100 -- Beautiful report!

Data Analysis of Longitudinal Clinical Trial Studies of Diladopram Treatment for Depression in the Elderly

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Content

1 Introduction

Depression in the Elderly

Depression in the elderly is the occurrence of major depressive disorder in adults who is more than 60 years old, and it is common with an estimated of 3% prevalence in the population. However, depression in the elderly is often under-diagnosed and untreated due to lack of screening and mistreat the symptoms of depression as the signs of old age. At the same time, depression in the later life is often associated with coexisting medical illness, and/or cognitive dysfunction. For example, older patients with depression are more likely to have neurologic abnormalities and cardiovascular disease, as well as at higher risk of suicide.

Beside of the encouragement of the lifestyle changes for depressed older patients, the treatment of depression in the elderly can include pharmacotherapy and psychotherapy. The current pharmacotherapy for older depression patients is often guided by studies based on younger depression patients, however, there might be risks for the elderly. The antidepressant drugs may take longer to start working in the older patients, and declines of drug metabolism in the elderly causes increased risks of medication side effects. Dosing regimens might be different between younger adults and the elderly. The front-line drug treatment for depression in the elderly is selective serotonin reuptake inhibitor (SSRI) and some SSRI drugs show efficiency of reducing depressive symptoms in some randomized trials.

Administration routes of antidepressants often include oral and intravenous infusion administrations. While both administrations have their advantages and oral administration is the most widely used, intravenous infusion administration also appeals as it is more rapid onset and avoids first-pass metabolism. These are some evidences from studies of the younger depression patients that combination of both oral and intravenous infusion with intravenous infusion in the first several weeks then switching to the oral may be more effective than only using oral administration for patients with moderate to severe depression. However, this strategy has not been widely studied in the elderly patients.

Description of Studies

In this data analysis report, we analyze two separate clinical studies about a new SSRI drug, diladopram, for the elderly depression patients. Both studies are in longitudinal study design with multiple depression evaluations for each patient at different time points after starting drug treatment.

In the first study (study of diladopram vs. placebo), the goal is to evaluate the efficacy of diladopram by comparing it to a placebo. The regimen of diladopram is administered by intravenous infusion daily for two weeks followed by daily oral administration in elderly subjects suffering from moderate to severe depression as determined by the Hamilton Rating Scale for Depression (HAM-D). The HAM-D score is the sum of the scores over the 17 items and ranges in value from 0 to 54, which is used to classify an individual as normal (< 9), mildly depressed (10 to 13), mildly to moderately depressed (14 to 17), or moderately to severely depressed (> 17). In this study, there are 350 adults age 60 years or older with HAM-D score equal to 17 or greater at baseline. Subjects were randomly assigned to diladopram or placebo treatment group. In each group, subjects

received a daily intravenous infusion for two weeks of their assigned treatment starting at baseline followed by oral administration of the treatment for the rest of the study. Besides the baseline, HAM-D score was to be ascertained on each subject at weeks 2, 4, 6, 8, 10, and 12. At week 12, each subject was also asked to provide his/her own self-reported assessment of whether or not he/she was feeling moderately to severely depressed. At baseline, information on each individual's gender, age, marital status, whether or not he/she had suffered previous depression as a younger adult, and whether or not he/she was currently suffering from chronic pain was also recorded.

In the second study (study of infusion strategy vs. oral diladopram), the researchers conducted a randomized clinical trial to compare the effectiveness of the diladopram regimen involving initiation by intravenous infusion followed by oral administration to oral-only regimen. 250 subjects living in several continuing care retirement communities who had been diagnosed previously as suffering from depression were recruited to participate and were randomized to the two regimens. At baseline (week 0), each was evaluated for depression using the Geriatric Depression Scale (GDS), which is based on 15 "yes or no" questions and a score of 5 "yes" responses indicates depression. At weeks 2, 4, and 8 thereafter, each subject was again evaluated for depression using the GDS. At baseline, information on each subject's gender, age, whether or not he/she suffered from mild dementia, and whether or not he/she was currently suffering from chronic pain was also recorded.

Goals of the Analysis

Goals of our analysis are to evaluate the efficacy of diladopram by comparing it to a placebo and compare the the effectiveness of the diladopram regimen involving initiation by intravenous infusion followed by oral administration to oral-only regimen. Specifically, we will address the following questions in this report:

1. What subject characteristics are associated with average HAM-D score prior to treatment with diladopram or placebo? What is the nature of the pattern of change of HAM-D score after the start of each regimen? In particular, is there evidence that HAM-D score decreases over the study period for either regimen? Is the average rate of change of HAM-D score at any time different for elderly individuals following the diladopram regimen and those receiving placebo? Is the average rate of change associated with any of the subject characteristics recorded in the study? What is the average rate of change of HAM-D score for subjects receiving diladopram?

2. Are the odds that an individual from this population taking either diladopram or placebo assesses him/herself to be moderately or severely depressed at the end of the study (week 12) associated with his/her individual rate of change in HAM-D score during the study? Can you describe this association? Namely, are the odds lower the more dramatic decrease in an individual's HAM-D score during the study?

3. In the population of older adults previously diagnosed with depression and living in continuing care retirement communities, what is the proportion who are depressed (as reflected by GDS) prior to treatment with diladopram? Is this proportion different for those suffering mild

dementia and those who are not? For those suffering chronic pain and those who are not? For males and females? Can you provide estimates of these proportions?

4. Do the odds of being depressed (as reflected by GDS) decrease over the study period under treatment with either of the infusion or oral-only regimens of diladopram in this population? Do they decrease more rapidly under the infusion regimen than under the oral regimen?

The remainder report is organized as follows. We will first summarize the data by obtaining summary statistics for subject characteristics, exploring the missingness pattern in data sets. Next, we will address each of the questions of interest above separately using different statistical models and then summarize the results with conclusions. The detail of modeling procedure such as model selection results, main SAS code and output are given at the appendix part.

2 Results

2.1 Summary of the Data

In this section, we summarized the data from these two studies separately by obtaining summary statistics for subject characteristics, exploring the missingness pattern in data sets and making plots to visualize the data pattern.

Table 1: Clinical and demographic characteristics of the study populations

	Study 1		Study 2	
	Placebo	Diladopram	Oral-only	Infusion + oral
Total Number	176 (50.3%)	174 (49.7%)	116 (46.4%)	134 (53.6%)
Age	74(60-95)	75.5(60-95)	75(60-95)	76(60-95)
Gender				
Male	97 (53.0%)	86 (47.0%)	63 (47.4%)	70 (52.6%)
Female	79 (47.3%)	88 (52.7%)	53 (45.3%	64 (54.7%)
Chronic pain				
Yes	25 (50.0%)	25 (50.0%)	13 (40.6%)	19 (59.4%)
No	151 (50.3%)	149 (49.7%)	103 (47.2%)	115 (52.8%)
Marital status				
Married	116 (52.3%)	106 (47.7%)		
Single/widowed	60 (46.9%)	68 (53.1%)		
Previous depression				
Yes	41 (48.2%)	44 (51.8%)		
No	135 (50.9%)	130 (49.1%)		
Dementia				
Mild			24 (42.1%)	33 (57.9%)
None			92 (47.7%)	101 (52.3%)

$*$ The percentage is calculated between different treatments or regimens. Age is summarized as median (min. - max.)

The clinical and demographic characteristics of the study populations have been shown in Table 1. For study of diladopram vs. placebo (study 1), there are 176 subjects in the placebo

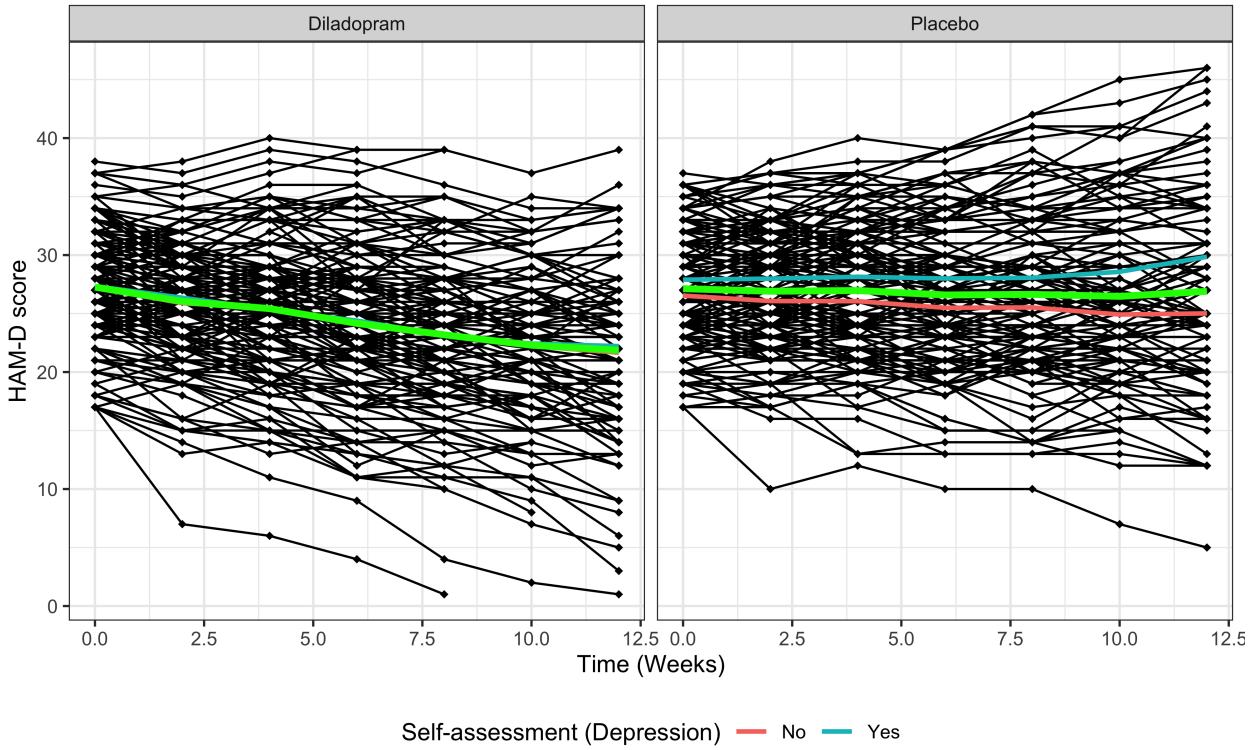


Figure 1: The spaghetti plots and the average summaries of HAM-D score for each treatment (green line) and the average summaries based on the self-assessment depression (blue and red).

treatment group and 174 subjects in the diladopram treatment. For study of infusion strategy vs. oral diladopram (study 2), 116 subjects are assigned to oral-only regimen and 134 subjects to infusion plus oral regimen. The summary of subject characteristics suggests that the randomization for both studies is carried out correctly.

Next we used the spaghetti plot (Figure 1) to gain insight into the overall mean HAM-D score for each treatment and the mean HAM-D score based on the self-assessment depression in study 1. We observed that a linear overall mean trajectories for both placebo and diladopram treatment. Patients in diladopram tend to have a a higher rate of declines of HAM-D score over the study period compared with the placebo. In addition, we also observed that in the placebo group, the HAM-D score rates of change are different between with or without self-assessment depression. Box plot is used to show the association between baseline average HAM-D score with different subject characteristics (Figure 2). We observed that the average HAM-D score is higher in subjects who were suffering from chronic pain have higher HAM-D score compared to the subjects without chronic pain, higher in female subjects compared to male subjects, higher in single/widowed subjects compared to married subjects.

Furthermore, we calculated the estimates of the probabilities and log odds of be depression using the data from study 2 and also plotted the estimated log odds for each regimen over the study period (Figure 3). We observed an approximately linear trajectories of the change of log odds of being depressed over time. We can also notice that the decline rate for infusion plus oral regimen is larger than oral-only regimen.

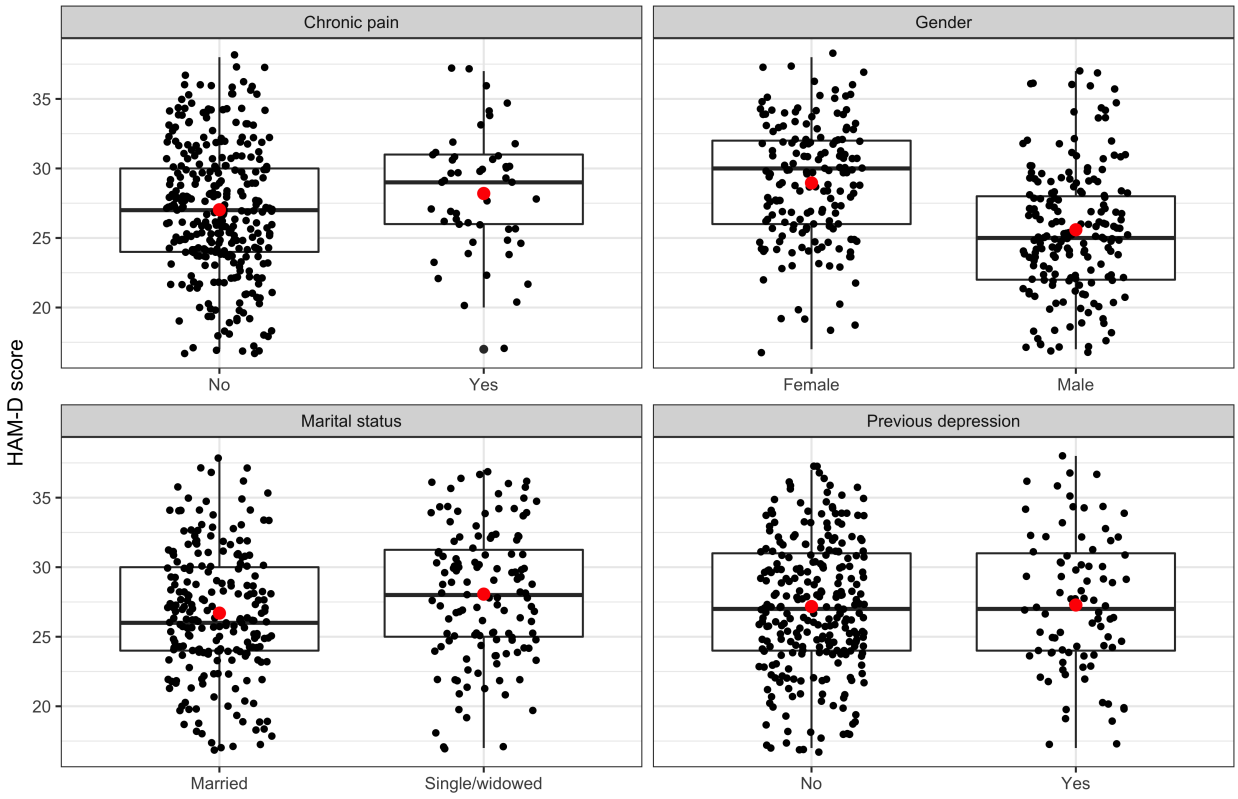


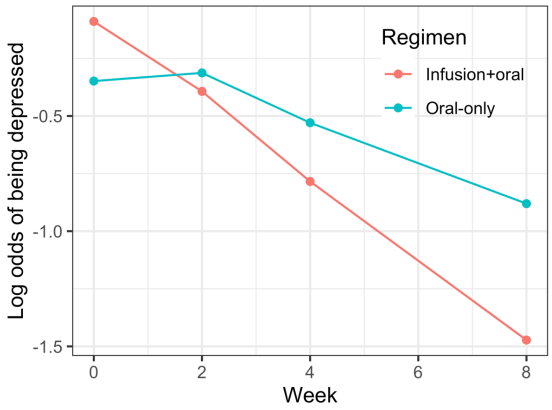
Figure 2: Box plots between baseline HAM-D score and different subject characteristics, including gender, marital status, if suffers chronic pain, if had previous depression as a younger adult. The average HAM-D score is indicated by the red dots.

Lastly, we also explored the missingness pattern of these two data sets. There are missing visits in the data from study 1 and all the missing data is due to drop out. 41 subjects dropped out at week 8; 54 subjects dropped out at week 10 and 49 subjects dropped out at the last visit, week 12. There is no missing data for study 2.

2.2 Analysis of Diladopram vs. Placebo

To model longitudinal data set, i.e., one subject has multiple data points at different time points, we need to account for correlation among the data points from the same subject. A linear mixed effect model is commonly used to capture the correlation thus is widely used to model the longitudinal data. A linear mixed model can be specified at two stages. In the first stage, we specify the subject-level model with parameters for a specific subject and a covariance matrix for within-subject deviation can be used to capture the within-subject source of correlation. At the second stage, the subject-specific parameters can be specified by the population-level parameters and random effects. The covariance matrix of the random effects can be used to capture the among-subject source of correlation.

Based on the observation from the spaghetti plots (Figure 1), we assume HAM-D score changes



Time (Week)	Probabilities		Log odds	
	Oral-only	Infusion + oral	Oral-only	Infusion + oral
0	0.414	0.478	-0.348	-0.090
2	0.422	0.403	-0.313	-0.393
4	0.371	0.313	-0.529	-0.784
8	0.293	0.187	-0.880	-1.472

* Probabilities and log odds are the estimated probabilities and log odds of being depressed.

Figure 3: Estimated log odds of being depression for each regimen during the study period (left panel) and the table of the estimated probabilities and log odds of being depression.

linearly with a constant rate of change over time and different treatments have different rates of change. The same average baseline HAM-D score is assumed for both treatments based on the observation that the randomization is carried out correctly. However, we consider different average baseline HAM-D score for different subject characteristics to explore their associations. We first let the rate of change of HAM-D score be the same for different subject characteristics. Thus, for a given subject i, $i = 1, \cdots, m$, we can have the subject model at stage 1 to be:

$$Y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + e_{ij} \tag{1}$$

where Y_{ij} is the HAM-D score for subject i at week j, $j = 0, 2, 4, 6, 8, 10$. Under this individual model, β_{1i} characterizes the rate of change for subject i; β_{0i} characterizes the average baseline HAM-D score for subject i.

At stage 2, we allow the subject-specific parameters β_{1i} to vary about mean values for each treatment according to random effect b_{1i} and β_{0i} to vary about mean values for different subject characteristics according to random effect b_{0i}. Thus the population model can be written as

$$\begin{aligned} \beta_{0i} &= \beta_0 + \beta_{0,A} a_i + \beta_{0,G} g_i + \beta_{0,C} c_i + \beta_{0,MS} m_i + \beta_{0,P} p_i + b_{0i} \\ \beta_{1i} &= \beta_{1,D}(1 - r_i) + \beta_{1,Pl} r_i + b_{1i} \end{aligned} \tag{2}$$

where $g_i = 1$ if subject i is female and 0 if male, $c_i = 1$ if subject i was not suffering chronic pain and 0 otherwise, $m_i = 1$ if subject i is married and 0 if single/widowed, $p_i = 1$ if subject i had not suffered previous depression and 0 otherwise, $r_i = 1$ if subject i has placebo regimen and 0 if diladopram. Therefore, in the model 2, $\beta_{0,A}$, $\beta_{0,G}$, $\beta_{0,C}$, $\beta_{0,MS}$, $\beta_{0,P}$ characterize the effect of subject age, gender, if has chronic pain, marital status and if has previous depression to the average baseline HAM-D score, respectively. $\beta_{1,D}$ and $\beta_{1,Pl}$ characterize the rate of change of HAM-D score for diladopram and placebo, respectively.

We use the model of form (1) and (2) to answer the first part of question 1 and will then adjust model (2) to answer the rest of the question. A model selection step to select the best correlation structure is performed and the detail is shown at the Appendix 4.1. The assumption of the missing mechanism of the data can is shown at the Appendix 4.2. We implement the linear mixed model using SAS 9.4 *PROC MIX* procedure. A significant level at 0.05 is used to evaluate any hypothesis testing performed in this report.

Q1.1: What subject characteristics are associated with average HAM-D score prior to treatment with diladopram or placebo? What is the nature of the pattern of change of HAM-D score after the start of each regimen? In particular, is there evidence that HAM-D score decreases over the study period for either regimen? Is the average rate of change of HAM-D score at any time different for elderly individuals following the diladopram regimen and those receiving placebo? What is the average rate of change of HAM-D score for subjects receiving diladopram?

The estimates of parameters from model (1) and (2) and corresponding p-values of testing each parameter equals to 0 are shown at Table 2. We can see small p-values only for $H_0 : \beta_{0,G} = 0$ (p-value < 0.0001) and $H_0 : \beta_{0,MS} = 0$ (p-value 0.0021), and this suggests the gender and marital status of subjects are significantly associated with average HAM-D score prior to treatment with diladopram or placebo. There is not enough evidence that if has chronic pain or not, age of subjects, if had previous depression are associated with average HAM-D score prior to treatment with diladopram or placebo.

As mentioned above $\beta_{1,D}$ and $\beta_{1,Pl}$ characterize the rate of change of HAM-D score for diladopram and placebo, respectively. From Table 2, we have $\hat{\beta}_{1,Pl} = -0.031$ and p-value for $H_0 : \beta_{1,Pl} \geq 0$ is 0.133 (obtained based on two-side test p-value 0.266), which suggest there is not enough evidence that HAM-D score decreases for placebo treatment. For diladopram treatment, $\hat{\beta}_{1,D} = -0.465$ and p-value for $H_0 : \beta_{1,D} \geq 0$ is < 0.0001. Thus we can conclude HAM-D score decreases significantly for diladopram treatment, and the average rate of change of HAM-D score for subjects receiving diladopram is -0.465 with SE 0.028. The hypothesis test $H_0 : \beta_{1,D} = \beta_{1,Pl}$ is used to test the difference of the rate of change between two treatments. The very small p-value (< 0.0001) suggests the average rate of change of HAM-D score is significantly different between subject in diladopram treatment and placebo treatment.

Table 2: Estimates of parameters from model (1) and (2)

Effect	Estimate	Standard Error	DF	t Value	p-value
β_0	26.5125	1.9313	344	13.73	<.0001
$\beta_{0,G}$	3.1982	0.4326	1470	7.39	<.0001
$\beta_{0,A}$	0.00225	0.02336	1470	0.1	0.9232
$\beta_{0,MS}$	-1.3782	0.4479	1470	-3.08	0.0021
$\beta_{0,P}$	-0.073	0.5043	1470	-0.14	0.885
$\beta_{0,C}$	-0.2366	0.6142	1470	-0.39	0.7001
$\beta_{1,Pl}$	-0.031	0.02786	1470	-1.11	0.2659
$\beta_{1,D}$	-0.4653	0.02782	1470	-16.72	<.0001
$\beta_{1,Pl} - \beta_{1,D}$	0.4343	0.03827	1470	11.35	<.0001

Q1.2 Is the average rate of change associated with any of the subject characteristics recorded in the study?

Based on the fit result from model (1) and (2), we revised the model (2) by removing non-significant terms and allow the rate of change of HAM-D score for each treatment different for

different subject characteristics. The revised model can be written as

$$\begin{aligned}\beta_{0i} &= \beta_0 + \beta_{0,G}g_i + \beta_{0,MS}m_i + b_{0i} \\ \beta_{1i} &= (\beta_{1,D} + \beta_{1,D,A}a_i + \beta_{1,D,G}g_i + \beta_{1,D,C}c_i + \beta_{1,D,MS}m_i + \beta_{1,D,P}p_i)(1 - r_i) \\ &\quad + (\beta_{1,Pl} + \beta_{1,Pl,A}a_i + \beta_{1,Pl,G}g_i + \beta_{1,Pl,C}c_i + \beta_{1,Pl,MS}m_i + \beta_{1,Pl,P}p_i)r_i + b_{1i}\end{aligned} \tag{3}$$

where $g_i = 1$ if subject i is female and 0 if male, $c_i = 1$ if subject i was not suffering chronic pain and 0 otherwise, $m_i = 1$ if subject i is married and 0 if single/widowed, $p_i = 1$ if subject i had not suffered previous depression and 0 otherwise, $r_i = 1$ if subject i has placebo regimen and 0 if diladopram. Therefore, in the model 3, $\beta_{1,D,A}$, $\beta_{1,D,G}$, $\beta_{1,D,C}$, $\beta_{1,D,MS}$, $\beta_{1,D,P}$ characterize the effect of subject age, gender, if has chronic pain, marital status and if has previous depression to the rate of change of baseline HAM-D score at diladopram treatment group, respectively. Similarly, $\beta_{1,Pl,A}$, $\beta_{1,Pl,G}$, $\beta_{1,Pl,C}$, $\beta_{1,Pl,MS}$, $\beta_{1,Pl,P}$ characterize the effect of subject age, gender, if has chronic pain, marital status and if has previous depression to the rate of change of baseline HAM-D score at placebo treatment group, respectively.

The estimates of parameters from model (1) and (3) and corresponding p-values of testing each parameter equals to 0 are shown at Table 2. We can see small p-values only for H_0 : $\beta_{0,Pl,C} = 0$ (p-value 0.0012) and H_0 : $\beta_{0,Pl,C} = 0$ (p-value 0.034), and it suggests if a subject has chronic pain or not is significantly associated with the rate of change of HAM-D score for both diladopram and placebo treatment. There is not enough evidence that gender, age and marital status of subjects, if had previous depression are associated with the rate of change of HAM-D score for neither treatments.

Table 3: Estimates of parameters from model (1) and (3)

Effect	Estimate	Standard Error	DF	t Value	p-value
β_0	26.426	0.425	347	62.18	<.0001
$\beta_{0,G}$	3.3506	0.4553	1470	7.36	<.0001
$\beta_{0,MS}$	-1.4931	0.4721	1470	-3.16	0.0016
$\beta_{1,Pl}$	0.5113	0.2414	1470	2.12	0.0343
$\beta_{1,D}$	-0.3307	0.2337	1470	-1.42	0.1572
$\beta_{1,Pl,A}$	-0.0041	0.00291	1470	-1.42	0.1563
$\beta_{1,D,A}$	-0.0003	0.00284	1470	-0.1	0.9217
$\beta_{1,Pl,G}$	0.08747	0.05465	1470	1.6	0.1097
$\beta_{1,D,G}$	0.00445	0.05416	1470	0.08	0.9346
$\beta_{1,Pl,MS}$	-0.0526	0.0573	1470	-0.92	0.3591
$\beta_{1,D,MS}$	0.00369	0.05538	1470	0.07	0.9469
$\beta_{1,Pl,P}$	-0.0398	0.06315	1470	-0.63	0.5284
$\beta_{1,D,P}$	0.02431	0.06062	1470	0.4	0.6884
$\beta_{1,Pl,C}$	-0.2425	0.0747	1470	-3.25	0.0012
$\beta_{1,D,C}$	-0.159	0.07488	1470	-2.12	0.0339

Q2: Are the odds that an individual from this population taking either diladopram or placebo assesses him/herself to be moderately or severely depressed at the end of the study (week 12) associated with his/her individual rate of change in HAM-D score during the study? Can you describe this association? Namely, are the odds lower the more dramatic decrease in an individual's HAM-D score during the study?

To investigate the association between odds of self-assessment depressed at week 12 and rate of change in HAM-D score during the study, we can first obtain the estimated rate of change $\hat{R}_i$ for each subject and perform a logistic regression model

$$\text{logit}(p(S_i = 1|r_i)) = \alpha 0 + (\alpha_{1,Pl} r_i + \alpha_{1,D}(1 - r_i))\hat{R}_i \tag{4}$$

where $r_i = 1$ if subject i has placebo regimen and 0 if diladopram. $p(S_i = 1|r_i)$ is the probability of subject i from this population taking either diladopram or placebo assesses him/herself to be moderately or severely depressed at week 12. $\text{logit}(p(S_i = 1|r_i)) = \log \frac{p(S_i=1|r_i)}{1-p(S_i=1|r_i)}$, i.e., the log odds of self-assessment depressed at week 12. Thus, $\alpha_{1,Pl}$ and $\alpha_{1,D}$ characterize the effect of rate of change of HAM-D score to log odds of self-assessment depressed at week 12 for placebo and diladopram, respectively.

Based on the results from model (2) and (3), we revised our population model by removing these non-significant terms and a revised model can be written to be

$$\begin{aligned} \beta_{0i} &= \beta_0 + \beta_{0,G} g_i + \beta_{0,MS} m_i + b_{0i} \\ \beta_{1i} &= (\beta_{1,D} + \beta_{1,D,C} c_i)(1 - r_i) + (\beta_{1,Pl} + \beta_{1,Pl,C} c_i) r_i + b_{1i} \end{aligned} \tag{5}$$

and the estimated rate of change of HAM-D score can be calculated as

$$\hat{R}_i = (\hat{\beta}_{1,D} + \hat{\beta}_{1,D,C} c_i)(1 - r_i) + (\hat{\beta}_{1,Pl} + \hat{\beta}_{1,Pl,C} c_i) r_i + \hat{b}_{1i}$$

The estimates of parameters from model 4 are shown at Table 4. We can have $\hat{\alpha}_{1,Pl} = 1.75$ and the p-value for $H_0 : \alpha_{1,Pl}$ is 0.0021, which suggested the odds that an subject from this population taking placebo assesses him/herself to be moderately or severely depressed at week 12 is significantly associated with his/her rate of changes in HAM-D score and the log odds or odds is lower when the rate of change decreases. Similarly, we can have $\hat{\alpha}_{1,D} = 0.71$ and the p-value for $H_0 : \alpha_{1,D}$ is 0.053, which suggested there is not strong evidence that the odds that an subject from this population taking placebo assesses him/herself to be moderately or severely depressed at week 12 is significantly associated with his/her rate of changes in HAM-D score at 0.05 level. Since $\hat{\alpha}_{1,D}$ is larger than 0, thus the log odds or odds is lower when the rate of change decreases.

2.3 Analysis of Infusion Strategy vs. Oral Diladopram

To model the GDS score, which is a binary outcome, in the study of analysis of infusion strategy vs. oral diladopram, we can consider the logistic mean model with linear predictor in time based on the observation from Figure 3 and allow different coefficients of time for each regimen. We first assume the proportion who are depressed at baseline the same for different subject characteristics and we can have the mean model as

Table 4: Estimates of parameters from model (4)

Effect	Estimate	Std. Error	z value	Pr(>|z|)
α_0	-0.3146	0.1381	-2.2775	0.0228
$\alpha_{1,Pl}$	1.7528	0.5697	3.0765	0.0021
$\alpha_{1,D}$	0.7057	0.3641	1.9380	0.0526

$$\text{logit}(P(Y_{ij} = 1|\boldsymbol{x}_i)) = \beta_0 + \beta_{1O}t_{ij}(1 - \delta_i) + \beta_{1IO}t_{ij}\delta_i \tag{6}$$

where $\delta_i = 1$ if subject i is in infusion + oral regimen and 0 if in oral-only regimen. $P(Y_{ij} = 1|\boldsymbol{x}_i)$ is the probability of being depressed (as reflected by GDS) given covariates, and we have $E(Y_{ij}|\boldsymbol{x}_i) = P(Y_{ij} = 1|\boldsymbol{x}_i)$. In model 6, β_{1IO} and β_{1O} characterize the population-level rate of change of log odds of being depressed under infusion + oral and oral-only, respectively. β_0 characterizes the log odds of being depressed at baseline.

In this longitudinal data set, we also need to account for correlation among the data points from the same subject. Thus, a covariance model $\boldsymbol{V}(\boldsymbol{Y}_i|\boldsymbol{x}_i)$ need to be specified to characterize correlation among the evaluations for the same patients. We tried unstructured and compound symmetric working correlation models, then used the compound symmetric model for our following analysis. The detail of the correlation model selection is shown at Appendix. Next, we will address part of question 3 and question 4 based model 6 and will adjust model 6 to answer rest of part of question 3. We implement model 6 using SAS 9.4 *PROC GENMOD* procedure.

Q3: In the population of older adults previously diagnosed with depression and living in continuing care retirement communities, what is the proportion who are depressed (as reflected by GDS) prior to treatment with diladopram? Is this proportion different for those suffering mild dementia and those who are not? For those suffering chronic pain and those who are not? For males and females? Can you provide estimates of these proportions?

Table 5: Observed counts and proportion of being depressed

	Total	Dementia		Chronic pain		Gender	
		Mild	None	No	Yes	Female	Male
GDS = 0	138 (55.2%)	25 (43.9%)	113 (58.5%)	118 (54.1%)	20 (62.5%)	67 (57.3%)	71 (53.4%)
GDS = 1	112 (44.8%)	32 (56.1%)	80 (41.5%)	100 (45.9%)	12 (37.5%)	50 (42.7%)	62 (46.6%)

We first show the observed counts and proportion of being depressed based on the data (Table 5) and then estimated these proportions using model 6. To estimate the proportion of being depressed based on subject characteristics, we can adjust model 6 accordingly as

$$\begin{aligned}
&\text{logit}(P(Y_{ij} = 1|\boldsymbol{x}_i)) = \beta_{0,D,m}d_i + \beta_{0,D,n}(1 - d_i) + \beta_{1O}t_{ij}(1 - \delta_i) + \beta_{1IO}t_{ij}\delta_i \\
&\text{logit}(P(Y_{ij} = 1|\boldsymbol{x}_i)) = \beta_{0,C,n}c_i + \beta_{0,C,y}(1 - c_i) + \beta_{1O}t_{ij}(1 - \delta_i) + \beta_{1IO}t_{ij}\delta_i \\
&\text{logit}(P(Y_{ij} = 1|\boldsymbol{x}_i)) = \beta_{0,G,f}g_i + \beta_{0,G,m}(1 - g_i) + \beta_{1O}t_{ij}(1 - \delta_i) + \beta_{1IO}t_{ij}\delta_i
\end{aligned} \tag{7}$$

where $d_i = 1$ if subject i has mild dementia and 0 if none, $c_i = 1$ if subject i was not suffering chronic pain and 0 otherwise, $g_i = 1$ if subject i is female and 0 if male, $\delta_i = 1$ if subject i is in infusion + oral regimen and 0 if in oral-only regimen. In models 7, $\beta_{0,D,m}$ and $\beta_{0,D,n}$ characterize the log odds of being depressed at baseline for subjects with mild dementia and no dementia, respectively. Similarly, $\beta_{0,C,y}$ and $\beta_{0,C,n}$ characterize the log odds of being depressed at baseline for subjects have chronic pain and don't have chronic pain , respectively. $\beta_{0,G,m}$ and $\beta_{0,G,f}$ characterize the log odds of being depressed at baseline for males and females, respectively.

Table 6: Estimates of parameters from model (6) and (7)

	Total	Dementia		Chronic pain		Gender	
		Mild	None	No	Yes	Female	Male
βs	-0.16	0.1748	-0.2692	-0.1412	-0.2981	-0.197	-0.1289
SE	0.1236	0.2363	0.1383	0.1301	0.3321	0.173	0.1633
Proportion	46.0%	54.4%	43.3%	46.5%	42.6%	45.1%	46.8%
Lower CI	40.1%	42.8%	36.8%	40.2%	27.9%	36.9%	39.0%
Upper CI	52.1%	65.4%	50.1%	52.8%	58.7%	53.5%	54.8%

The following hypothesis testing can be used to test is the proportion of being depressed different between subject characteristics.

$$H_0 : \beta_{0,D,m} = \beta_{0,D,n}$$

$$H_0 : \beta_{0,C,y} = \beta_{0,C,n}$$

$$H_0 : \beta_{0,G,m} = \beta_{0,G,f}$$

The p-values of the above tests are 0.089, 0.66, and 0.77, respectively, which suggests there is not enough evidence that proportion of being depressed is different between subjects suffering mild dementia and subjects who are not, between subjects suffering chronic pain and subjects who are not, between males and females.

Q4: Do the odds of being depressed (as reflected by GDS) decrease over the study period under treatment with either of the infusion or oral-only regimens of diladopram in this population? Do they decrease more rapidly under the infusion regimen than under the oral regimen?

Based on the hypothesis testing results from question 3, we used the fit results from model 6 to answer question 4. The estimates of parameters are show on Table 7. The estimates $\hat{\beta}_{1IO} = -0.074$ with p-value of $\beta_{1IO} = 0$ < 0.0001, $\hat{\beta}_{1IO} = -0.1695$ with p-value of $\beta_{1IO} = 0$ < 0.0001 suggest that the odds of being depressed decrease significantly over the study period under both regimens. The 95% confidence interval of $\hat{\beta}_{1O} - \hat{\beta}_{1IO}$ is [0.0373, 0.1535], which suggests the odds of being depressed decrease more rapidly under the infusion regimen than under the oral-only regimen and the difference is significant at 0.05 level.

Table 7: Estimates of parameters from model (6)

Effect	Estimates	SE	Lower CI	Upper CI	Chi-square	Pr >Chisq
β_{1O}	-0.0741	0.0163	-0.106	-0.0423	20.79	<.0001
β_{1IO}	-0.1695	0.0265	-0.2214	-0.1176	41.01	<.0001
$\beta_{1O} - \beta_{1IO}$	0.0954	0.0297	0.0373	0.1535	10.34	0.0013

3 Discussion and Conclusion

In summary, in this report we analyzed the data from two randomized clinical trials to evaluate the efficacy of diladopram by comparing it to a placebo and compare the the effectiveness of the diladopram regimen involving initiation by intravenous infusion followed by oral administration to oral-only regimen. From the above analysis results, we can have the following conclusions:

1. We have found that the gender and marital status of subjects are significantly associated with average HAM-D score prior to treatment with diladopram or placebo.
2. With diladopram treatment, HAM-D score decreases significantly over the study period and the decline rate is 0.465 per week with SE 0.028. The rate of change of HAM-D score at placebo treatment is not significant, but is significantly different with the rate of change for diladopram treatment. We also found that the rate of change of HAM-D score for both diladopram and placebo treatment is significantly associated with subjects suffer from chronic pain.
3. The odds that an subject from this population taking placebo assesses him/herself to be moderately or severely depressed at the end of the study is significantly associated with his/her rate of changes in HAM-D score and the log odds or odds is lower when the rate of change decreases. This association is not significant for subjects taking diladopram.
4. There is not enough evidence that proportion of being depressed is different between subjects suffering mild dementia and subjects who are not, between subjects suffering chronic pain and subjects who are not, between males and females.
5. The odds of being depressed decrease significantly over the study period under both oral-only and infusion regimen and the delince rate in infusion regimen is significantly larger than in oral-only treatment.

However, the following limitations and concerns need to be noted.

- The above analysis is based on the assumption that the missing data mechanism is missing at random. This needs to further discuss with the investigators to see if it is reasonable.
- The sample size for chronic pain patients in both studies are relatively small based on Table 1. We might pay the price for the precision of parameter estimation if the correlation model is misspecified.

- We assume the same correlation structure for different subject characteristics and one can consider different correlation structure based on subject characteristics.

4 Appendix

4.1 Correlation Structure Model Selection for Linear Mixed Effect Model

We perform the model selection to select the best combination of among-individual covariance model $Var(\boldsymbol{b_i}|\boldsymbol{X_i})$ and within-individual covariance model $Var(\boldsymbol{e_i}|\boldsymbol{X_i})$. The following models are considered.

Table 8: AIC/BIC table for model selection

Criterion	Model (a)	Model (b)	Model (c)	Model (d)	Model (e)	Model (f)
AIC	**9800.4**	9802.1	9804.9	9804.2	9804.2	9810.7
AICC	**9800.5**	9802.1	9805.1	9804.4	9804.4	9811.0
BIC	**9842.8**	9848.4	9862.8	9854.4	9854.4	9880.2

Model (a): diagonal matrix for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$ with constant variance same for both treatments; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ same for both treatments.

Model (b): diagonal matrix for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$ with constant variance different for each gender; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ same for both treatments.

Model (c): diagonal matrix for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$ with constant variance different for both treatments; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ different for each gender.

Model (d): AR(1) within-individual realization component plus diagonal measurement error for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$ same for both treatments; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ same for both treatments.

Model (e): Exponential within-individual realization component plus diagonal measurement error for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$ same for both treatments; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ same for both treatments.

Model (f): AR(1) within-individual realization component different for each treatment plus diagonal measurement error same for both treatments for $Var(\boldsymbol{e_i}|\boldsymbol{x_i})$; unstructured matrix for $Var(\boldsymbol{b_i}|\boldsymbol{x_i})$ different for each gender.

From the Table 8, model (a) has the smallest AIC and BIC and thus we select model (b) for further analysis.

4.2 Assumption of Missingness

As we recognized that there are missing observations in study of placebo vs. diladopram, we would assume that the drop out choices are based solely on a review of HAM-D scores up to that evaluations, i.e, the missing at random (MAR) mechanism is assumed, and the HAM-D scores given covariates is follow a multivariate normal distribution. With these assumptions, we can use maximum likelihood (ML) methods to carry out the analysis.

4.3 Working Correlation Structure for Population-Averaged Logistic Model

We used both unstructured and compound symmetric working correlation model for the population-averaged logistic model. The estimated unstructured correlation matrix is shown at Table 9. From the table, we can notice the correlation between different time points are approximately a constant, we consider to use **compound symmetric working correlation model**. The estimate of the correlation parameter in the compound symmetric model is 0.5968.

Table 9: Estimated working correlation matrix from the unstructured model

Working Correlation Matrix				
	Week 0	Week 2	Week 4	Week 8
Week 0	1.0000	0.7095	0.6698	0.5286
Week 2	0.7095	1.0000	0.6458	0.5538
Week 4	0.6698	0.6458	1.0000	0.5097
Week 8	0.5286	0.5538	0.5097	1.0000

4.4 Main SAS Code

We performed the analysis in the SAS 9.4 with *PROC MIXED* procedure. *Random* statement is used to specify among-individual covariance model. *Estimate* statement is used to report the estimates of the parameters and confidence interval. *PROC GENOMD* procedure can also be used to fit the logistic model.

```
title "PROC MIXED, SUBJECT CHARACTERISTIC AT BASELINE";
proc mixed data=hamd method=ml;
  class pid gender marital pdepression chronic trt week;
  model hamdscore = gender age marital pdepression chronic trt*time /
     solution ;
  random intercept time / type=un subject=pid g gcorr v vcorr;
  repeated week / subject=pid rcorr r;
  estimate "d-p" trt*time 1 -1 ;
  estimate "d-p1" trt*time 1 0/lower ;
run;

title "PROC MIXED, REMOVE NON-SIGNIFICANT TERM";
proc mixed data=hamd method=ml;
  class pid gender marital pdepression chronic trt week;
  model hamdscore = gender marital trt*time trt*time*chronic/ solution ;
  random intercept time / type=un subject=pid g gcorr v vcorr solution;
  repeated week / subject=pid rcorr r;
run;

title "PROC GENMOD, COMPOUND SYMMETRIC CORRELATION";
proc genmod data=ger DESCENDING;
  class pid trt week;
  model gds = trt*time / dist = bin link = logit;
  repeated subject=pid / within=week type=cs corrw covb modelse;
  estimate "int" int 1;
run;
```

4.5 Main SAS Output

We reported the main SAS output from the models we used in the report below and the complete output is attached in a separate file.

Estimates from Model (2)

Solution for Fixed Effects										
Effect	gender	marital	pdepression	chronic	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept						26.5125	1.9313	344	13.73	<.0001
gender	0					3.1982	0.4326	1470	7.39	<.0001
gender	1					0	.	.	.	.
age						0.002254	0.02336	1470	0.10	0.9232
marital		0				-1.3782	0.4479	1470	-3.08	0.0021
marital		1				0	.	.	.	.
pdepression			0			-0.07295	0.5043	1470	-0.14	0.8850
pdepression			1			0	.	.	.	.
chronic				0		-0.2366	0.6142	1470	-0.39	0.7001
chronic				1		0	.	.	.	.
time*trt					0	-0.03100	0.02786	1470	-1.11	0.2659
time*trt					1	-0.4653	0.02782	1470	-16.72	<.0001

Estimates from Model (3)

Solution for Fixed Effects										
Effect	gender	marital	pdepression	chronic	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept						26.4260	0.4250	347	62.18	<.0001
gender	0					3.3506	0.4553	1470	7.36	<.0001
gender	1					0	.	.	.	.
marital		0				-1.4931	0.4721	1470	-3.16	0.0016
marital		1				0	.	.	.	.
time*trt					0	0.5113	0.2414	1470	2.12	0.0343
time*trt					1	-0.3307	0.2337	1470	-1.42	0.1572
time*age*trt					0	-0.00412	0.002907	1470	-1.42	0.1563
time*age*trt					1	-0.00028	0.002839	1470	-0.10	0.9217
time*gender*trt	0				0	0.08747	0.05465	1470	1.60	0.1097
time*gender*trt	0				1	0.004445	0.05416	1470	0.08	0.9346
time*gender*trt	1				0	0	.	.	.	.
time*gender*trt	1				1	0	.	.	.	.
time*marital*trt		0			0	-0.05257	0.05730	1470	-0.92	0.3591
time*marital*trt		0			1	0.003691	0.05538	1470	0.07	0.9469
time*marital*trt		1			0	0	.	.	.	.
time*marital*trt		1			1	0	.	.	.	.
time*pdepression*trt			0		0	-0.03982	0.06315	1470	-0.63	0.5284
time*pdepression*trt			0		1	0.02431	0.06062	1470	0.40	0.6884
time*pdepression*trt			1		0	0	.	.	.	.
time*pdepression*trt			1		1	0	.	.	.	.
time*chronic*trt				0	0	-0.2425	0.07470	1470	-3.25	0.0012
time*chronic*trt				0	1	-0.1590	0.07488	1470	-2.12	0.0339
time*chronic*trt				1	0	0	.	.	.	.
time*chronic*trt				1	1	0	.	.	.	.

Estimates from Model (6)

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept		-0.1600	0.1236	-0.4022	0.0821	-1.30	0.1953
time*trt	0	-0.0762	0.0176	-0.1106	-0.0418	-4.34	<.0001
time*trt	1	-0.1716	0.0267	-0.2239	-0.1194	-6.44	<.0001

Analysis Of GEE Parameter Estimates							
Model-Based Standard Error Estimates							
Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept		-0.1600	0.1154	-0.3862	0.0661	-1.39	0.1655
time*trt	0	-0.0762	0.0201	-0.1157	-0.0367	-3.78	0.0002
time*trt	1	-0.1716	0.0221	-0.2150	-0.1283	-7.75	<.0001
Scale		1.0000	.	.	.	.	.