Longitudinal Analysis for the effect of DAR-0100A

Lupe Antonio, Liner Ge

Columbia University
Department of Biostatistics

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Outline

Outline

Cognitive deficits and DAR-0100A

Cognitive deficits are common problem among schizophrenia patients. DAR-0100A is an agonist that can stimulate dopamine-1 recepters in the brain. The goal of this study is to estimate whether DAR-0100A can improve cognitive deficits in schizophrenia patients.

Study design

A randomized clinical trial has been conducted. 47 clinically stable patients with schizophrenia has been recruited and randomized into 3 groups, high dose group, low dose group and placebo group.

For high dose group, low dose group and placebo group, 15mg DAR-0100A, 0.5mg DAR-0100A and normal saline were be administered via intravenous infusion respectively. The treatment conducted on day 1 to day 5 and day 15 to day 19 with an inpatient setting and at the end of day 19, patients were released. Patients were required to complete a battery of cognitive rating at day 0 (before treatment), day 5 (after treatment), day 19 (after treatment), and day 90.

Objectives

Primary objective

Assess whether low dose DAR-0100A or high dose DAR-0100A can improve memory (as measured by composite memory score) compared to placebo at each time point.

Secondary objective

1) Assess whether the treatment effect (as measured by change of composite memory score from baseline) changes over time within each group;
2) Assess whether the trajectory of treatment effect between time points differs between groups.

Outline

Subject characteristics by treatment group

	Treatment Group		
Variable	**High dose**, N = 16[1]	**Low dose**, N = 14[1]	**Placebo**, N = 17[1]
Day			
0	16 (100 %)	14 (100 %)	17 (100 %)
5	15 (93.75 %)	13 (92.86 %)	17 (100 %)
19	13 (81.25 %)	9 (64.29 %)	13 (76.47 %)
90	10 (62.5 %)	10 (71.43 %)	11 (64.71 %)
Age	39.5 (23 , 54)	37.571 (21 , 49)	40.353 (20 , 54)
Gender			
Female	7 (43.75 %)	6 (42.86 %)	9 (52.94 %)
Male	9 (56.25 %)	8 (57.14 %)	8 (47.06 %)

[1] n (%); Mean(Range)

Figure 2.1: Summary statistics

Score over time by treatment group

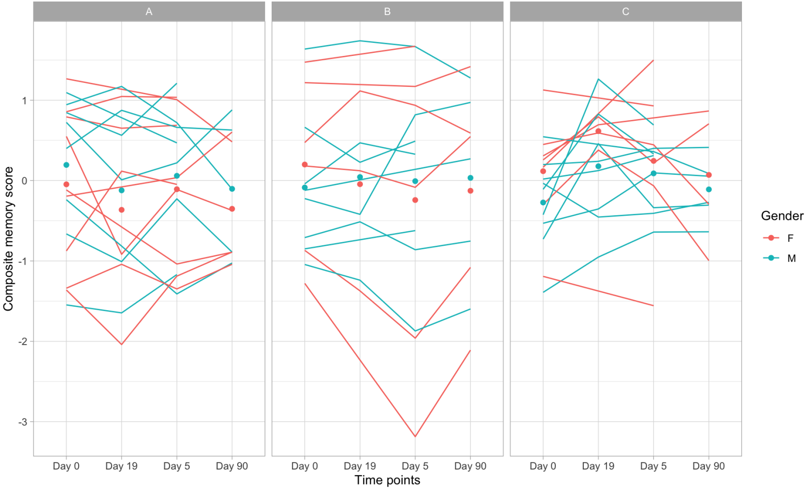

Figure 2.2: Change of composite memory score over time by treatment group

Average score in missing vs. complete data

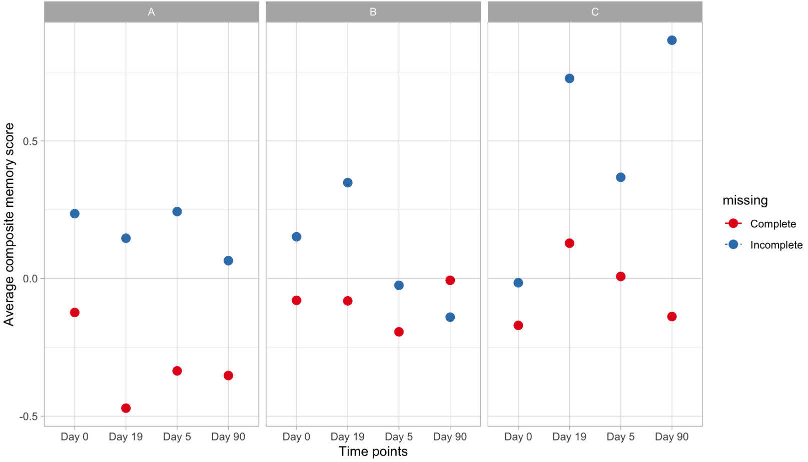

Figure 2.3: Average composite memory score over time by treatment group

LMM Model assumptions

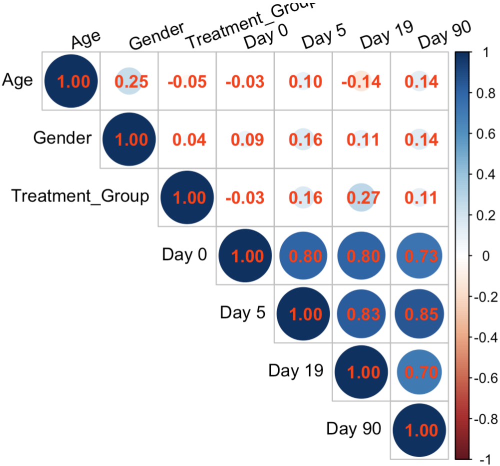

Figure 2.4: Correlation matrix

LMM Model assumptions

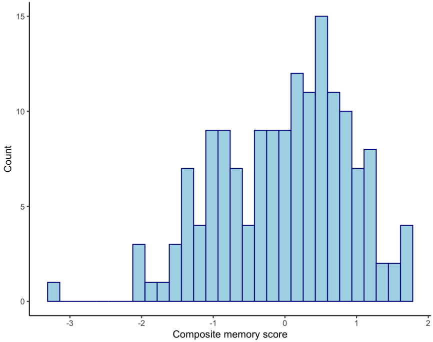

Figure 2.5: Composite memory score distribution

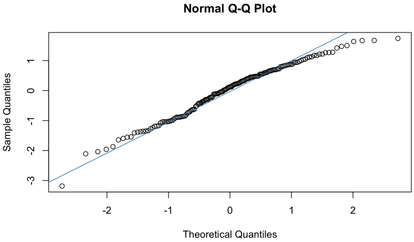

Figure 2.6: Composite memory score Q-Q plot

Outline

Linear mixed effect model

$$
\begin{aligned}
Y_{ij} = {} & \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i \\
& + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}
\end{aligned}
$$

- Y_{ij} denotes the composite memory score for ith patient at time j. $i = 1, 2, 3, \ldots, 47$ and $j = 1, 2, 3, 4$.
- Day_j denotes the time points when the composite memory score been measured, which is a categorical variable.
- $Group_i$ denotes the treatment group assigned to the ith patient, which is a categorical variable.
- Age_i denotes the age of the ith patient, which is a continuous variable.
- $Gender_i$ denotes the gender the ith patient, which is a categorical variable.
- b_{0i} is the random intercept for the ith patient.

Coefficients

Table 3.1: Coefficients estimated by LMM with unconstructed correlation.

Coefficients	Value	Std.Error	P-value
β_0	0.8960	0.6204	0.1518
β_1^{d5}	-0.0951	0.1410	0.5014
β_1^{d19}	-0.2330	0.1581	0.1436
β_1^{d90}	-0.1495	0.1688	0.3778
β_2^{B}	-0.0917	0.3423	0.7901
β_2^{C}	-0.1881	0.3276	0.5689
$\beta_5^{d5\times B}$	-0.0515	0.2120	0.8084
$\beta_5^{d19\times B}$	0.1749	0.2437	0.4745
$\beta_5^{d90\times B}$	0.2543	0.2468	0.3050
$\beta_5^{d5\times C}$	0.3860	0.2040	0.2215
$\beta_5^{d19\times C}$	0.6547	0.2240	0.0042
$\beta_5^{d90\times C}$	0.2993	0.2433	0.2215

Primary objective: Compare treatment effect between group

Definition 3.1

We define the **treatment effect** *at time point j as change of memory score from baseline to time point j.*
(Noted that by definition, there won't be treatment effect on day 0.)

Example 1 (Treatment effect for placebo group at day 5)

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Treatment effect at day 5 for group A: β_1^{d5}

Treatment effect

Hypothesis testing

To determine whether there is treatment effect of placebo at the day 5, we test $H_0 : \beta_1^{d5} = 0$ vs. $H_1 : \beta_1^{d5} \neq 0$.

Table 3.2: Treatment effects of placebo group at each time point

Time point	Parameter	Value	P-value
Day 5	β_1^{d5}	-0.0951	0.5014
Day 19	β_1^{d19}	-0.2330	0.1436
Day 90	β_1^{d90}	-0.1495	0.3778

Treatment effect

Table 3.3: Treatment effects of low dose group at each time point

Time point	Parameter	Value	P-value
Day 5	$\beta_1^{d5} + \beta_5^{d5\times B}$	-0.1466	0.3541
Day 19	$\beta_1^{d19} + \beta_5^{d19\times B}$	-0.0581	0.8741
Day 90	$\beta_1^{d90} + \beta_5^{d90\times B}$	0.1049	0.7840

Treatment effect

Table 3.4: Treatment effects of high dose group at each time point

Time point	Parameter	Value	P-value
Day 5	$\beta_1^{d5} + \beta_5^{d5\times C}$	0.2909	0.0484
Day 19	$\beta_1^{d19} + \beta_5^{d19\times C}$	0.4217	0.2333
Day 90	$\beta_1^{d90} + \beta_5^{d90\times C}$	0.1498	0.6938

Results

Result 3.1

The treatment effect (0.2909, 95%CI: 0-0.58) of 15mg DAR-0010A on improving memory on day 5 is significantly different from 0 at a significant level of 0.05.

Difference in treatment effect between groups

Example 2 (Difference in treatment effect between low dose and placebo at group day 5)

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Treatment effect at day 5 for group A: β_1^{d5}

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Treatment effect at day 5 for group B: $\beta_1^{d5} + \beta_5^{d5 \times B}$
The difference in effect between group B and group A at day 5: $\beta_5^{d5 \times B}$

Results

Hypothesis testing

To determine whether the treatment effect is different between group B and group A at day 5, we test $H_0 : \beta_5^{d5\times B} = 0$ vs. $H_1 : \beta_5^{d5\times B} \neq 0$.

Table 3.5: Difference in treatment effect between treatment and placebo group at each time point

	Low Dose Group		High Dose Group	
Time Point	**Estimate**	**P-value**	**Estimate**	**P-value**
Day 5	-0.0515	0.8084	0.3860	0.0612
Day 19	0.1749	0.4745	0.6547	0.0043
Day 90	0.2544	0.3051	0.2993	0.2215

Results

Result 3.2

The treatment effect of 15mg DAR-0010A on improving memory is significantly higher (effect size: **0.3860**, 90%CI: 0.05 - 0.72) than the effect of placebo at day 5 with a significant level of **0.1**.
The power to detect a standard effect size of 1.89 with a sample size of 17 subjects in placebo group and 15 subjects in high dose group at a significant level of 0.1 is 100%.

Result 3.3

The treatment effect of 15mg DAR-0010A on improving memory is significantly higher (effect size: **0.6547**, 95%CI: 0.22 - 1.09) than the effect of placebo at day 19 with a significant level of **0.05**.
The power to detect a standard effect size of 2.92 with a sample size of 13 subjects in placebo group and 13 subjects in high dose group at a significant level of 0.05 is 100%.

Secondary objective 1)
Change of treatment effect over time within group

Example 3 (Change of treatment effect from day 5 to day 19 within placebo group)

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Treatment effect at day 5 for group A: β_1^{d5}

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Treatment effect at day 19 for group A: β_1^{d19}
The change of treatment effect from day 5 to day 19 for group A: $\beta_1^{d19} - \beta_1^{d5}$

Change of treatment effect over time within group

Hypothesis testing

To determine whether there is a change of treatment effect from day 5 to day 19 for placebo group, we test $H_0 : \beta_1^{d19} - \beta_1^{d5} = 0$ vs. $H_1 : \beta_1^{d19} - \beta_1^{d5} \neq 0$.

Table 3.6: Treatment effects change over time within placebo group

Change	Parameter	Value	P-value
Day 19 - Day 5	$\beta_1^{d19} - \beta_1^{d5}$	-0.1379	0.2974
Day 90 - Day 5	$\beta_1^{d90} - \beta_1^{d5}$	-0.0544	0.6995
Day 90 - Day 19	$\beta_1^{d90} - \beta_1^{d19}$	0.0835	0.6622

Change of treatment effect over time within group

Table 3.7: Treatment effects change over time within low dose group

Change	Parameter	Value	P-value
Day 19 - Day 5	$\beta_1^{d19} + \beta_5^{d19\times B} - (\beta_1^{d5} + \beta_5^{d5\times B})$	0.0886	0.5740
Day 90 - Day 5	$\beta_1^{d90} + \beta_5^{d90\times B} - (\beta_1^{d5} + \beta_5^{d5\times B})$	0.2515	0.1018
Day 90 - Day 19	$\beta_1^{d90} + \beta_5^{d90\times B} - (\beta_1^{d19} + \beta_5^{d19\times B})$	0.1630	0.4541

Change of treatment effect over time within group

Table 3.8: Treatment effects change over time within high dose group

Change	Parameter	Value	P-value
Day 19 - Day 5	$\beta_1^{d19} + \beta_5^{d19\times C} - (\beta_1^{d5} + \beta_5^{d5\times C})$	0.1308	0.3269
Day 90 - Day 5	$\beta_1^{d90} + \beta_5^{d90\times C} - (\beta_1^{d5} + \beta_5^{d5\times C})$	-0.1411	0.3393
Day 90 - Day 19	$\beta_1^{d90} + \beta_5^{d90\times C} - (\beta_1^{d19} + \beta_5^{d19\times C})$	-0.2719	0.1561

Secondary objective 2) Difference in trajectory between groups

Example 4 (Difference in the trajectories from day 5 to day 19 between low dose group and placebo group)

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Trajectory from day 5 to day 19 for group A: $\beta_1^{d19} - \beta_1^{d5}$

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij}$$

Trajectory from day 5 to day 19 for group B:
$\beta_1^{d19} + \beta_5^{d19\times B} - (\beta_1^{d5} + \beta_5^{d5\times B})$
The difference in the trajectories from day 5 to day 19 between low dose group and placebo group: $\beta_5^{d19\times B} - \beta_5^{d5\times B}$

Difference in trajectory between groups

Hypothesis testing

To determine whether there is difference in trajectory from day 5 to day 19 between low dose group and placebo group, we test
$H_0 : \beta_5^{d19\times B} - \beta_5^{d5\times B} = 0$ vs. $H_1 : \beta_5^{d19\times B} - \beta_5^{d5\times B} \neq 0$.

Table 3.9: Difference in trajectories between low dose group and placebo group

Trajectory	Parameter	Value	P-value
Day 5 to Day 19	$\beta_5^{d19\times B} - \beta_5^{d5\times B}$	0.2265	0.2710
Day 5 to Day 90	$\beta_5^{d90\times B} - \beta_5^{d5\times B}$	0.3059	0.1423
Day 19 to Day 90	$\beta_5^{d90\times B} - \beta_5^{d19\times B}$	0.0794	0.7840

Difference in trajectory between groups

Table 3.10: Difference in trajectories between high dose group and placebo group

Trajectory	Parameter	Value	P-value
Day 5 to Day 19	$\beta_5^{d19\times C} - \beta_5^{d5\times C}$	0.2687	0.1527
Day 5 to Day 90	$\beta_5^{d90\times C} - \beta_5^{d5\times C}$	-0.0867	0.6709
Day 19 to Day 90	$\beta_5^{d90\times C} - \beta_5^{d19\times C}$	-0.3554	0.1892

Outline

Sensitivity Analysis

The Linear Mixed Effect Model with random intercept

$$
\begin{aligned}
Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i \\
+ \beta_5 \times Day_j \times Group_i + b_{0i} + e_{ij}
\end{aligned}
$$

was fit on the following datasets:

- Original data
- Complete data; subjects with all 4 days reported
- Missing data; subjects with at least 1 day not reported

Coefficient comparison among models/data

	Main Model			Complete Data			If Any Missing		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.90	-0.33 – 2.13	0.152	-0.21	-2.16 – 1.74	0.831	1.42	-0.28 – 3.12	0.099
day [5]	-0.10	-0.37 – 0.18	0.501	-0.21	-0.60 – 0.17	0.277	0.01	-0.44 – 0.46	0.973
day [19]	-0.23	-0.55 – 0.08	0.144	-0.35	-0.71 – 0.02	0.062	-0.24	-0.88 – 0.40	0.453
day [90]	-0.15	-0.48 – 0.19	0.378	-0.23	-0.66 – 0.21	0.296	0.09	-0.62 – 0.80	0.797
Age	-0.02	-0.05 – 0.01	0.165	-0.00	-0.05 – 0.05	0.962	-0.03	-0.07 – 0.01	0.162
Gender [M]	0.02	-0.51 – 0.55	0.952	0.21	-0.54 – 0.97	0.566	-0.19	-1.03 – 0.65	0.647
Treatment Group [B]	-0.09	-0.78 – 0.60	0.790	0.05	-0.95 – 1.05	0.919	-0.05	-1.13 – 1.02	0.919
Treatment Group [C]	-0.19	-0.85 – 0.47	0.569	-0.06	-0.98 – 0.86	0.898	-0.27	-1.33 – 0.80	0.605
day [5] × Treatment Group [B]	-0.05	-0.47 – 0.37	0.808	0.10	-0.47 – 0.66	0.731	-0.25	-0.92 – 0.43	0.467
day [19] × Treatment Group [B]	0.17	-0.31 – 0.66	0.475	0.35	-0.19 – 0.88	0.202	-0.10	-1.15 – 0.95	0.851
day [90] × Treatment Group [B]	0.25	-0.24 – 0.74	0.305	0.30	-0.33 – 0.94	0.346	0.38	-0.64 – 1.40	0.456
day [5] × Treatment Group [C]	0.39	-0.02 – 0.79	0.061	0.39	-0.14 – 0.92	0.147	0.38	-0.30 – 1.06	0.260
day [19] × Treatment Group [C]	0.65	0.21 – 1.10	**0.004**	0.65	0.14 – 1.15	**0.013**	0.88	-0.07 – 1.82	0.067
day [90] × Treatment Group [C]	0.30	-0.18 – 0.78	0.221	0.26	-0.34 – 0.86	0.385	0.78	-0.56 – 2.12	0.245

Key Points

Key Points

- At $\alpha = 0.05$, the interaction term is no longer significant, but is significant at $\alpha = 0.1$.
- The confidence intervals for the coefficients among all models overlap.

Treatment effect

Hypothesis testing

To determine whether there is treatment effect of placebo at the day 5, we test $H_0 : \beta_1^{d5} = 0$ vs. $H_1 : \beta_1^{d5} \neq 0$.

Table 4.1: Treatment effects of placebo group at each time point

Time point	Parameter	Value	P-value	C.Value	C.P-value
Day 5	β_1^{d5}	-0.0951	0.5014	-0.2122	0.2768
Day 19	β_1^{d19}	-0.2330	0.1436	-0.3476	0.0623*
Day 90	β_1^{d90}	-0.1495	0.3778	-0.2290	0.2959

*At $\alpha = 0.10$ level, becomes significant. Suggest there is a treatment effect of placebo at Day 19 in the complete data.

Treatment effect of high dose group

Table 4.2: Treatment effects of high dose group at each time point

Time point	Parameter	Value	P-value	C.Value	C.P-value
Day 5	$\beta_1^{d5} + \beta_5^{d5\times C}$	0.2909	0.0484	0.1778	0.3296
Day 19	$\beta_1^{d19} + \beta_5^{d19\times C}$	0.4217	0.2333	0.2985	0.4611
Day 90	$\beta_1^{d90} + \beta_5^{d90\times C}$	0.1498	0.6938	0.0321	0.9467

M.Value	M.P-value
0.3892	0.1160
0.6383	0.3719
0.8697	0.3289

Treatment effect

Table 4.3: Difference in treatment effect between high dose and placebo group at each time point

	Full		Complete	
Time Point	**Estimate**	**P-value**	**Estimate**	**P-value**
Day 5	0.3860	0.0612	0.3899	0.1474
Day 19	0.6547	0.0043	0.6461	0.0127
Day 90	0.2993	0.2215	0.2611	0.3852

Missing	
Estimate	**P-value**
0.3815	0.2597
0.8781	0.0670
0.7793	0.2448

Change of treatment effect over time within group

Table 4.4: Treatment effects change over time within low dose group

Change	Parameter	Value	P-value
Day 19 - Day 5	$\beta_1^{d19} + \beta_5^{d19\times B} - (\beta_1^{d5} + \beta_5^{d5\times B})$	0.0886	0.5740
Day 90 - Day 5	$\beta_1^{d90} + \beta_5^{d90\times B} - (\beta_1^{d5} + \beta_5^{d5\times B})$	0.2515	0.1018
Day 90 - Day 19	$\beta_1^{d90} + \beta_5^{d90\times B} - (\beta_1^{d19} + \beta_5^{d19\times B})$	0.1630	0.4541

M.Value	M.P-value
-0.1001	0.7316
0.7045	0.0080
0.8046	0.0400

At $\alpha = 0.05$ level, differences in treatment effects among Day 90 and 5 and Day 90 and 19 are significant in missing data.

Outline

Discussions

- Things to consider regarding study design:
  - Choice of low dose drug level (0.5mg) vs high dose drug level (15mg)
  - Subjects with incomplete data have higher memory scores; why?
- Missingness seems to affect treatment effects.
  - Some treatment effects were not significant in the full model, but significant in sub-datasets.
- Interestingly, some treatment effects are not significant in subset datasets, but become significant in full data; could be due to sample size.
- Further work can be done to impute missing data in order to use full data.
- Potential reasons why treatment effects were significant:
  - Drug or dose level is ineffective.
  - Composite memory test does not capture the effect well.

Thank you!