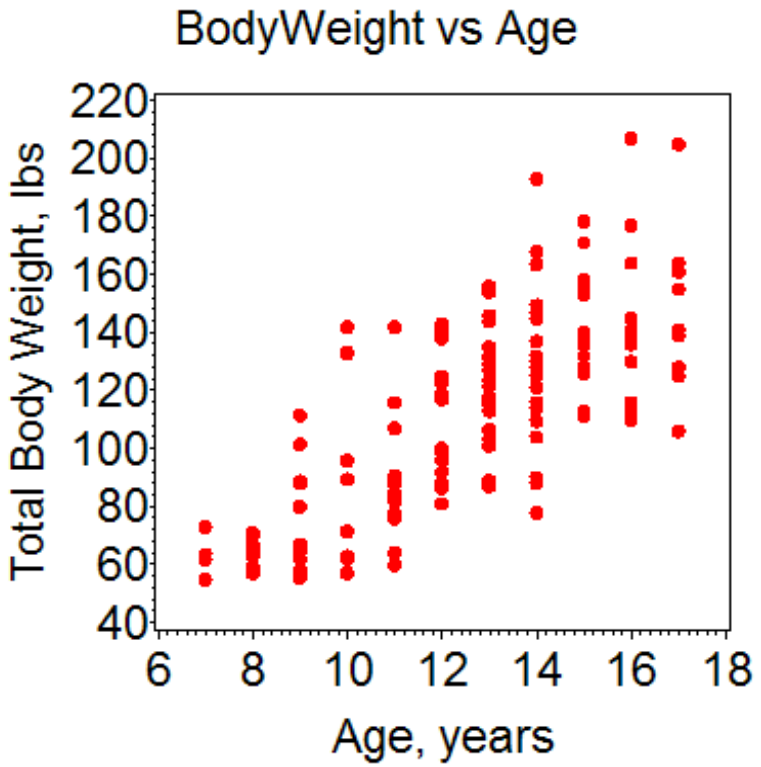
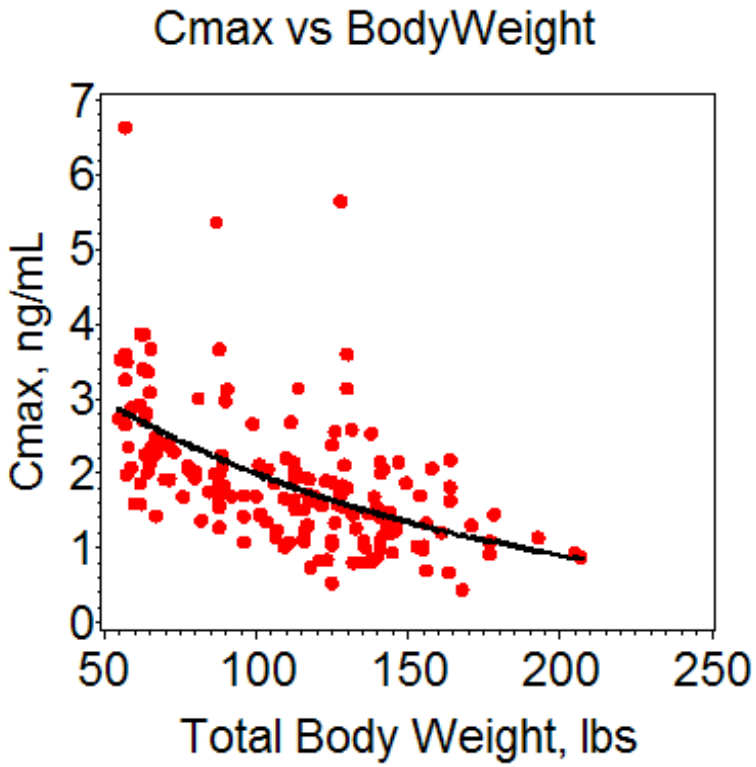
Drug Concentrations Are Lower for Adolescents





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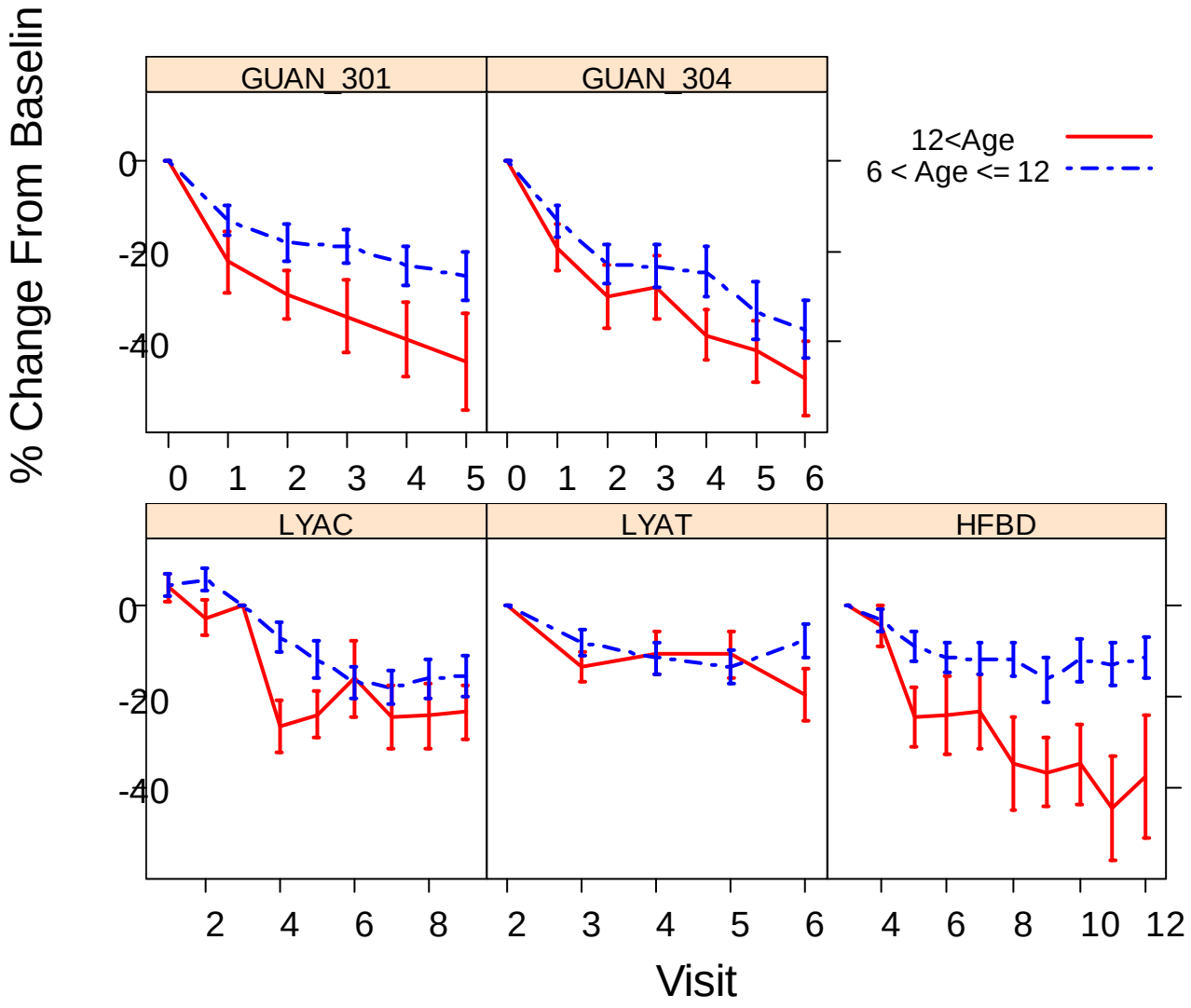
Placebo Effects Are Larger for Adolescents



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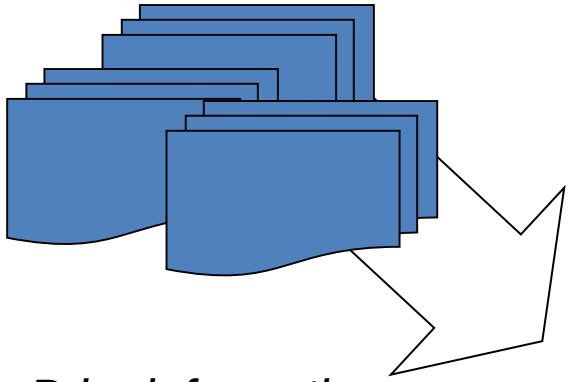
Clinical Trial Simulation

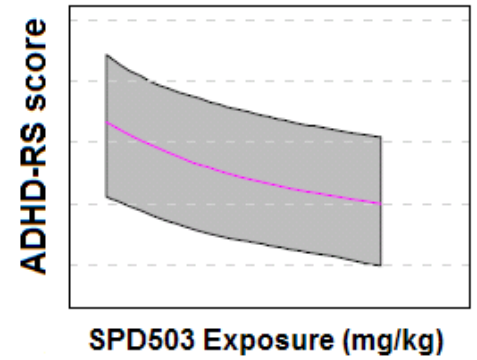


Prior information (data from 9 trials)

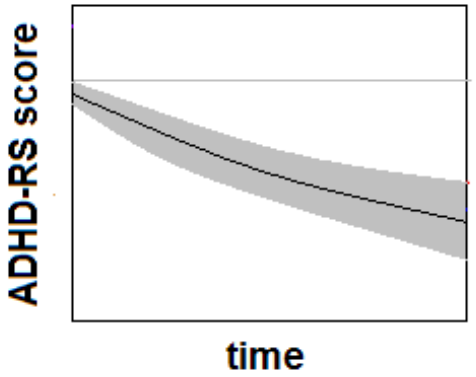
Pediatrics (6-17)

5 trials - placebo and active SPD503

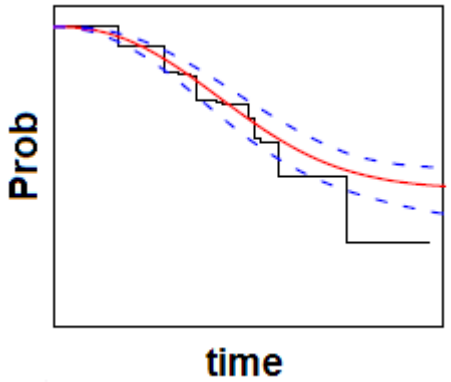
4 trials - placebo arms from different programs



Exposure-response model



Placebo model



Dropout model

Simulate experimental design

- 312 Protocol

Probability of Success

97%

Knebel W, et al, Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD, J Pharmacokinet Pharmacodyn. 2015 Feb;42(1):45-65

STUDY	301	304	312
Age range	6 – 17	6 – 17	13 – 17
# subjects	345 (~ 86 per group)	324 (~65 per group)	280 (140 per group)
Titration	Forced	Forced	Flexible
Target Doses	Placebo, 2, 3 or 4 mg/day	Placebo, 1, 2, 3, or 4 mg/day	Placebo, Based on weight, maximum 4-7 mg/day
Duration (weeks)	8	9	15
Titration	5	3	7 (optimization)
Maintenance	0	3	6
Tapering	3	3	2
Notes:			Min ADHD-RS IV of 32 at baseline

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Successful Study 312

Table 1: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 (FAS) - Study SPD503-312

	Placebo (N=155)	SPD503 (N=157)
Baseline		
N	155	157
Mean (SD)	40.0 (6.11)	39.9 (5.57)
Visit 13		
N	106	109
Mean (SD)	20.3 (13.35)	14.1 (9.38)
Change from baseline		
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)
Comparison to placebo [a]		
LS mean	-18.527	-24.552
Difference in LS means	NA	-6.026
(95% CI)	NA	-8.865, -3.187
Effect Size	NA	0.52
p-value		<0.001

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Summary

- Placebo effect is common in clinical trials
- To improve the chance of success for a clinical trial:
  - Understand the reasons for placebo effect
  - Quantify placebo effect
  - Conduct clinical trial simulation

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Acknowledgements

- Division of Pharmacometrics
- Office of Clinical Pharmacology
- Office of Biostatistics
- Office of New Drugs
- Sponsors

THANK YOU

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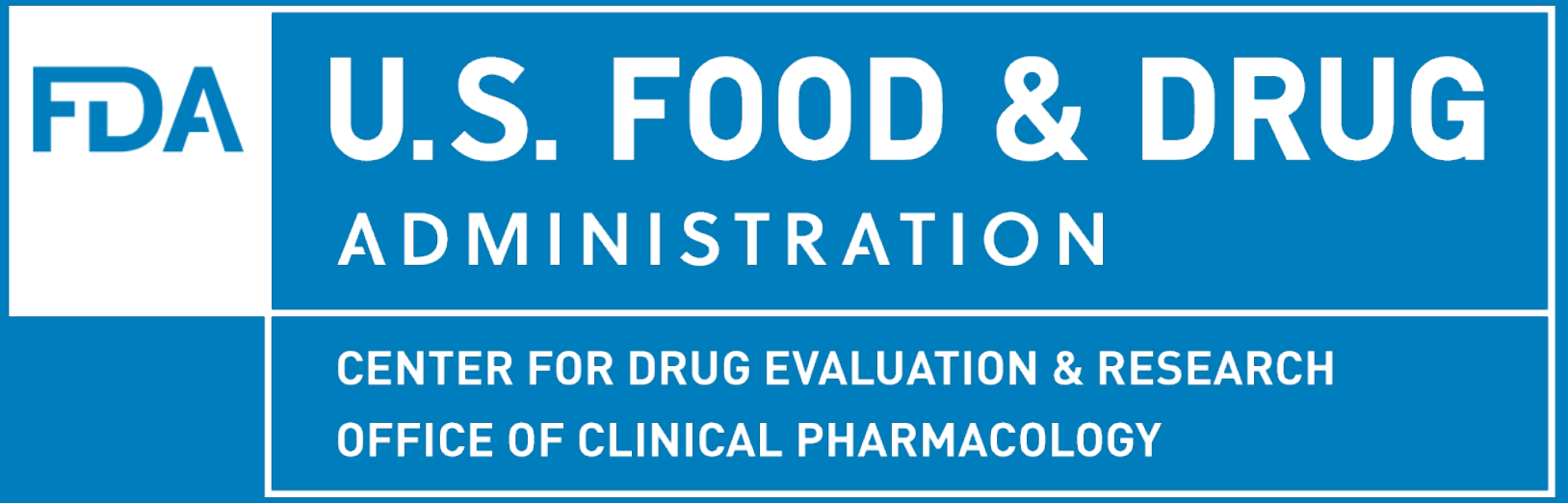
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