Multivariate two-stage approach for assessing heterogeneity of the treatment effect across participants in the CitAD clinical trial

We applied the following two-stage estimation method based on the work of Cai and colleagues (Cai T, Tian L, Wong PH, Wei LJ: Analysis of randomized comparative clinical trial data for personalized treatment selections. Biostatistics 2011; 12:270–282).

Stage 1. Model-based assessment of covariate-specific treatment effect

In the first stage, a preliminary estimate of treatment effect for different covariate profiles was obtained using "working" parametric models. By working models, we mean that, ultimately, the results of the method will be valid even if the models are incorrect. Specifically, for each patient i, we label the covariate vector, the randomized treatment, and the binary CGIC-A response outcome, by Cov_i , $Treatment_i$ and Y_i respectively. The working parametric model is

$$\text{logit } Pr^{approx}(Y_i=1 \mid Treatment_i, Cov_i, \alpha) = approx(Treatment_i, Cov_i, \alpha) \quad (1)$$
$$= \alpha_0 + \alpha_T * Treatment_{i+} \alpha_P * Cov_{i+} \alpha_{TP} * Cov_i * Treatment_i$$

The model is fitted using maximum likelihood, and the index score for each patient is defined as

$$s_i(\hat{\alpha}) = Pr^{approx}(Y_i=1 \mid Treatment_i=1, Cov_i, \hat{\alpha}) - Pr^{approx}(Y_i=1 \mid Treatment_i=0, Cov_i, \hat{\alpha}),$$

that is, $s_i(\hat{\alpha})$ is the difference in the fitted probabilities, under assignment to citalopram versus placebo group. The estimates of the fitted parameters are given in Table S1.

TABLE S1. CGIC response multiple logistic regression for pre-specified and post hoc predictors

	Citalopram Working Model		Placebo Working Model	
	Estimate	Std. Error	Estimate	Std. Error
Intercept	-1.27	0.70	-1.68	0.95
Residence: long term care	-0.76	0.94	3.48	1.56
MMSE: moderate, 11-20	-1.39	0.61	0.03	0.86
MMSE: severe, 0-10	-1.30	0.79	-0.62	0.93
NBRS: middle tertile, 6-8	1.52	0.73	-0.78	1.09
NBRS: largest tertile, 9+	2.37	0.76	1.97	0.82
Age: middle tertile, 76-82	0.74	0.64	-0.33	0.74
Age: oldest tertile, 83-92	0.19	0.65	-1.13	0.84
Lorazepam (use)	-0.02	1.30	2.23	1.29

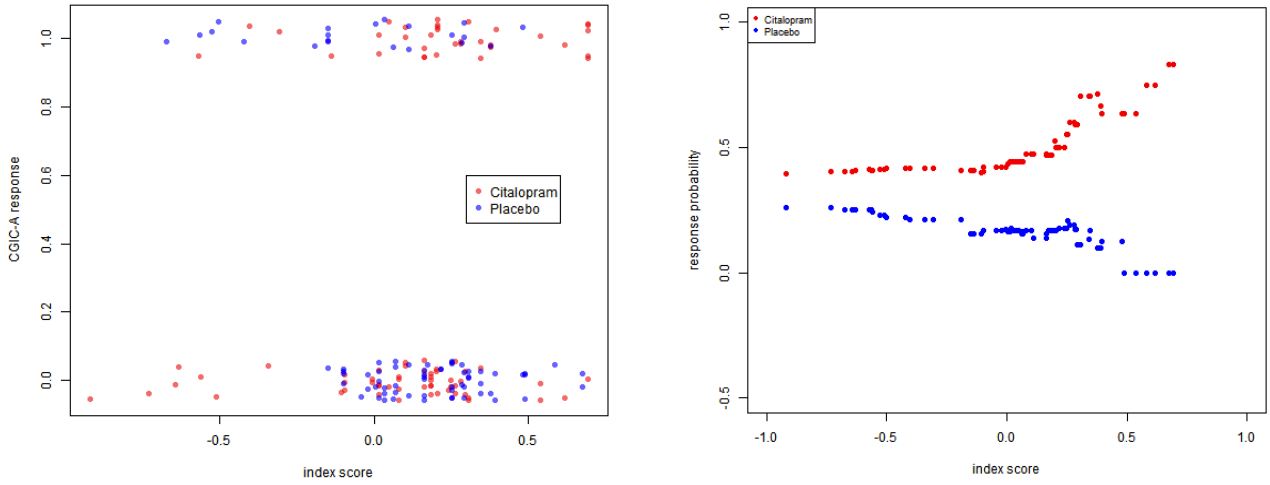
Because interpretation of this index as a treatment effect is valid only if the working model is correct, a second stage is used to obtain a model-free assessment of effect heterogeneity.

Stage 2. Model-free assessment of covariate-specific treatment effect

In the second stage, the response Y_i is plotted against the index score $s_i(\hat{\alpha})$ for each randomized treatment separately (Fig S1(a)). Then, for every threshold of the index score, the probability of response under citalopram is estimated (Fig S1(b), red) for all patients with $s_i(\hat{\alpha})$ greater than the threshold (similarly for placebo, FigS1(b), blue). So the left-most estimates will be the average probability of response for all participants. The right-most estimates will be the proportion of persons with a response at the largest index score alone. An estimate for the 50 percentile index score would be an estimate of the probability of response for the half of participants with the largest index scores.

FIGURE S1. (a) Actual outcome response values versus index score. (b) Empirical proportion of response for patients with index scores greater than each threshold.

Since the values on the y axis can only be 1 or 0, the points have been jittered to show all of the data. Each point is colored according to the participant's treatment assignment, with citalopram in red and placebo in blue.



The last step to obtaining the non-parametric estimates of the treatment effect is to subtract the estimates for the placebo group (shown in red) from the estimates for the citalopram group (shown in blue) at each index score. The resulting values are the non-parametric estimates of the treatment effect shown in black in Figure 2 (see main text).