Analyzing the Effect of DAR-0100A on Schizophrenic Individuals

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Background

Motivation

Schizophrenic individuals are susceptible to cognitive deficits (e.g. poor memory, poor attention). Thus, a randomized trial was conducted to test whether a drug (DAR-0100A) improves cognitive deficits in schizophrenic individuals. DAR-0100A is a full, selective agonist that stimulates dopamine-1 receptors in the brain.

Study Design

Participants consisted of 47 clinically stable individuals with schizophrenia. They were randomized into three treatment groups; high dose (15mg) of DAR-0100A, low dose (0.5mg) of DAR-0100A, or placebo (normal saline). The drug was administered via intravenous infusion within an inpatient setting due to the possibility of adverse outcomes (e.g. fainting). The individuals were admitted to an inpatient clinic for 19 days. Day 0 consisted of subjects completing a battery of cognitive ratings, with no drug infusion. For 5 consecutive days after, treatment was administered and at Day 5 the same battery of cognitive ratings was completed. The subjects did not receive the treatment for 10 days. Then, received the treatment from Day 15 to 19. At Day 19, the subjects completed the same battery of cognitive ratings and later released from the inpatient clinic. On Day 90, the subjects returned to the clinic to complete the final battery of the same cognitive ratings. A composite memory score was created by combining all cognitive ratings at each assessment time, where higher values indicate better memory and lower values indicate poorer memory. Other information collected from subjects consisted of age (years), gender (M = Male, F = Female), and treatment group (A = low dose, B = high dose, C = placebo).

Objectives

The primary objective of this analysis is to assess whether DAR-0100A treatment at a low dose or high dose, when compared to placebo, improves memory as measured through the memory composite score. More specifically, we assess whether treatment effect (measured by change in composite score at baseline Day 0) changes over time between treatment groups and placebo, and whether the trajectory of treatment effect between time points differed between treatment groups and placebo.

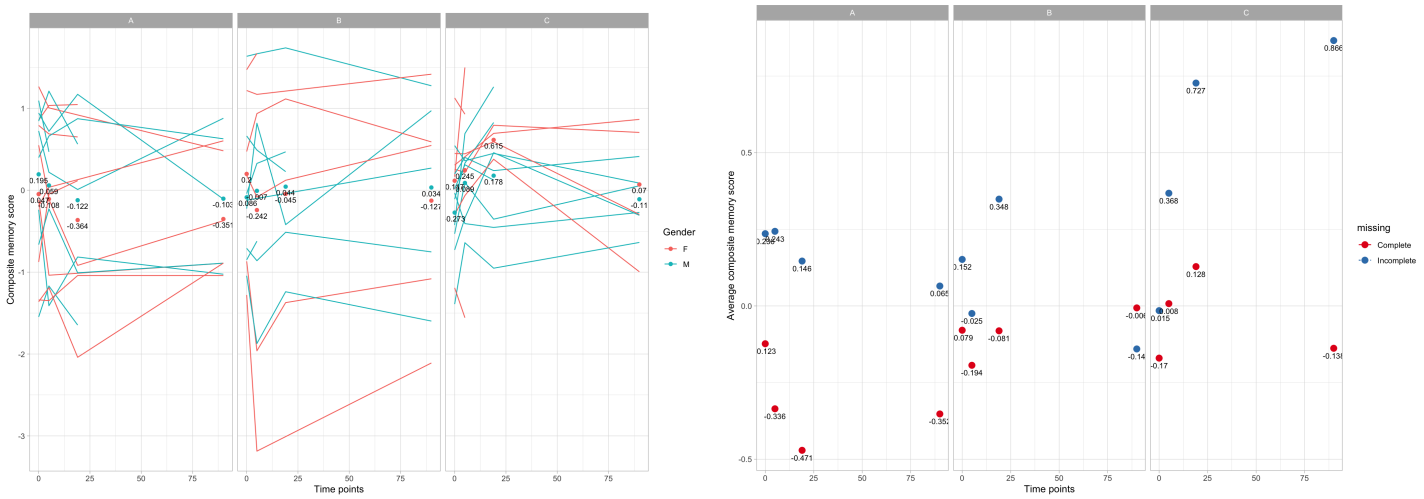
Exploratory Data Analysis

Variable	Treatment Group		
	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 1: Table 1. Summary Statistics

A total of forty-seven (47) clinically stable individuals with schizophrenia were randomized into the three treatment groups. Seventeen (17) in the placebo group, fourteen (14) in the low dose group, and sixteen (16) in the high dose group. Each group had an even distribution of male and female participants. Furthermore, the average age across treatment groups remained consistent. **Figure 1: Table 1** showcases a noticeable decline in subjects over time in each treatment group. For example, in the high dose group, at Day 90 only 62.5% of participants recorded memory scores. The decline in participants over time is noticeable across the three groups. See **Figure 1: Table 1** for more details.



(a) Change in composite memory score by gender

(b) Average composite memory score in missing vs complete data

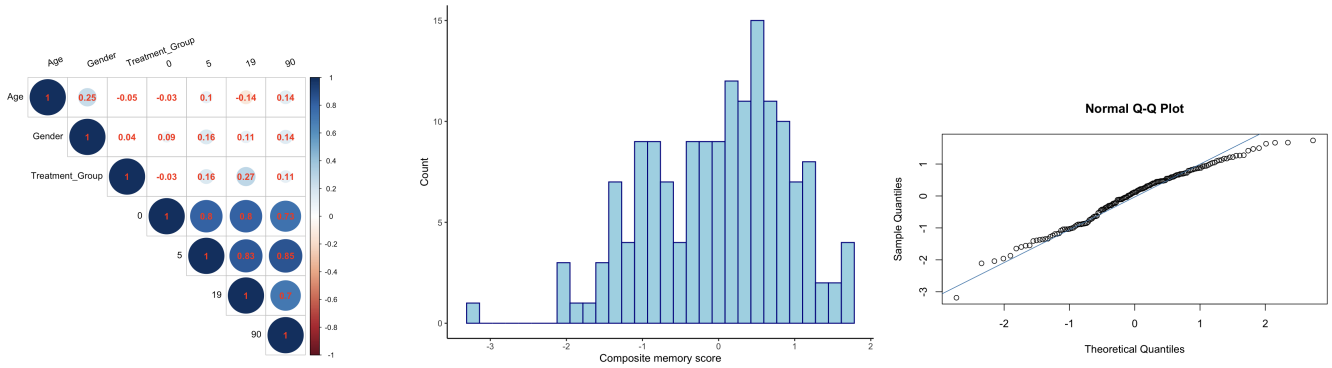
Figure 2: Composite memory scores over time by treatment group

Figure 2a showcases the change in composite memory score over time by treatment group while identifying individual male and female subjects. The points on this plot show represent the average score at a given day (e.g. Day 0, 5, 19, 90). Interestingly, those in the high dose group, when compared to the placebo or low dose group, tend to have more increasing

composite scores over time. Additionally, those in the low dose group, when compared to the placebo or high dose group, tend to have more variability in overall composite memory score and among gender.

Figure 2b showcases the average composite memory scores by treatment group while identifying a difference in complete and missing data. Complete data was classified as subjects that had recorded memory scores for all four time points (Day 0, 5, 19, 90), while missing data was classified as subjects that had at least one time point missing. Note that on average those with incomplete or missing data tend to have high memory scores, specifically in the high dose group.

As a preview, a Linear Mixed Effects Model was fit. Thus, multicollinearity and normality of the response was verified.



(a) Correlation Matrix (b) Composite memory score distribution (c) Composite memory score Q-Q plot

Figure 3: LMM Assumptions

Figure 3a shows that multicollinearity among predictors is not an issue as there is no significant correlation among them. Based on **Figure 3b** and **Figure 3c**, the composite memory score distribution looks approximately normal. Thus, the normality of response assumption is not violated.

Main Analysis

The following Linear Mixed-Effects Model with random intercept

$$Y_{ij} = \beta_0 + \beta_1 \times Day_j + \beta_2 \times Group_i + \beta_3 \times Age_i + \beta_4 \times Gender_i + \beta_5 \times Day_j \times Group_i + b_{0i} + \xi_{ij} \tag{1}$$

was fit to adjust for the variability of each subject. Note the following:

- 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 was 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 of the ith patient, which is a categorical variable.
- b_{0i} is the random intercept for the ith patient.

After fitting the Linear Mixed-Effects Model (LMM) on the data, the only significant coefficient, at an $\alpha = 0.05$ level, was the interaction term between day 19 and high dose group. This suggests that holding all other predictors constant, the composite memory score for an individual at Day 19 in the high dose group, holding all other predictors constant, increases by 0.6547 compared to one at Day 0 in the Placebo group. See **Table 2** in the Appendix for more details.

Next, we assessed whether treatment effect differed between the treatment groups and placebo. Treatment effect at time point j was defined as the change in composite memory score from baseline to time point j. Refer to **Example 1** in the Appendix for more information on calculating the difference in treatment effect between the lose dose group and placebo. To determine whether the treatment effect differed between the low dose or high dose group and placebo at Day 5, $H_0 : \beta_5^{d5\times B/C} = 0$ vs. $H_1 : \beta_5^{d5\times B/C} \neq 0$ was tested. At an $\alpha = 0.05$ level*, the treatment effect between the high dose group and placebo at Day 19 was significantly different than 0. This suggests that the treatment effect of 15mg of DAR-0100A on improving cognitive deficits is significantly higher (effect size: 0.6547, 95% CI: 0.22 - 1.09) than the effect of placebo at Day 19. Refer to **Table 1** below for more details.

Table 1: 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

Furthermore, we assessed whether treatment effects differed over time within each group. To determine whether there is a change of treatment effect from day 5 to 19 for the placebo group, $H_0 : \beta_1^{d19} - \beta_1^{d5} = 0$ vs. $H_1 : \beta_1^{d19} - \beta_1^{d5} \neq 0$ was tested. Similarly, to determine whether there is a change of treatment effect from day 5 to 19 for either the low or high dose group, $H_0 : \beta_1^{d19} + \beta_5^{d19\times B/C} - (\beta_1^{d5} + \beta_5^{d5\times B/C})$ was tested. No significant differences between any time point within each group were found. Refer to **Tables 3-5** for more details.

The difference in trajectories over time between low or high dose group and placebo was also assessed. Please refer to **Example 2** in the Appendix for more information on calculating difference in trajectory from time point A to B between low/high dose group and placebo. To determine whether there is a difference in trajectory from Day 5 to 19 between the low dose or high dose group and placebo, $H_0 : \beta_5^{d19\times B/C} - \beta_5^{d5\times B/C} = 0$ vs. $H_1 : \beta_5^{d19\times B} - \beta_5^{d5\times B} \neq 0$ was tested. No significant differences in trajectory from time points between low/high dose group and placebo were found. Refer to **Tables 6-7**.

Sensitivity Analysis

Due to missing data being a concern, a sensitivity analysis was performed to test the robustness of the missing data assumption. First, using the Little's test, we tested whether the missing values were Missing Completely At Random (MCAR), with H_0: the data is MCAR. At an $\alpha = 0.05$ level, we reject the null hypothesis ($\chi^2 = 1.72e^{-31}$, p-value = 0) and conclude that the data is not MCAR.

Thus, we proceed to assess whether the data is Missing At Random (MAR) or Missing Not At Random (MNAR). To do so, we fit the Linear Mixed-Effect Model (LMM) to three datasets; original data, complete data, and missing data. Complete

data consisted of 24 subjects that recorded memory scores at all four time points, while missing data consisted of 23 subjects that had at least one time point missing.

Figure 4 showcases the coefficients, confidence intervals, and p-values for the three datasets. The significant difference between the original and complete data with the missing data is that the interaction between day 19 and treatment group C becomes insiginificant at an $\alpha = 0.05$ level. Additionally, the confidence intervals for each coefficient across the three models overlap, suggesting that the uncertainty of the estimates and the true value all lie within the same interval.

To further explore if there is a significant difference when dealing with missing data, we tested the equality of the coefficients between the model with complete data and the model with missing data using Wald Test's. At an $\alpha = 0.05$ level, we fail to reject the null hypothesis (that a given coefficient is equal amongst the two models) for all the coefficients. We can conclude that there is no significant evidence that suggests that the coefficients are not equal. Furthermore, we assume that the data is Missing At Random (MAR). See **Table 8** for the Wald Test P-values.

Discussion

After fitting a Linear Mixed-Effects model, we notice that the treatment effect on Day 19 between the high dose group and placebo was the only significant treatment effect on a given day between the treatment groups and placebo. Furthermore, there were no significant differences between any time points within each group. Potential reasons for the insignificance of many treatment effects could be that the drug or dose level is ineffective or the compostie memory test does not capture the effect well. Another thing to consider regarding the study design is that subjects with incomplete data tend to have higher memory scores. We wonder whether there could be potentially bias if subjects are told their memory score or the memory ratings/tests are too obvious to whether a subject has good memory or not. Regarding the missing data, we performed the sensitivity analysis and conclude that there is no significant evidence to suggest that there is a difference in a model with complete data vs missing data.

Appendix

Table 2: Coefficients estimated by LMM with unconstructed correlation.

Coefficients	Value	Std.Error	P-value
(Intercept)	0.8960	0.6204	0.1518
day[5]	-0.0951	0.1410	0.5014
day[19]	-0.2330	0.1581	0.1436
day[90]	-0.1495	0.1688	0.3778
Age	-0.0207	0.0147	0.1646
Gender[M]	0.0158	0.2627	0.9523
Treatment Group[B]	-0.0917	0.3423	0.7901
Treatment Group[C]	-0.1881	0.3276	0.5689
day[5] × Treatment Group[B]	-0.0515	0.2120	0.8084
day[19] × Treatment Group[B]	0.1749	0.2437	0.4745
day[90] × Treatment Group[B]	0.2543	0.2468	0.3050
day[5] × Treatment Group[C]	0.3860	0.2040	0.2215
day[19] × Treatment Group[C]	0.6547	0.2240	0.0042*
day[90] × Treatment Group[C]	0.2993	0.2433	0.2215

Example 1. 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: $\beta_5^{d5\times B}$

Table 3: 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

Table 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

Table 5: 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

Example 2. 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: $\beta_5^{d19\times B} - \beta_5^{d5\times B}$

Table 6: 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

Table 7: 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

	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

Figure 4: Model Coefficients for Original, Complete, and Missing data

Table 8: Coefficient Comparison (P-Values)

Coefficients	P-value
(Intercept)	0.2039
day[5]	0.4544
day[19]	0.7672
day[90]	0.4358
Age	0.3455
Gender[M]	0.4611
Treatment Group[B]	0.8839
Treatment Group[C]	0.7546
day[5] × Treatment Group[B]	0.4327
day[19] × Treatment Group[B]	0.4452
day[90] × Treatment Group[B]	0.8993
day[5] × Treatment Group[C]	0.9842
day[19] × Treatment Group[C]	0.6593
day[90] × Treatment Group[C]	0.4726