Estimating drug effects in the presence of placebo response: Causal inference using growth mixture modeling

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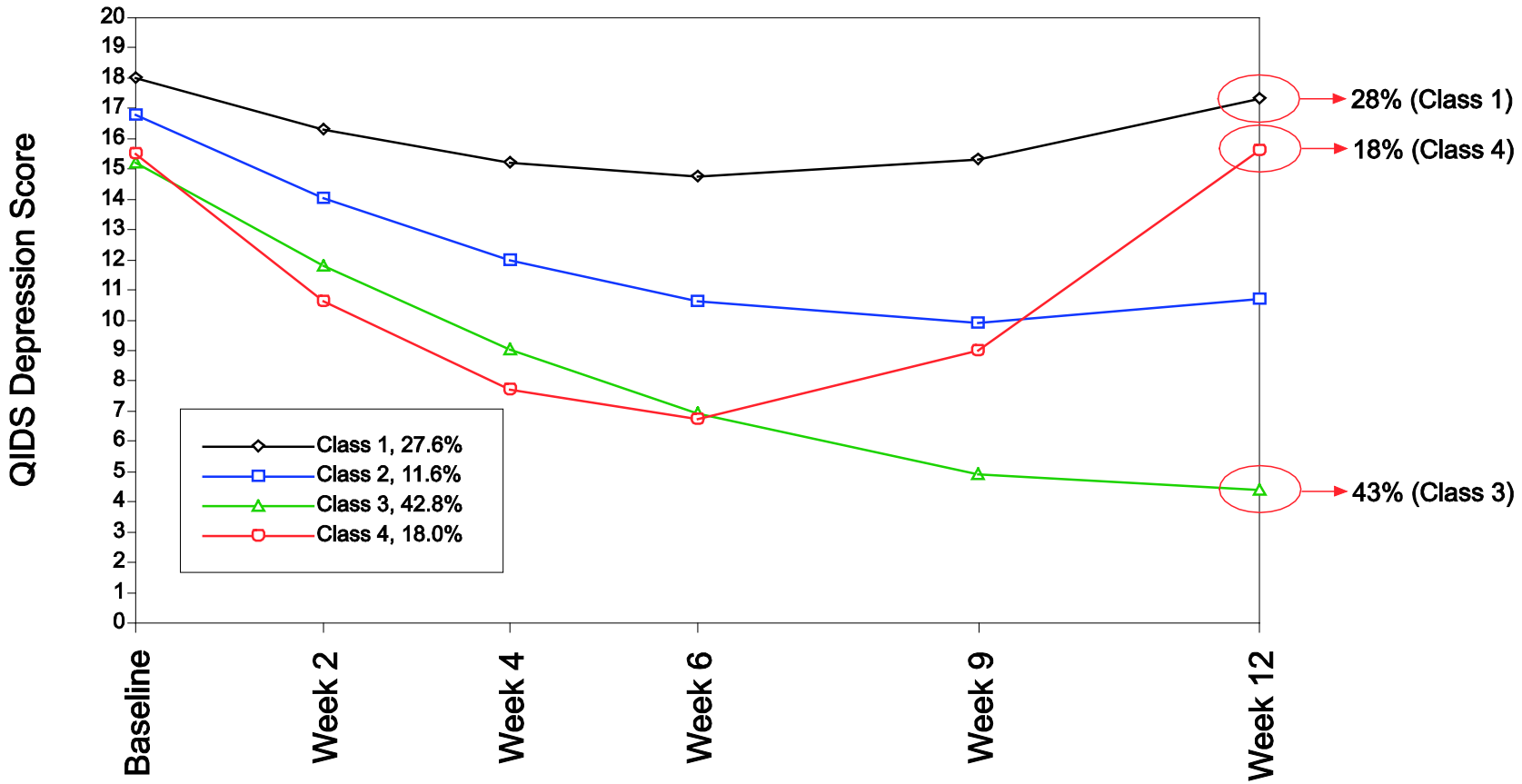
Prelude: A growth mixture model for a large antidepressant trial of citalopram (no placebo group, $n = 4041$; STAR*D)



How many of those who respond to the drug would have responded to placebo?

Overview

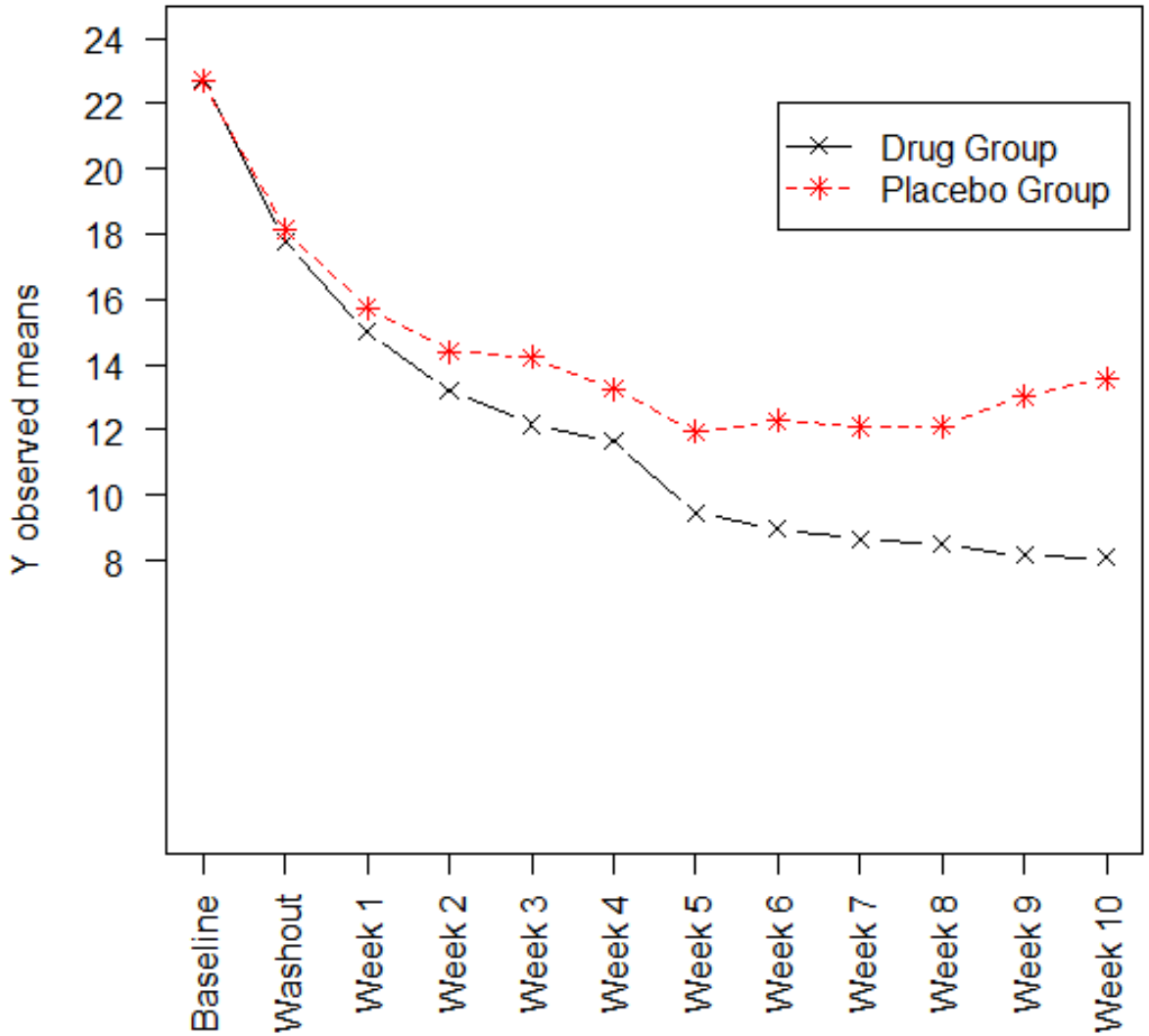
- Source: Muthén & Brown (2009). Estimating drug effects in the presence of placebo response: Causal inference using growth mixture modeling. Statistics in Medicine, 28, 3363-3385.

1. An antidepressant trial with a drug and a placebo group
2. Limitations of conventional assessment of drug effects
3. A new approach to assessing drug effects
4. Brief recap of Rubin causal inference with non compliance (Angrist, Imbens & Rubin, 1996)
5. Analysis of the antidepressant trial data
   - Using a simple growth mixture model
   - Using a fuller growth mixture model

Data used in this presentation: A smaller antidepressant trial with a drug and placebo group

- 10-week double-blind clinical trial with a 1 week single-blind washout period (McGrath et al., 2000)
- Fluoxetine and imipramine ($n = 102$) versus placebo ($n = 52$)
- 28-item Hamilton Depression rating scale
- Evidence of placebo response

Antidepressant trial ($n = 154$)



Limitations of conventional assessment of drug effects

- End-point analysis: Response if $\geq 50\%$ drop
  - LOCF
  - Irrelevant time-specific variation, trend ignored
- ITT analysis: Causal effect of randomization, not of drug
  - Some of the drug responders may have responded to placebo as well
  - Some of the drug non-responders may have responded to placebo

Background: The causal inference model with non-compliance (Angrist, Imbens & Rubin, 1996, JASA)

Consider $Y_i(X_i, D_i(X_i))$, where Y_i is the outcome for individual i, X_i is the treatment status, and D_i indicates whether or not the individual takes up treatment. Using the idea of potential outcomes, AIR considers 4 classes of subjects:

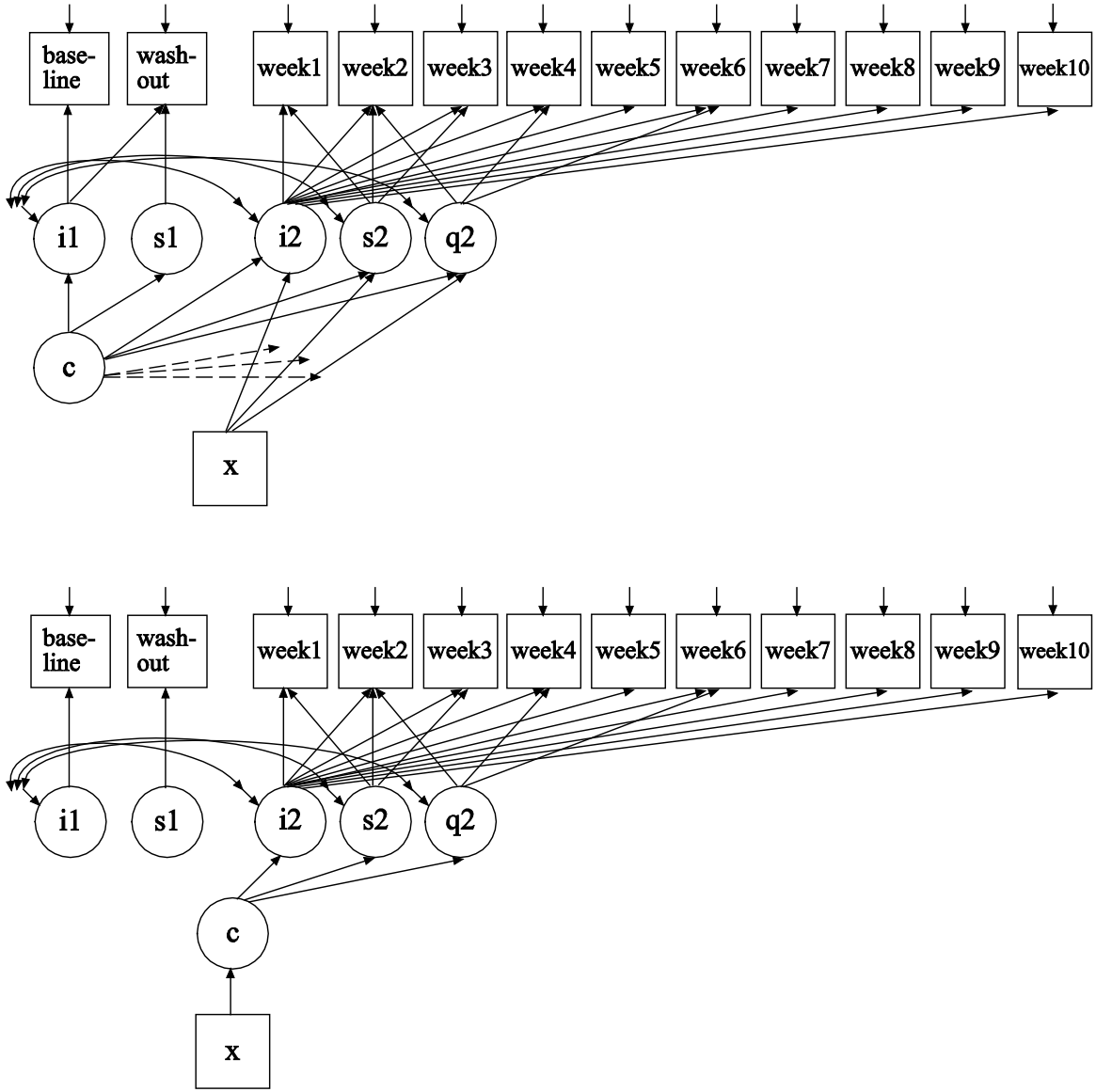
- Never takers ($D_i(1) = 0, D_i(0) = 0$): subjects who would not take up treatment if randomized to either treatment or control (causal effect $= 0$ under the exclusion restriction)
- Compliers ($D_i(1) = 1, D_i(0) = 0$): subjects who would take up treatment if randomized to treatment and otherwise not (causal effect $= Y_i(1,1) - Y_i(0,0)$)
- Defiers ($D_i(1) = 0, D_i(0) = 1$): subjects who would do the opposite of their treatment assignment (causal effect $= -(Y_i(1,1) - Y_i(0,0))$)
- Always takers ($D_i(1) = 1, D_i(0) = 1$): subjects who would take up treatment whether randomized to treatment or control (causal effect $= 0$ under exclusion restriction)

A new drug assessment approach: Four classes of subjects, probabilities, and means for placebo (0) and drug (1) groups

Placebo Group	Drug Group		
	Non-Responder	Responder	
Non-Responder	Never Responder π_n, μ_{n0}, μ_{n1}	Drug Only Responder π_d, μ_{d0}, μ_{d1}	Non-Responder
Responder	Placebo Only Responder π_p, μ_{p0}, μ_{p1}	Always Responder π_a, μ_{a0}, μ_{a1}	Responder
	Non-Responder	Responder	

The 4 classes are principal strata in the sense of Frangakis & Rubin (2002), Biometrics: Principal stratum membership is not influenced by treatment and ”can be used as any pre-treatment covariate”.

Alternative growth mixture models for clinical trial data



Growth mixture modeling analysis

- A special case of the general latent variable modeling framework in Mplus (www.statmodel.com)
- Maximum-likelihood estimation using EM in combination with FS and QN
- Number of classes informed by BIC and bootstrapped likelihood-ratio test

A simpler model alternative: The AIR 3-class moment estimator applied to drug and placebo response

The hypothesized 4-class mixture model has the following outcome means for the placebo and drug groups at a certain time point:

$$\mu_0 = \pi_n\ \mu_{n0} + \pi_d\ \mu_{d0} + \pi_p\ \mu_{p0} + \pi_a\ \mu_{a0}, \tag{1}$$

$$\mu_1 = \pi_n\ \mu_{n1} + \pi_d\ \mu_{d1} + \pi_p\ \mu_{p1} + \pi_a\ \mu_{a1}, \tag{2}$$

ITT effect: $\mu_1 - \mu_0$ (drug minus placebo).
AIR assumes monotonicity, i.e. no "defier", i.e. no Placebo Only Responders, $\pi_p = 0$ (i.e only 3 classes), and exclusion restriction, $\mu_{n0} = \mu_{n1}$, $\mu_{a0} = \mu_{a1}$, so that (2) minus (1):

$$\mu_1 - \mu_0 = \pi_d\ (\mu_{d1} - \mu_{d0}) \tag{3}$$

identifying the average causal effect of the drug in the Drug Only Responder class as

$$\mu_{d1} - \mu_{d0} = (\mu_1 - \mu_0)/\pi_d. \tag{4}$$

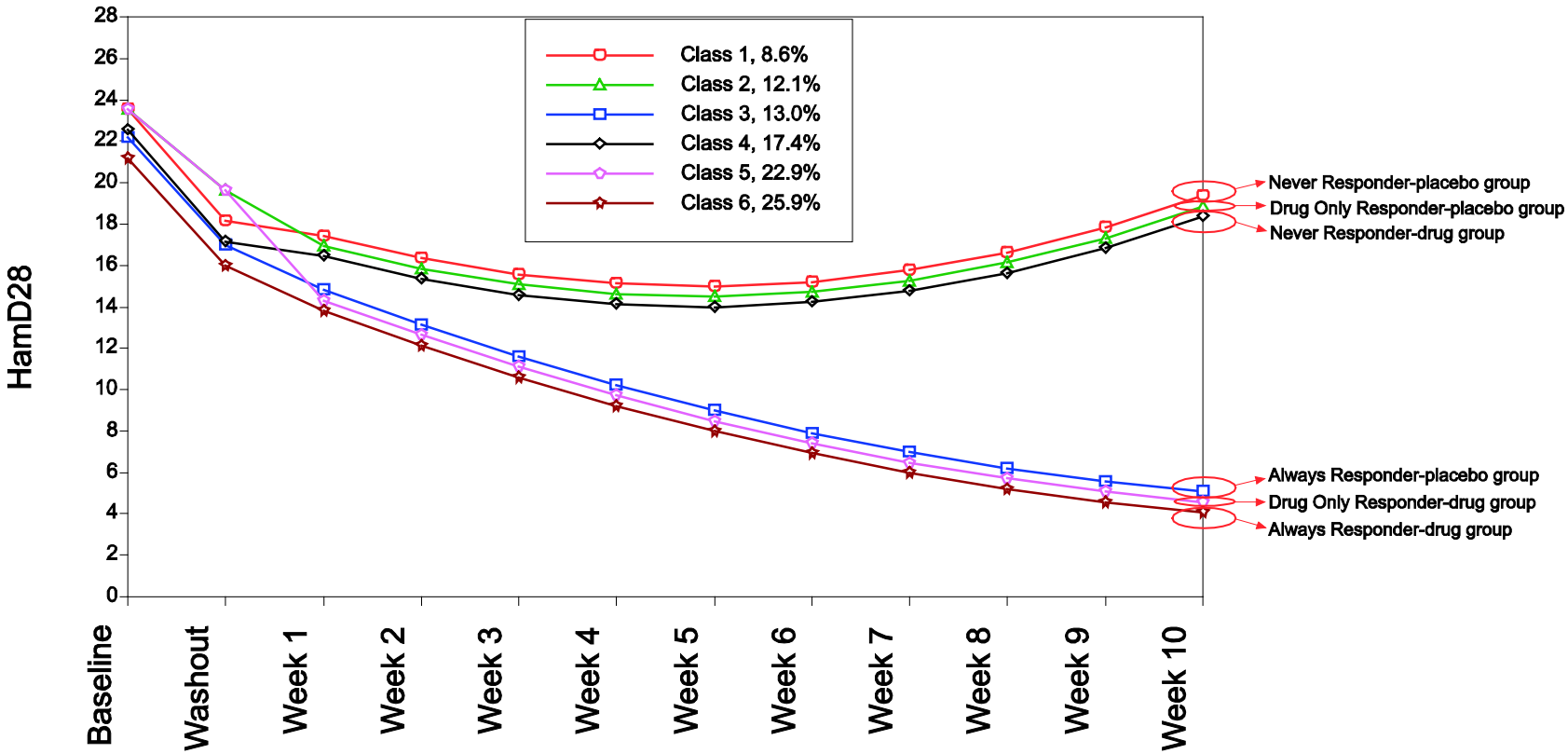
A simpler growth mixture model: 3-class model with only two sets of means

- Exclusion restriction: $\mu_{n0} = \mu_{n1}$, $\mu_{a0} = \mu_{a1}$
- Add the assumption of one mean for responders and one mean for non-responders: $\mu_{n0} = \mu_{d0}$, $\mu_{d1} = \mu_{a1}$

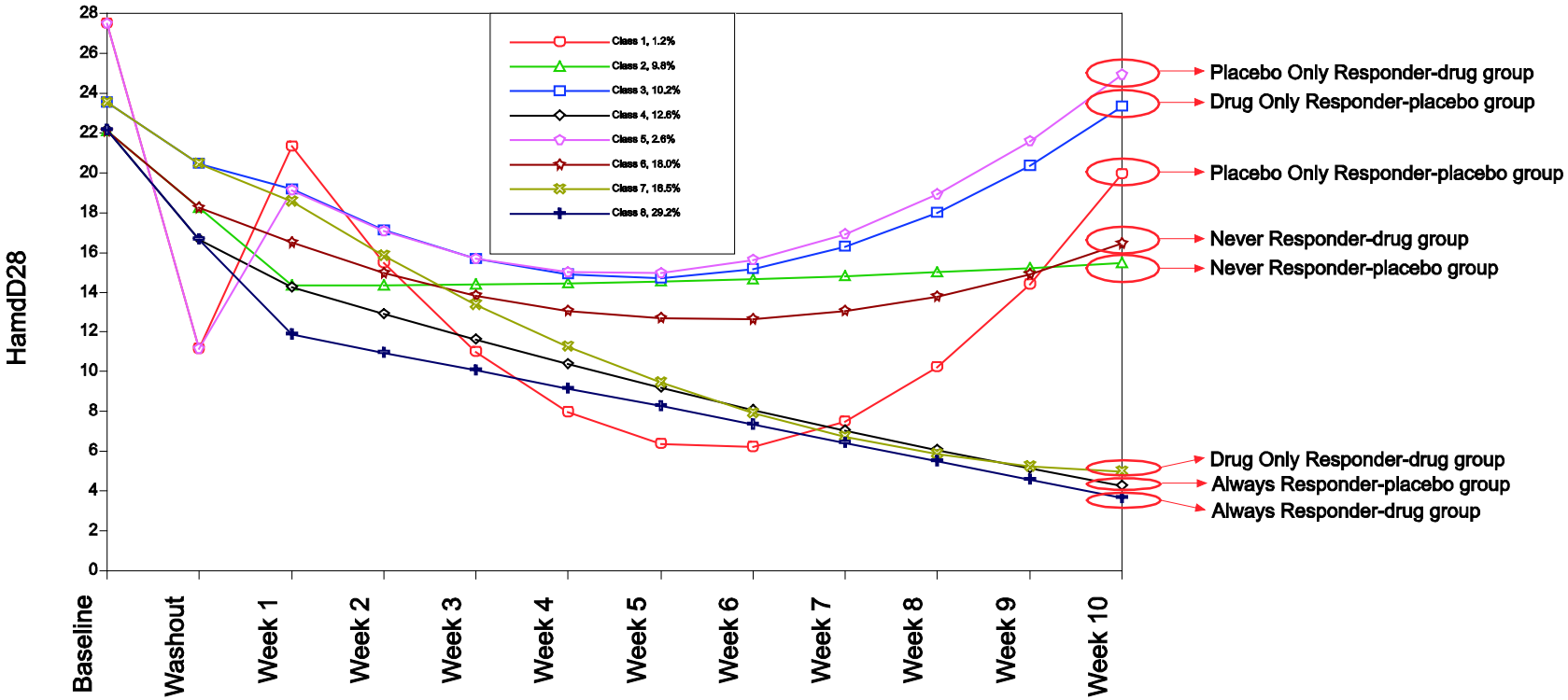
This results in only non-responder and responder means, assuming:

1. A non-responder mean is the same if the subject is
   - in the placebo group and in the Never Responder class,
   - in the placebo group and in the Drug Only Responder class,
   - in the drug group and in the Never Responder class.
2. A responder mean is the same if the subject is
   - in the drug group and in the Drug Only Responder class,
   - in the drug group and in the Always Responder class,
   - in the placebo group and in the Always Responder class.

Estimated mean curves for the simple model: 3-classes, 2 sets of means



Estimated mean curves for the full model: 4-classes, 8 sets of means



Comparing the simple and the full model

Model	LL	#par.	BIC
Simple model: 3 classes, 2 sets of means	-4688	37	9562
Full model: 4 classes, 8 sets of means	-4652	58	9597

Prevalence of four types of subjects under simple and full model. Drug Only Responder tx effect is 14 vs 18

Placebo Group	Drug Group		
	Non-Responder	Responder	
Non-Responder	Never Responder 26%	Drug Only Responder 35%	61%
Responder	Placebo Only Responder 0%	Always Responder 39%	39%
	26%	74%	

Placebo Group	Drug Group		
	Non-Responder	Responder	
Non-Responder	Never Responder 28%	Drug Only Responder 26%	54%
Responder	Placebo Only Responder 4%	Always Responder 42%	46%
	32%	68%	

Further Information: www.statmodel.com

- Muthén & Brown (2009). Estimating drug effects in the presence of placebo response: Causal inference using growth mixture modeling. Statistics in Medicine, 28, 3363-3385.
- Muthén, Brown, Leuchter & Hunter (2009). General approaches to analysis of course: Applying growth mixture modeling to randomized trials of depression medication. Forthcoming in P.E. Shrout (ed.), Causality and Psychopathology: Finding the Determinants of Disorders and their Cures. Washington, DC: American Psychiatric Publishing.