Longitudinal Study of Drilanzapine

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1 Introduction

Psychotic depression occurs when an individual suffering from a severe depressive illness is also experiencing psychosis, where the psychosis could include hallucinations or delusions, such as feelings of worthlessnes, in addition to symptoms including agitation, anxiety, insomnia, and hypochondria. Psychotic depression affects about 25% of all people admitted to the hospital for depression, and it differs from other forms of major depression in that sufferers are out of touch with reality. Individuals with psychotic depression may have strange ideas, claim they hear "voices," become angry for no reason, or think they are being pursued by the police for crimes that they really did not commit. They may also be unable to engage in social interactions and may spend most of their time alone. Psychotic depression increases the risk of developing bipolar disorder, mania, and, most ominously, suicide, so is a serious mental health challenge.

Individuals suffering from psychotic depression typically are treated with different drugs, which may include both antidepressants, such as fluoxetine (Prozac) or other selective serotonin reuptake inhibitors (SSRIs) or duloxetine (Cymbalta) or other serotonin-nonradrenaline reuptake inhibitors (SNRIs); and antipsychotic or neuroleptic medications, such as Olanzapine, aripiprazole, or cariprazine. They may also be treated with one-to-one talking therapy, such as cognitive behavioral therapy (CBT).

Recent research has shown that a new antipsychotic drug named Drilanzapine might be considerably more effective than other medications for treating adults 18 years old and older with psychotic depression. In order to study the effectiveness of Drilanzapine, three clinical trials have been carried out to separately test for its pharmacokinetics, short term effectiveness and long term effectiveness. Following the completion of each clinical trial, the collected data set was analyzed to answer several research questions of interest. In the following paragraphs, we will provide detailed introduction to how each clinical trial was conducted together with the proposal of our research questions of interest.

The Pharmacokinetic study is conducted by the manufactuer of Drilanzapine. In this study, 90 adults suffering from psychotic depression were recruited and assigned a single 1000 mg oral dose of Drilan-

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zapine. After the drugs were taken, blood samples for each patient were drawn and assayed for Drilanzapine concentration at multiple subsequent time points during the next 24 hours. Also recorded are exogenous variables gender, age and weight. Moreover, since it is known that individuals are different in metabolism of antipsychotic agents like Drilanzapine due to their different CYP2D6 phenotypes, this extra information of the patients are also included. If an individual has the poor CYP2D6 phenotype, s/he may exhibit elimination of the drug at a slower rate than an individual who has the extensive (normal) phenotype. Intermediate metabolizers might show elimination rate somewhere between poor and extensive metabolizers. In the data, CYP2D6 phenotype is recorded as 1 for poor, 2 for intermediate and 3 for extensive. It is noteworthy that availability of information about CYP2D6 phenotypes for patients is crucial in Pharmacokinetic study, since it is highly likely that it is not the drug itself but a metabolite that actually has the therapeutic effect. If the effect of the drug is mainly through a metabolite, poor metabolizers may require higher, more frequent doses than extensive metabolizers to achieve the desired therapeutic effect. Likewise, extensive metabolizers may experience exaggerated effects and an increased risk of adverse events when on a standard dosing regimen. The main goal of analyzing this data set is to test whether the pharmacokinetic properties of Drilanzapine, such as absorption, distribution, and elimination, are systematically associated with subject characteristics and identify the significant characteristics. Moreover, we would like to find out whether different CYP2D6 phenotypes of patients are associated with different elimination characteristics of Drilanzapine. We would like to estimate the typical value of Drilanzapine clearance rate for each phenotype, and lastly we would like to test whether patient specific variables gender, weight and age play a role in determining these typical values.

The second clinical trial is conducted to compare the short term effectiveness of Drilanzapine relative to Olanzapine on psychotic depression. For this study, 250 patients were randomized to begin a regimen of either oral Drilanzapine or oral Olanzapine at week 0. The severity of each patient's psychotic depression is then evaluated on each subsequent week using the Brief Psychiatric Rating Scale (BPRS), where higher BPRS score indicates higher severity. Each individual's gender, weight, age and smoking status were also collected at baseline. Eight weeks after taking the treatments, the patients were contacted and asked to indicate whether or not their symptoms had improved. Their feedback were recorded as 0 for no improvement and 1 otherwise. It should be noted that not all patients completed all clinic visits, but the assessment of whether or not each subject had improved symptoms is available for all. The main objective of this clinical trials is to determine whether the typical rate of change in

BPRS score among adult psychotic depression sufferers different for the two agents. We would also like to test whether that rate of change is associate with patient specific covariates gender, weight age and smoking status. Furthermore, we would like to see whether average BPRS score prior to treatments is associated with the patient specific covairates. Lastly, we would like to estimate the rate of change for a typical male/female smoker.

The third clinical trial is conducted to study the longer-term effectiveness of Drilanzapine for controlling symptoms of psychotic depression when used in addition to antidepressants and CBT. For this study, 300 adult patients with psychotic depression who were taking the anti-depressant fluoxetine and receiving CBT were randomly assigned to continue to receive this regimen plus a placebo or to continue to receive this regimen plus oral Drilanzapine. At baseline (month 0), prior to beginning placebo or Drilanzapine, each subject was classified by a psychiatrist as either having his/her symptoms under control or not (receiving fluoxetine and CBT only). At week 2 (0.5 months) and months 1, 3, and 6, a psychiatrist again classified each subject as having his/her symptoms under control (receiving either placebo or Drilanzapine in addition to fluoxetine and CBT). Some other information recorded were each individual's gender and age.The goal of this last clinical trial is to test whether the percentage of psychotic depression patients in the population whose symptoms were under control using fluoxetine and CBT prior to initiation of placebo or Drilanzapine depends on age or gender. Secondly, we would like to estimate the percentages for typical male and female patient in the population. Thirdly, we would like to test whether the odds of having symptoms under control increase over 6 months for either of the treatments, and if so we would like to further test whether the odds show a more rapid increase among patients taking Drilanzapine in addition to fluoxetine and CBT than in patients taking fluoxetine and CBT only.

2 Explanatory Analysis

2.1 Pharmacokinetic Study

In order to have a rough visualization of the pharmacokinetics properties of Drilanzapine, we plot its concentration against the time after taking it for each individual by their CYP2D6 phenotypes in Figure 1. It is obvious from the plot that the pattern of change of concentration throughout the study period is different for patients with different phenotypes. Specifically, Drilanzapine concentration of patients with poorer phenotype seems to increase at a faster rate early on and reaches a higher peak value,

whereas Drilanzapine concentration of patients with more extensive phenotype decreases at a faster rate after peak and reaches value 0 sooner. Moreover, the pattern of change of concentration for patients with poor phenotype seems to have a very high variability, whereas in other groups the patterns of different patients are more similar to each other.

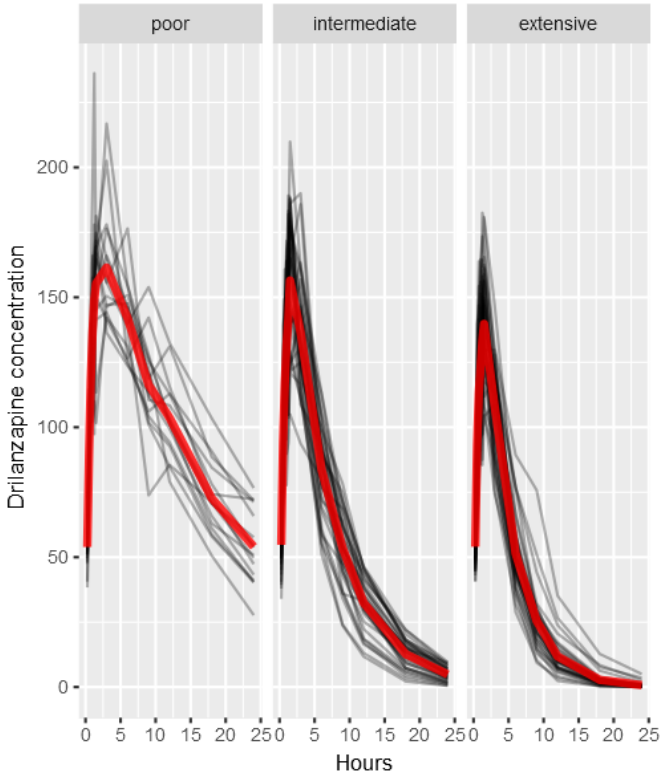

Figure 1: Drilanzapine concentration trend for different CYP2D6 phenotypes. The solid red line represents overall mean pattern of Drilanzapine's pharmacokinetic for each phenotype.

The pattern of change of concentration against time is also plotted separately for different subject characteristic groups to study their potential effect on the pharmacokinetics. In Figure 2, Drilanzapine concentration is plotted against time for different levels of gender, weight and age respectively. The weight and age groups are constructed by binning the observations for each variable in terms of their values relative to (higher or lower than) the sample mean. For each characteristic variable, the plot does not provide clear indication of different patterns of concentration change by level.

2.2 Short-term effectiveness

For the comparison of short-term effectiveness of Drilanzapine relative to Olanzapine, we first plot the distribution of BPRS score at baseline against gender and smoking status side by side in Figure 3. We

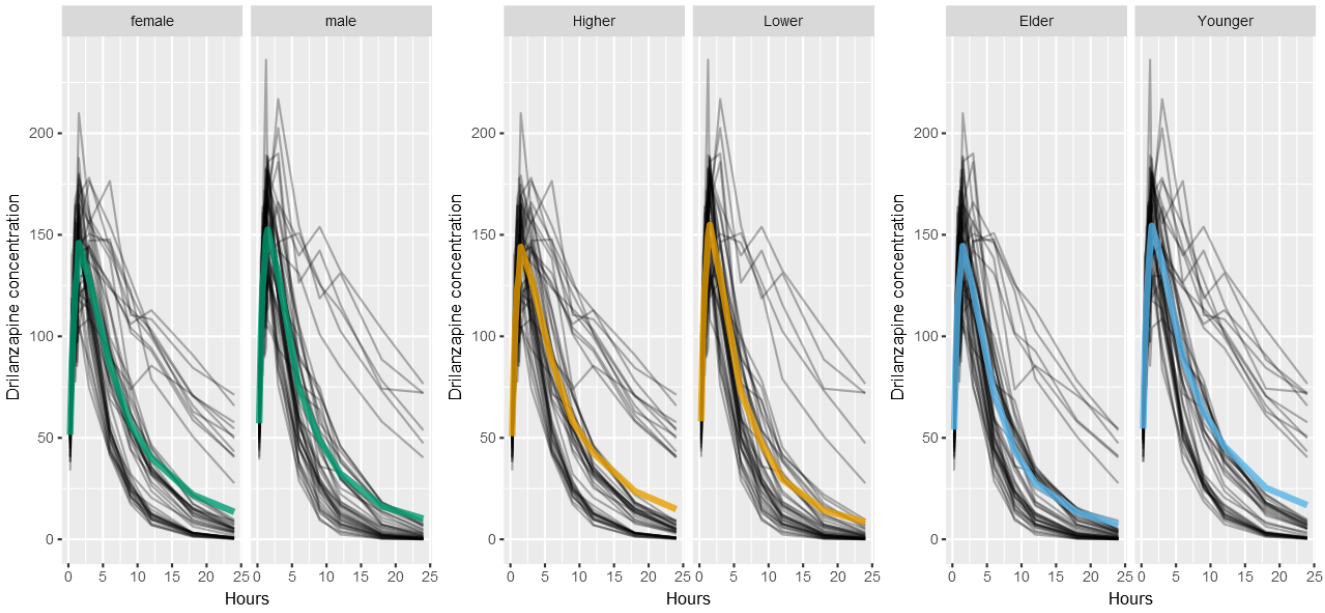

Figure 2: Drilanzapine concentration trend for different subject characteristic. From left to right the comparing characteristics are gender, weight and age respectively. The solid colored line represents overall mean pattern of Drilanzapine's pharmacokinetic for each characteristic group.

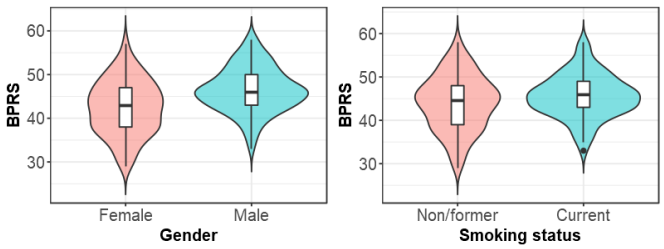

Figure 3: Distribution of BPRS score at baseline. From left to right the grouping factor is gender and smoking status respectively.

can see that relative to that of female patients, the distribution of baseline BPRS of male patients has a slightly higher mean and smaller variance; the distribution of baseline BPRS for patients who were active smokers at the time of experiment seems to have a smaller variance, but the mean of two levels seem to be similar. The spaghetti plots of BPRS score for Olanzapine and Drilanzapine are provided in Figure 4. We observe that for both agents BPRS score seems to decrease linearly through time, and the rate of change seems to be similar for the two agents. We also observe that the variance of BPRS score seems to increase through time. In general, the variation of BPRS score at each time point for patients taking Drilanzapine seems to be similar to those who took Olanzapine. Because we are also interested in identifying patient characteristics that impact the probability of improvement at week 8, we also plot

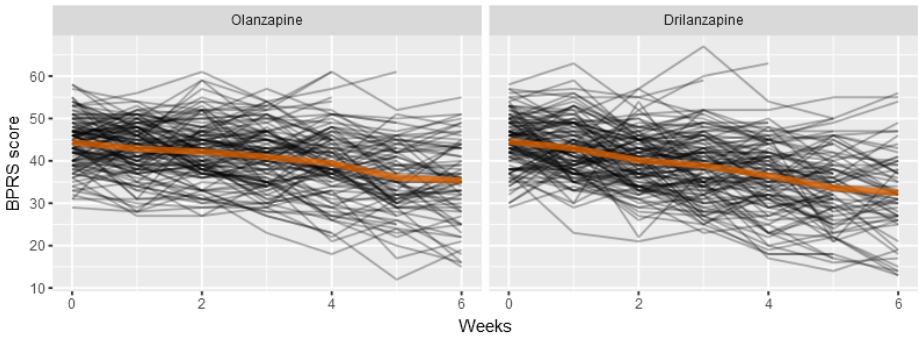

Figure 4: BPRS score against time for Olanzapine and Drilanzapine.

age of patients against their assessment results. Figure 5 shows that patients who took Olanzapine and improved have a significantly higher median age than those who reported no improvement. For patients who took Drilanzapine the pattern is similar, however the difference between age is less significant. For patients who took Olanzapine, 41 out of 62 (66.1%) female and 35 out of 63 (55.6%) male reported improvement. Whereas for patients who took Drilanzapine, 38 out of 61 (62.3%) female and 40 out of 64 (62.5%) male reported improvement. From these statistics, it seems like Olanzapine might have an better effect on female patients while Drilanzapine performs similar on patients with either gender. As mentioned above, the response variable BPRS score contains missingness since not all patients (In fact, only about half of them) attended all visits. In order to ensure that valid inference could still be applied, it is necessary to make sure that the missing mechanism is not missing not at random (MNAR). Figure 7 displays the BPRS against time plot for patients who did not show up on all visits. There does not seem to be anything special about the patients who stopped showing up. Therefore, it might be safe to assume that missingness is due to drop out and completely at random (MCAR).

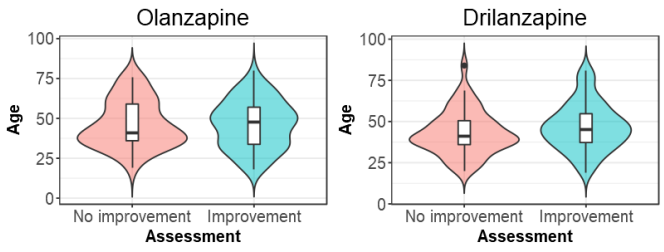

Figure 5: Age against assessment for Olanzapine and Drilanzapine.

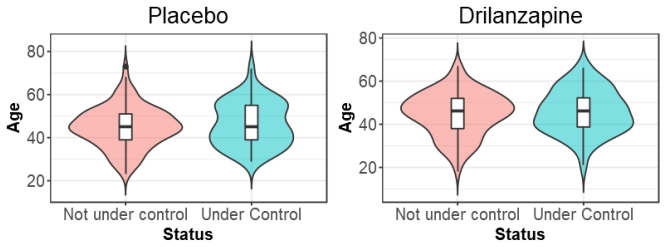

Figure 6: Age against symptom status for Placebo and Drilanzapine.

2.3 Longer-term Study

Using the data set obtained from the longer-term study of the effectiveness of Drilanzapine. We first compare the age distribution of the two symptom status levels at baseline for two treatments. Base on what we observed from Figure 6, there does not seem to be any significant difference of age distribution between people coming with the two status. For patients who took placebo, 27 out of 78 (34.6%) female and 18 out of 71 (25.4%) male had their symptoms classified as under control. Whereas for patients who took Drilanzapine, 21 out of 64 (32.8%) female and 27 out of 87 (31.0%) male had their symptoms classifed under control. From these statistics, it seems like male patients were particularly benefited from Drilanzapine. Figure 8 further shows the change of percentage of patients whose symptoms were classified as undercontrol throughout the study for both treatments. We can clearly see that for patients who took the placebo, the percentage changed immediately after baseline. However the drug effect seems to have died out after a month, and the percentage then remained constant afterwards. Whereas for patients who took the Drilanzapine, the percentage did not change significantly over the first month, but after that a consistent increase was observed.

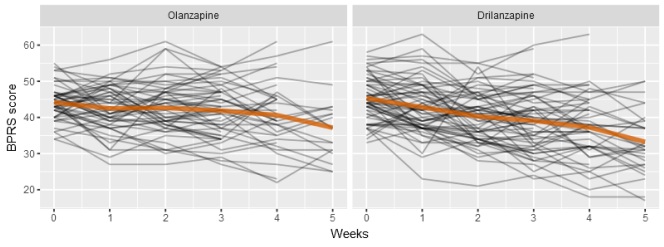

Figure 7: BPRS score against time for Olanzapine and Drilanzapine of patients who did not attend all visits.

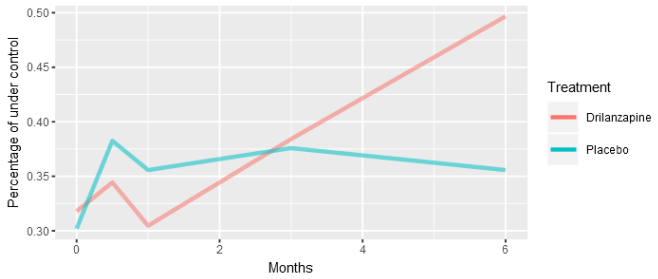

Figure 8: Percentage of patients whose symptom were classifed as undercontrol at each time point for Placebo and Drilanzapine.

3 Model

3.1 Pharmacokinetic study

In order to capture the relationship between pharmacokinetics of Drilanzapine and patient characteristics, a model that could relate the change of concentration to the gender, weight, age etc. of an individual subject is required. By observing the non-linear trend and potential heteroscadasticity in Figure 1, an ordinary least square model does not seem to be appropriate here. Logistic regression is automatically ruled out since we are modelling concentration, which is a continuous variable. A famous and often applied model for drug pharmacokinetics is the one-compartment open model which model drug concentration has a function of individual fractional absorption rate , clearance , and volume of distribution. The model originates from a theoretical description of biological processes taking place over time within a given subject, as that subject processes the drug. Moreover, to accommodate the assumption that each individual has a possibly different concentration curve we would adapt the one-compartment open model with a two-stage hierarchy. Where the first stage describes the individual level behavior and the second stage models population parameters as functions of exogenous variables. A fully specified model can be written as follow:

$$C_i(t) = \frac{e^{k^*_{ai}} D_i}{e^{V^*_i}\left(e^{k^*_{ai}} - e^{CI^*_i}/e^{V^*_i}\right)} \left[\exp\left\{-\left(e^{CI^*_i}/e^{V^*_i}\right) t_{ij} - \exp\left(-e^{k^*_{ai}} t_{ij}\right)\right\}\right] \tag{1}$$

where D_i is the dose amount assigned at baseline for subject i, ka_i, Cl_i , and V_i are individual specific parameters characterizing the processes of absorption, elimination, and distribution, respectively. As mentioned above, Equation (1) itself does not suffice to completely characterize the relationship between pharmacokinetics and individual characteristics, the second stage of the hierarchy is then

$$\log ka_i = \beta_{ka0} + \beta_{kaw} w_i + \beta_{kaa} a_i + \beta_{kag} g_i + b_{i,ka} \tag{2}$$

$$\log Cl_i = \beta_{Cl0} + \beta_{Clw} w_i + \beta_{Cla} a_i + \beta_{Clg} g_i + \sum_{l=1}^{2} \beta_{Clp,l} p_{li} \delta_{li} + b_{i,Cl} \tag{3}$$

$$\log V_i = \beta_{V0} + \beta_{Vw} w_i + \beta_{Va} a_i + \beta_{Vg} g_i + b_{i,V} \tag{4}$$

where each of (2),(3) and (4) assumes a log-linear relationship between individual specific PK parameters and weight (w_i), age (a_i), gender (g_i) or phenotype (p_{li}). δ_{li} is a dummy variable and equals 1 when the subject has phenotype $l + 1$. Testing the effect of any of the aforementioned variables will be equivalent to testing the corresponding coefficient effect. The reason that we choose log-linear model and the parametrization in (1) is based on the knowledge that PK parameters are strictly positive and have right-skewed distributions. Also from Figure 1 it seems like the variation of concentration for patients is differed by their phenotypes, therefore we would like to allow different variation by group in our model.

3.2 Short-term effectiveness

Based on what we observe in Figure 4, a linear mixed effect model seems appropriate to compare the rate of change of BPRS score for Olanzapine and Drilanzapine throughout the study. Since interest is on the typical rate of change, it suggests that we should consider the slope effects as random. A specific step about fitting linear mixed effect model is choosing appropriate working correlation structure. Since the response variable contain missingness, we would start by fitting unstructured covariance to get a sense of the structure of the underlying correlation. If necessary, we could try multiple working models and select the best option by comparing fitting statistics. Notice that the model proposed above can at the same time study the effect of gender, weight, age and smoking status on baseline BPRS score if we include them as covariates that only affect the model intercept. Let Y_{ij} denotes the BPRS score measured for i^{th} patient at j^{th} visit, and δ_i = 1(0) if i^{th} patient is taking Olanzapine(Drilanzapine). We write the model as follows

$$\mathbb{E}(Y_{ij}) = \beta_{0i} + \beta_g g_i + \beta_w w_i + \beta_a a_i + \beta_s s_i + \beta_{1i} t_{ij} + \beta_{2i} \delta_i t_{ij} \tag{5}$$

where

$$\beta_{0i} = \beta_0 + b_{0i},\ \beta_{1i} = \beta_1 + b_{1i},\ \beta_{2i} = \beta_2 + b_{2i},\ b_{0i} \perp b_{1i} \perp b_{2i} \overset{iid}{\sim} \mathcal{N}(0,1)$$

In Equation (5), the gender, weight, age, smoking status of i^{th} patient are denoted as g_i, w_i, a_i, s_i respectively. g_i=0(1) if the i^{th} patient is female(male), s_i=0(1) if the i^{th} patient is not currently smoking(currently smoking). We assume that their effect on the baseline BPRS score is similar for all patients. β_{0i} is the individual intercept, and β_{1i} and β_{2i} are individual specific slope effects. It is noteworthy that this parametrization ensures that β_2 is interpreted as the difference between the typical rate of change of BPRS for patients taking two drugs. All random effects as well as the error term are assumed to follow independent and identical standard normal distribution.

The relationship between a patient's individual rate of change in BPRS score and the probability of his/her improvement in symptoms after 8 weeks can be studied naturally following the result of previous question. An univariate logistic regression seems sufficient here since the response assessment is binary. If we let Y_i = 0(1) if i^{th} patient's symptom is (not improved)improved after 8 weeks, then the proposed model has the form

$$\mathbb{E}(Y_i|r_i) = \frac{\exp(\beta_0 + \beta_1 r_i)}{1 + \exp(\beta_0 + \beta_1 r_i)} \tag{6}$$

where r_i is the individual rate of change of i^{th} patient. Therefore testing $\beta_1 = 0$ is equivalent to testing the effct of individual rate of change on the probability of having symptoms controlled after 8 weeks.

3.3 Longer-term effectiveness

Due to the binary nature of symptom status, it seems straightforward to characterize its relationship with all the individual characteristics using a logistic regression. Furthermore, because the researchers are interested in the odds of having symptoms under control, a linear regression would not suffice to provide interpretation of this kind. Logistic regression also has weaker assumption on the data, allowing non-constant variance and non-normal error. Based on the questions of interest, a population-averaged version of logistic regression is sufficient. As mentioned above, Figure 8 suggests that patients taking placebo might experience a immediate increase in odds of having symptoms under control for a short period of time (less than a month), but afterwards the odds stay constant. As for patients who took Drilanzapine, the odds do not show a significant increase within the first month, but afterwards the increase is consistent. We will try to prove our conjecture statistically using the following

model. We define t_{ij} to be the time point of i^{th} patient's j^{th} classification and Y_{ij} = 0(1) if i^{th} patient's symptom is not under control(under control) at j^{th} classification, we also define w_{ij} to be 0 at month 0 and 1 if $t_{ij} > 0$ and t_{ij}^{+} = 0 if $t_{ij} < 2$ and $t_{ij} - 1$ otherwise:

$$\mathbb{E}(Y_{ij}|\mathbf{a}_i) = \frac{\exp(\beta_0 + \beta_g g_i + \beta_a a_i + \beta_1 w_{ij} + \beta_2 w_{ij} t_{ij}^{+} + \beta_3 w_{ij}\delta_i + \beta_4 w_{ij}\delta_i t_{ij}^{+})}{1 + \exp(\beta_0 + \beta_g g_i + \beta_a a_i + \beta_1 w_{ij} + \beta_2 w_{ij} t_{ij}^{+} + \beta_3 w_{ij}\delta_i + \beta_4 w_{ij}\delta_i t_{ij}^{+})} \tag{7}$$

where $\mathbf{a}_i = \begin{pmatrix} g_i & a_i & \delta_i \end{pmatrix}^T$ and δ_i is 0(1) if i^{th} patient was taking placebo(Drilanzapine). Notice that this parametrization allows us to test whether there is a significant difference in change of odds over first month study between the two treatments and difference in change of odds over rest of the study separately.

4 Result

In this section, numerical result from fitting the models proposed above are presented. The calculation steps are omitted. Interpretation of the results are also given based on the context of our study. A summary of findings will also appear in the conclusion section.

4.1 Pharmacokinetics Study

The model proposed in Equation (1) is fitted in `R`. We first ignore the phenotypes and only focus on the relationship between the relationship of pharmacokinetics parameters and subject characteristics. The starting values are naively chosen as all 1.5. Based on the result produced by `R`, none of the characteristics has significant effect on ka; age has a significant effect on cl; weight has a significant effect on V. Since the second question of interest for the Pharmacokinetics Study only focuses on Drilanzapine clearance rate, for this part it is convenient to just assume all other pharmacokinetics parameters contain only random error term. Based on this construction, the phenotype effect was tested to be significant. Compared to patients with poor phenotype, patients with intermediate and extensive phenotype seem to have higher Drilanzapine clearance rate. Moreover, the weight and age effect are both significant effects as well, with higher weights associated with higher clearance rate and elder people associated with lower clearance rate. The typical clearance rates for poor, intermediate and extensive metabolizers are 0.288, 0.823 and 1.3 respectively. The standard errors of these estimates can be approximated using delta method. An easy way to compute the standard errors of each phenotype effect

is to rotate the reference level and obtain estimate of standard error for the reference level directly from `nlme`. The estimated standard errors are 0.013, 0.024, 0.037 respectively.

4.2 Short-term Study

We fit the linear mixed effect model proposed in (6) in SAS 9.4 using the built-in function `PROC MIXED`. Based on what we observed in 3, we assumed a constant variation coefficient for the covariance matrix of patients taking both treatments, but different unstructured correlation by treatment. This flexible model allows us to have a detailed idea of how the covariance matrices look like, given that we were not able to visualize it due to presence of missingness. The estimated covariance matrices for patients taking both treatments show strong heteroscedasticity, also for most of the time points the variance of BPRS score for patients taking Drilanzapine seems to be larger than that of patients who took Olanzapine. For the purpose of comparison, we also fitted heterogeneous compound symmetry. The two models are compared based on fitting statistics $AIC, AICC, BIC$.

Table 1: Fitting statistics for model 6

Structure	AIC	AICC	BIC
UN	9468.3	9468.5	9517.6
CSH	9468.3	9468.5	9517.6

In Table 1 we can see that the values of fitting statistics are basically the same for the two models. Therefore we chose to adopt common within correlation and different unstructured D matrices by treatment. The fitted model claims that gender and smoking have significant effects on the baseline BPRS score. In particular, male patients and patients who were active smokers at the time of experiment seem to have relatively higher BPRS score at baseline. Time effect for both Olanzapine and Drilanzapine are significant, indicating that patients taking both treatments had experienced decrease in BPRS score, but rate of decrease was higher for patients taking Drilanzapine. In order to test whether gender, weight, age or smoking status are associated with average rate of change, we put together a model containing all interaction effects between time and subject characteristics. The result shows that none of the subject characteristics are associated with the average rate of change. Nonetheless, we can still get estimates of the average rate of change using the estimated coefficients. The average rate of change

of BPRS score for female patients of average weight and age who are smokers is -1.3 for Olanzapine group and -1.88 for Drilanzapine group. Whereas the average rate of change of BPRS score for male patients of average weight and age who are smokers is -1.12 for Olanzapine group and -1.7 for Drilanzapine group. The average weight and age for male or female patients are estimated using the observed dataset.

Using the estimated coefficients of time and subject characteristic interaction effect, we are able to estimate the individual rate of change for each patient. This enables us to adopt a univariate logistic regression to study the effect of individual rate of change on probability of improvement in symptoms after 8 weeks. The resulting p-value is 0.798, suggesting no significant relationship between individual rate of change and probability of improvement in symptoms after 8 weeks.

4.3 Longer-term Study

We fit the population average logistic regression model proposed in (7) in SAS 9.4 using the built-in function `PROC GENMOD`. We first adopt the working correlation structure as unstructured and found out that the estimated off-diagonal values of the correlation mixture take on similar values. This suggests that a compound symmetric working correlation structure might have a good performance as well. Other correlation structures are not considered since we did not find any other significant patterns suggesting them. We then compare the two models by their fitting statistics, which in this case is the GEE Fit Criteria from the output. Loosely speaking, a smaller GEE Criteria indicates a better model.

Table 2: Fitting statistics for model 7

Structure	QIC	QICu
UN	1971.6	1959.6
CS	1971.6	1959.5

In Table 2 we can see that using the much simpler compound symmetric (CS) correlation structure does not decrease either QIC or QICu. Therefore we choose to use the unstructured (UN) correlation structure since it in general captures the most detailed information of the underlying correlation. The estimated main effects for age and gender came out to be insignificant, with p-values 0.68 and 0.96 respectively. This suggests that age and gender might not affect the percentage of psychotic depression

patients in the population whose symptoms were under control using fluxetine and CBT prior to initiation of placebo or Drilanzapine. Ignoring the time and treatment effect for now, the estimated model for percentage of symptoms under control at baseline is

$$P(Y_{ij} = 1|\mathbf{a}_i) = \frac{\exp(-0.7772 - 0.084g_i + 0.0005a_i)}{1 + \exp(-0.7772 - 0.084g_i + 0.0005a_i)} \tag{8}$$

If we plug in the sample average age of 45.2 years old, the estimated percentage of symptoms under control at baseline is about 30.2% for a typical women patient and about 29.7% for a typical male patient. The coefficent for w_{ij} is significantly different from zero, with a p-value of 0.02. This suggests that the odds of having symptoms under control increase over the first month for patients who took the placebo. The slope effect for placebo has a p-value of 0.68, suggesting that the odds remains constant for the subsequent months. The coefficient for $w_{ij}\delta_i$ is not significantly different from zero, with a p-value of 0.1. This suggests that the odds of having symptoms under control increase over the first month for patients who took the Drilanzapine did not increase over the first month. The slope effect for Drilanzapine is significant, with a p-value less than 0.0001. Suggesting that the odds consistently increased over the subsequent month for patients taking Drilanzapine.

5 Conclusion

Based on the previous results, we are able to answer the questions of interest of the researchers statistically. For the pharmacokinetic study, we successfully show that pharmacokinetic properties of drilanzapine, such as absorption, distribution and elimination are indeed somehow systematically associated with subject characteristics such as age and weight. In particular, the clearance rate is associated with age and the volume of distribution is associated with weight of the patient. We also showed that the Drilanzapine clearance rate are associated with CYP2D6 phenotype, that patients with more extensive phenotype tend to have higher clearance rate.

For the short-term effectiveness study, we show that male patients and patients who were active smokers at the time of experiment have higher BPRS score on average. Both Olanzapine and Drilanzapine were observed to have decreased the BPRS score throughout the study, but Drilanzapine was shown to have a significantly larger decreasing rate. The subject characteristics were shown to have no effect on the typical rate of change, and the probability of improvement in symptoms after 8 weeks does not seem to be associated with a patient's individual rate of change in BPRS score during the first 6 weeks

of the study.

For the longer-term effectiveness study, we have shown that the percentage of psychotic depression patients in the population whose symptoms were under control using fluxetine and CBT prior to initiation of treatments is not dependent on age or gender. Over the 6 months, taking Drilanzapine leads to a significant increase in the odds of having symptoms under control, while taking fluxetine and CBT only leads to a short term increase with dosing effect dying out in the long run.

6 Appendix

In this section, we provide the codes that generated the plots and conclusions derived above, as well as outputs from statistical softwares.

6.1 SAS code

```
    libname ST732 "S:\Desktop\MySAS\";

ods pdf file="appendix.pdf";

data ST732.shortterm;
infile "S:\Desktop\MySAS\trial1.dat";
input id treatment gender weight age smoking time score assess @@;
foo = treatment;
run;

proc mixed  method=ml data=St732.shortterm;
  class  id treatment;
  model score = gender weight age smoking time foo*time / noint solution;
  random intercept time / type=un group=treatment subject=id g
  gcorr v=1,126 vcorr=1,126;
run;
```

```
329 data ST732.longterm;
330 infile "S:\Desktop\MySAS\trial2.dat";
331 input id gender age treatment time status @@;
332 run;
333
334
335
336 proc glimmix data=ST732.longterm method=laplace;
337   class id gender;
338   model status = gender age time treatment*time / dist=binomial
339   link=logit solution;
340   random intercept time / subject=id type=un g gcorr;
341 run;
342
343
344 proc genmod data=ST732.longterm descending;
345   class id gender(ref="0");
346   model status = gender age time treatment*time / dist=bin link=logit;
347   repeated subject=id/ type=un corrw covb modelse;
348 run;
349
350 proc genmod data=ST732.longterm descending;
351   class id gender(ref="0");
352   model status = gender age time treatment*time / dist=bin link=logit;
353   repeated subject=id/ type=cs corrw covb modelse;
354 run;
355
356 ods pdf close;
357 quit;
```