Beating the Blues

CHL5222 Final Project

Group E

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1 Introduction

According to the World Health Organization, major depressive disorder contributes significantly to disability and mortality in the world. For major depression treatment, the current clinical guidelines recommend a combination of pharmacotherapy and psychotherapy, such as cognitive-behavioural therapy (CBT). The evidence shows that patients receiving CBT are more likely to have a remission of the depression episode when compared with usual care. However, there are multiple barriers to CBT compliance, such as increased costs, availability of trained therapists, and heterogeneity of the therapy offered. Computer-based CBT can potentially overcome CBT limitations. We hypothesized that a CBT interactive multimedia program, "Beating the Blues (BtheB)," reduces the depression symptoms severity measured by Beck depression inventory when compared to treatment as usual (TAU) in patients diagnosed with depression and/or anxiety.

For our analysis, we included potential variables that affect treatment response in a depression episode. Our dataset provides information regarding concomitant drug treatment since combination therapy between CBT and antidepressants has demonstrated a higher likelihood of depression remission. Also, we considered the duration of the depression episode at study entry since depression episodes longer than 6 months have been associated with a reduced response to treatment.

2 Methods

Study Design

This is a randomized trial conducted in patients suffering from anxiety and/or depression. A total of 100 patients were randomly assigned to either receive BtheB therapy or treatment as usual (TAU). BtheB consisted of 8, 50-minute computerized weekly sessions with "homework" projects between sessions. TAU was defined as any treatment prescribed by the patient's general practitioner, including drug treatment or referral to a counselor. The primary outcome was the depression symptom severity defined by the Beck Depression Inventory (BDI) score. The BDI is a 21-question multiple-choice self-report inventory and ranges from 0 to 63 points. The baseline BDI level was collected at the time of study entry, then the follow-up BDI level was collected every two months, such as after 2, 4, 6, and 8 months. For every subject, we also registered whether the duration of depressive episode was longer than 6 months at the study entry, and whether subjects were receiving concomitant drug therapy for depression at baseline examination.

Data Format

Prior to the analysis, the data set was converted from a wide format to a long format. The number of patients was identified by the number of rows, and the data was lengthened by BDI level at each month. Some data were replaced to numerical variables: (i) the time variable month for each BDI level was added where 0 indicates the measurement occasion at the time of study entry for baseline BDI level, 2, 4, 6, and 8 for each follow-up months of BDI level (ii) a new variable time was created to represent the measurement occasion (iii)the assigned treatment was replaced with the level of 0 and l where 0 indicates TAU treatment and 1 indicates Beating the Blues therapy (iv) the presence of prescribed concomitant drug therapy was replaced with 1 if the prescribed drug was present, and 0 if not (v) the length of current episode of depression was replaced with 1 if the length was longer than 6 months and 0 if the length was shorter than 6 months.

Descriptive Statistics

In this study, descriptive statistics of continuous variables were presented as mean with their standard deviations,and categorical variables were presented as proportions. Additionally, an exploratory analysis was performed to evaluate the mean BDI level at each measurement occasion among different subgroups. The subgroups included the treatment groups, the patients with concomitant drug therapy, and patients with depression episode longer than 6 months. Patients with missing data at each measurement occasion were not included in the analysis. We illustrated the results graphically. Lastly, we displayed the individual trajectory of BDI level for patients according to their treatment group.

Data Analysis

The software used was R (R Foundation for Statistical Computing, Vienna, Austria) for statistical computing (v4.0.2), including the *nlme* package (v3.1-152) for fitting the generalized least square model.

We used a generalized least square model to analyze the effect of BtheB treatment on the BDI level (continuous variable) after accounting for the length of the depression episode (categorical variable) and the concomitant pharmacological therapy at baseline (categorical variable). Moreover, since the changes in mean BDI level are monotonically increasing and decreasing in a curvilinear way, a quadratic trend model was considered with the interaction between treatment group and the measurement occasion. We centered the time variable month to avoid collinearity. Then, we fitted models with different variance-covariance structure including unstructured, compound symmetry, toeplitz, autoregressive (AR1), and exponential. For each model, we calculated the Akaike information criterion (AIC), by -2 times the loglikelihood from the model minus the number of covariance parameters and selected the model with the smaller AIC as our final model. Final model results are presented graphically as the predicted mean BDI values per treatment group with their 95% confidence intervals (CI). All p-values were 2-sided, with p-values < 0.05 considered as statistically significant.

3 Analysis and Results

Descriptive Analysis

Analysis of Baseline

Given this is a randomized trial, baseline data check were conducted to examine whether variables were balanced between treatment groups before treatment began. A total of 100 patients were included in the study. 52 subjects received the BtheB therapy, and 48 subjects received TAU. Table 1 present the baseline subject characteristics. Both groups had similar mean BDI level at baseline (22.5 SD 11.7 vs. 24.19 SD 9.82 for BtheB and TAU respectively) and similar proportion of patients with depression episode length greater than 6 months at study entry (0.5 vs. 0.52 for BtheB and TAU respectively). However, there were a higher proportion of subjects with a concomitant depression drug therapy at study entry in the BtheB group (0.58 vs. 0.29 for BtheB and TAU respectively).

Treatment Group	Number Subjects	Mean BDI	SD BDI	Drug*	Length >6m**
Beating the blues	52	22.54	11.74	0.58	0.50
Treatment as usual	48	24.19	9.82	0.29	0.52

[a] BDI: Beck Depression Inventory
[b] SD: Standard deviation
[c] *Proportion of subjects with concomitant depression drug therapy at study entry
[d] **Proportion of patients with depression episode > 6 months at study entry

Table 1: Baseline Subjects Characteristics Beating the Blues Study

Number of Observations per Visit

There was a significant dropout during the study. Only 52 percent of study participants completed all 5 follow-up visits (Figure 1).

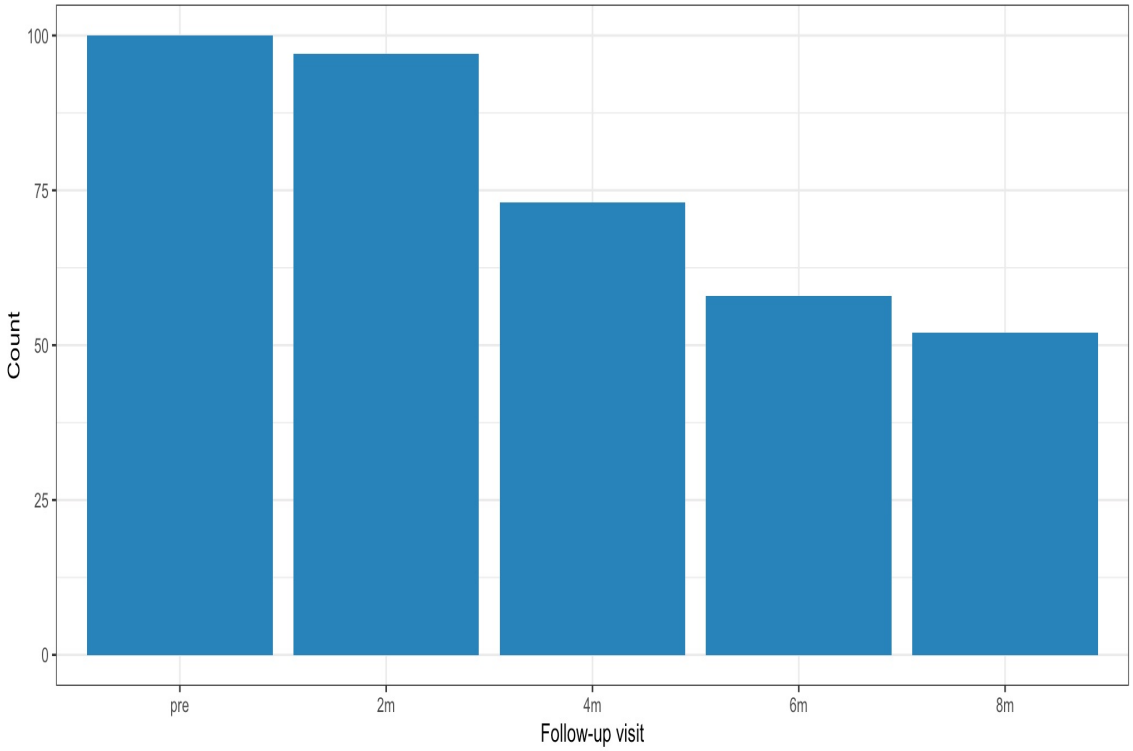

Figure 1: Number of Participants per visit

Longitudinal Mean Trajectory by Subgroups

Figure 2 shows the mean BDI trajectory by treatment group. The BtheB group had a greater drop in mean BDI level during the active treatment phase (between 0-2 months) compared to the TAU group. For the BtheB group the mean BDI level remained lower than the TAU group within 4 months after the treatment ended (between 2-6 months) and at each time interval.

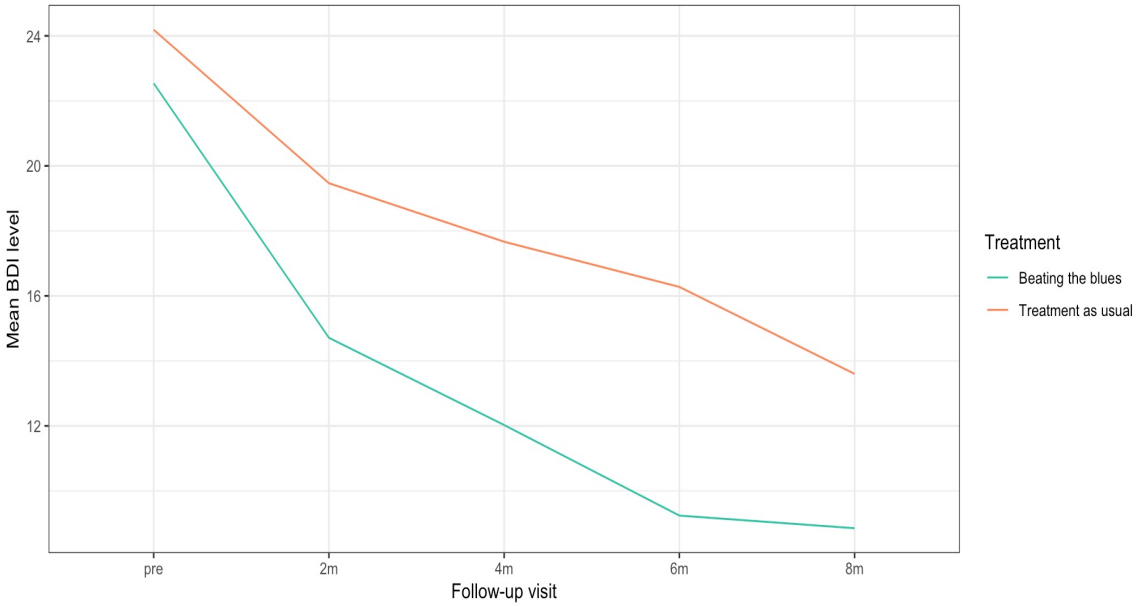

Figure 2: Mean Trajectory of BDI Level by Treatment

Figure 3 shows the trajectory of mean BDI level for patients with and without concomitant drug therapy at study entry. For patients with concomitant drug therapy at baseline, the decrease pattern in mean BDI level didn't differ much among the treatment groups. However, for patients without drug therapy, the BtheB group had lower mean BDI through the study period compared to the TAU group.

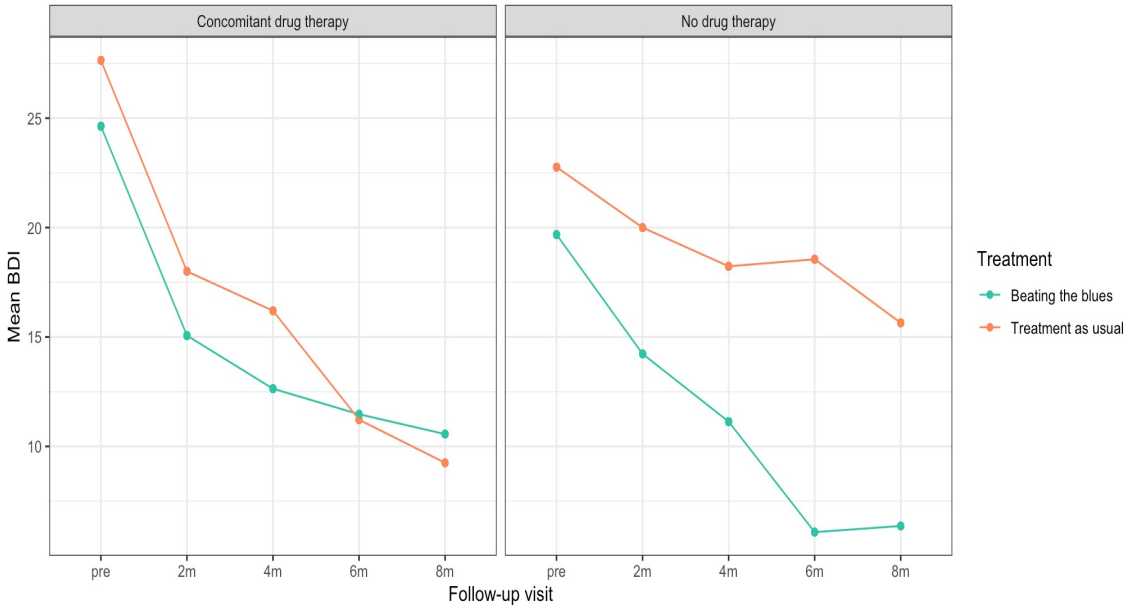

Figure 3: Mean BDI level Trajectories by concomitant drug therapy

Similarly, one might also investigate whether subject's current episode of depression at study entry was a confounding variable that influenced the BDI decrease respect to time. Figure 4 shows the trajectory of mean BDI level for patients with a depression episode duration greater than or less than 6 months at study entry. BtheB showed a greater decrease in mean BDI level than TAU for subjects had depressed more than 6 months before study entry. There was no difference in mean BDI level between the two treatments when depression episode before study entry was shorter than 6 months.

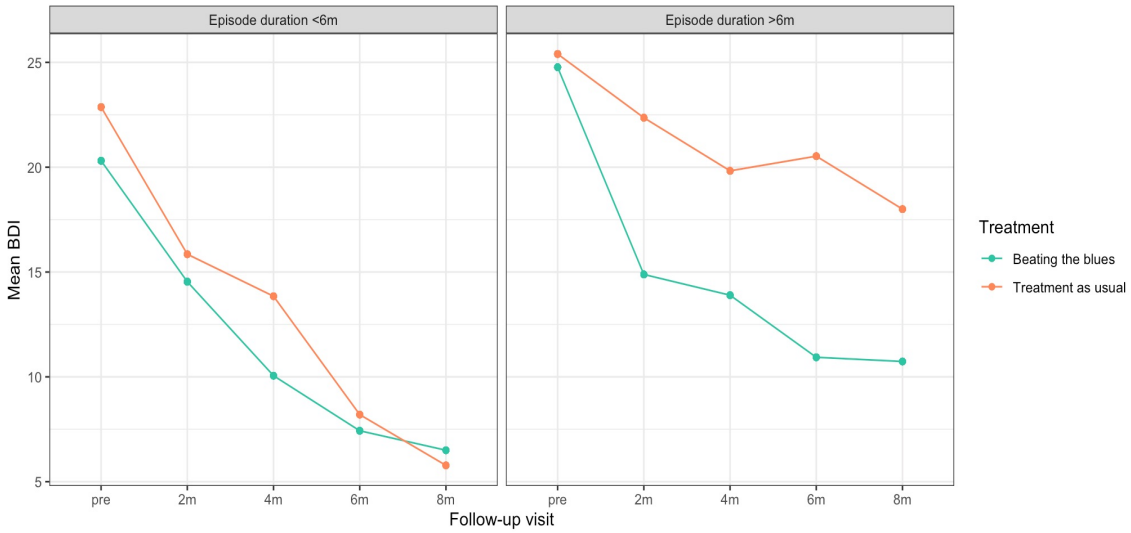

Figure 4: Mean Trajectories of BDI Level (Length $>$ 6m vs. Length $<$ 6m)

Longitudinal Individual Trajectory by Treatment

Figure 5 shows the individual trajectory of BDI by treatment group. The trajectories of individual BDI level were consistent with findings in the mean trajectory plot: the drop in BDI level for most patients treated with BtheB were greater than TAU especially in the active treatment phase.

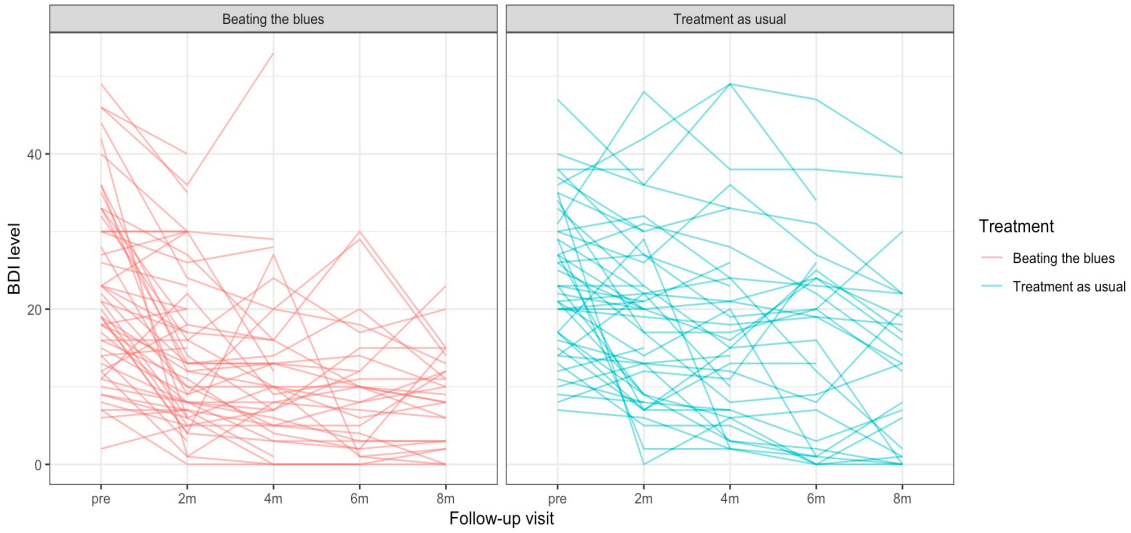

Figure 5: Individual Trajectory of BDI Level for patients

Assessing Efficacy of BtheB by modeling

We used a generalized linear model to determine the effect of BtheB therapy in depression symptoms severity (i.e. decreasing BDI level), after adjusting for concomitant drug therapy and depression episode duration at study entry. A quadratic time term (and its interaction with treatment) were considered due to the quadratic falling pattern for mean BDI level observed in the marginal plot (figure 2). Final model equation with variable description is shown below:

$$Y_{ij} = \beta_0 + \beta_1 drug_i + \beta_2 length6m_i + \beta_3 treatment_i + \beta_4 monthc_{ij} + \beta_5 monthcsq_{ij} + \beta_6 treatment_i * monthc_{ij} + \beta_7 treatment_i * monthcsq_{ij}$$

Y_{ij}: BDI level for subject i at time j
$drug_i$: whether subject i prescribed concomitant therapy (1: Yes, 0: No)
$length6m_i$: subject i's episode of depression at study entry (1: longer than 6 months, 0: shorter than 6 months)
$monthc_{ij}$: centered month (computed by $month_{ij}$ - mean(month))
$monthcsq_{ij}$: squared centered month ($monthcsq_{ij} = monthc_{ij}^2$)
$treatment_i$: treatment type for subject i (1: BtheB, 0: TAU)

Furthermore, we fitted models with different variance-covariance structure including unstructured, compound symmetry, Toeplitz, autoregressive (AR1), and exponential. Table 2 shows the AIC for each model. The model with an unstructured variance-covariance structure had the smallest AIC value and was selected as the final model. Although the unstructured pattern requires more computation due to a large number of parameters, AIC has already penalized for more parameters. Furthermore, there were fewer observations in this dataset.

Correlation Structure	AIC
Unstructured	2667.72
Compound Symmetry	2681.19
AR1	2678.68
Toeplitz	2670.07
Exponential	2678.68

Table 2: Akaike Information Criterion (AIC) of Correlation Structure

Results and Interpretations

Covariate	Estimate of Coefficient	P-value
$drug_i$	3.79	0.0432
$length6m_i$	4.46	0.0127
$treatment_i$	-6.28	0.0097
$monthc_{ij}$	-1.19	< 0.001
$monthcsq_{ij}$	0.06	0.4018
$treatment_i * monthc_{ij}$	-0.01	0.9811
$treatment_i * monthcsq_{ij}$	0.18	0.0521

Table 3: Summary of Results

Based on the result of coefficient estimates and p-values, there is at least moderate evidence that BDI level has a specific decrease patterns under different treatment conditions given the fact that the coefficient of interaction between treatment and squared centered month resulted with a p-value 0.0521 from likelihood ratio test ($H_0 : \beta_7 = 0$). The difference was also captured based on the predicted mean BDI trajectories by treatment (figure 6). Note that figure 6 is predicted BDI level for subgroup of patients (no drug therapy and episode of depression less than 6 months), but we assumed the rate of change in BDI by treatment was not confounded by drug or length in this model. The graph showed that predicted mean BDI for BtheB treatment type had a stronger quadratic association with time than TAU.

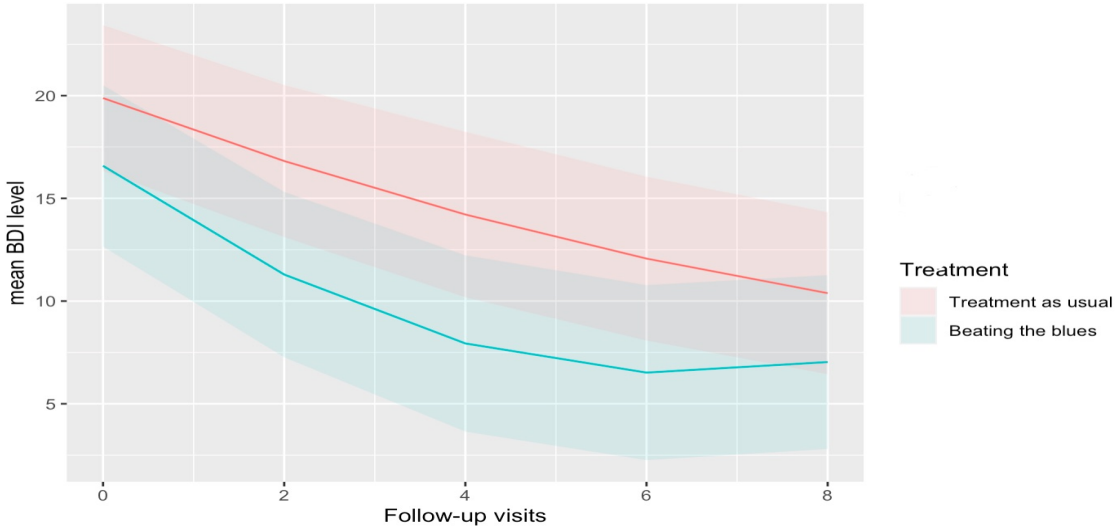

Figure 6: Predicted mean BDI with 95 % Confidence Interval (for patients with no concomitant depression drug therapy and shorter depression episode)

Mean BDI drop respect to time(month) were computed by regression estimates for different treatment types. Rate of change in mean BDI for treatment as usual was $0.12 * monthc - 1.19$ while $0.48 * monthc - 1.2$ for treatment BtheB. One might obtain these values by $\hat{\beta}_4 + 2 * \hat{\beta}_5 * monthc$ and $\hat{\beta}_4 + \hat{\beta}_6 + 2 * (\hat{\beta}_5 + \hat{\beta}_7 * monthc)$. (monthc = month - 4 in our dataset) The relationship between rate of change and month was shown in Figure 7. This results are in agreement with the initial exploratory visual analysis (figure 2), BtheB was more effective than TAU (in reducing BDI level) in the active treatment phase and two months after the intervention.

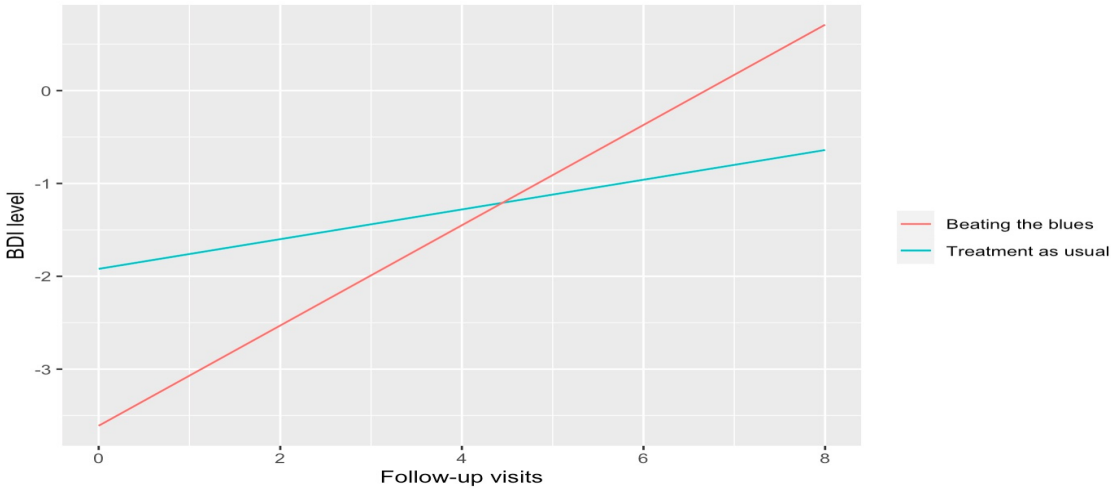

Figure 7: Rate of Change in Mean BDI by Treatment

4 Discussion

We analyzed the results of a randomized controlled trial assessing the efficacy of an interactive multimedia cognitive-based therapy program (Beating the Blues) to decrease the depression symptoms severity when compared with treatment as usual in patients with depression and anxiety. Our results showed that the "Beating the Blues (BtheB)" intervention significantly reduced the depression symptoms severity measured by Beck depression inventory when compared to treatment as usual (TAU). We found a significant quadratic effect of time and treatment group (p-value = 0.04). Also, we found a significant depression episode duration effect (p-value = 0.01). However, we did not find a significant effect of concomitant drug therapy in the BDI level (p-value = 0.1).

Our findings are similar to Proudfoot et al.'s 2004 study results (Proudfoot, 2004). A randomized control trial including 274 patients compared the clinical efficacy of computerized cognitive-behavioural therapy (BtheB) and TAU for patients with anxiety and depression. Using a linear mixed-effects model, they found a significant treatment and time effect in BDI level. They also reported a significant depression episode length and concomitant drug therapy effect.

Our study had important limitations. First, due to the intervention's nature, patients and care providers were not blinded to the treatment, which could bias the results towards the study intervention. Second, the BDI is a self-report inventory that can reduce the results' external validity and limit its application in populations with low literacy levels or non-English speakers. Third, we had a significant drop-out in our study. Only 52% of the subjects completed all study follow-up visits. We had limited information to understand the pattern of missing data in our research. However, we did not identify a difference in the pattern and frequency of missing data between treatment groups to suggest a relation between the missing data and the intervention group. Lastly, we had a small sample size, and our results can potentially be explained by a type I error.

In conclusion, Computerised cognitive behavioural therapy demonstrated a significant reduction in the depression symptoms severity in patients with depression and anxiety and is a potential alternative to treat depression.

5 Reference

Proudfoot J, Ryden C, Everitt B, Shapiro D, Goldberg D, Mann A, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. Br J Psychiatry 2004; 185:46–54.

Adrian G. Barnett, Nicola Koper, Annette J. Dobson, Fiona Schmiegelow and Micheline Manseau. Using information criteria to select the correct variance–covariance structure for longitudinal data in ecology. Methods in Ecology and Evolution 2010, 1, 15–24

Jaume Arnau, Roser Bono, Rebecca Bendayan and Maria J. Blanca. Analyzing longitudinal data and use of the generalized linear model in health and social sciences. Quality & Quantity volume 50, pages 693–707 (2016)

6 Appendix

```
#useful packages
library(tidyverse)
library(tinytex)
library(PupillometryR)
library(knitr)
library(kableExtra)
library(nlme)
library(car)
library(contrast)
library(AICcmodavg)
library(foreign)
library(geepack)
library(gee)
library(MASS)
library(lme4)
library(glmm)

#import data
btheb <- read.table("btheb.txt", header = TRUE)

#change wide format to long format
btheb_long <- btheb %>%
  mutate(id = row_number())%>%
  pivot_longer(
    cols = starts_with("bdi"),
    names_to = "bdi",
    values_to = "level"
  ) %>%
  mutate(treatment = factor(case_when(treatment == "TAU" ~ 0,
  treatment == "BtheB" ~ 1)),
    #Drug = yes -> 1, Drug = No -> 0
    dtherapy = factor(ifelse(drug == "Yes", 1, 0)),
    #Length > 6m -> 1, Length < 6m -> 0
    length6m = factor(ifelse(length==">6m", 1, 0)),
    time = case_when(
    bdi == "bdi.pre" ~ 1,
    bdi == "bdi.2m" ~ 2,
    bdi == "bdi.4m" ~ 3,
    bdi == "bdi.6m" ~ 4,
    bdi == "bdi.8m" ~ 5),
    # Create the variable that indicates the length of month
    month = case_when(
      bdi == "bdi.pre" ~ 0,
      bdi == "bdi.2m" ~ 2,
      bdi == "bdi.4m" ~ 4,
      bdi == "bdi.6m" ~ 6,
      bdi == "bdi.8m" ~ 8),
  )%>%mutate(month2 = month*month)%>%drop_na()
head(btheb_long,10)
}

head(bthebc ,10)
```

```
#Number of observations per subject
btheb_long %>%
  drop_na() %>%
  group_by(id) %>%
  summarise(nobs = n_distinct(time)) %>%
  count(nobs) #52% completed the trial

#Descriptive statistics
btheb_long %>%
  drop_na() %>%
  group_by(treatment, month) %>%
  summarise(plevel = mean(level), sdlevel = sd(level))

#Baseline statistics
btheb_long %>%
  drop_na() %>%
  filter(time==1)%>%
  group_by(treatment) %>%
  summarise(pdlevel = mean(level), pdlevel2 = sd(level), n = n(),
  pdrug = mean(drug == "Yes"), plength = mean(length6m == 1))

#mean trajectory plot
btheb_long %>%
  drop_na() %>%
  mutate(treatment = ifelse(treatment == 0, "TAU", "BtheB")) %>%
  group_by(treatment, month) %>%
  summarise(plevel = mean(level))  %>%
  ggplot(aes(y = plevel, x = month, color = treatment)) +
  geom_point() +
  geom_line() +
  labs(y = "BDI level", x = "Month")

#mean trajectory plot by drug
btheb_long %>%
  mutate(drug = ifelse(drug == "Yes", "concomitant drug therapy = Yes",
  "concomitant drug therapy = No")) %>%
  mutate(treatment = ifelse(treatment == 0, "TAU", "BtheB")) %>%
  ggplot(aes(x = as.factor(month), y = level, color = treatment)) +
  geom_boxplot(width = 0.1)  +
  labs(y = "BDI level", x = "Month") + facet_wrap(~ drug)  +
  stat_summary(aes(group = treatment), fun = mean, geom="line") +
  ggtitle("Treatment effect when drug = Yes")

#mean trajectory plot by length
btheb_long %>%
  mutate(length = ifelse(length == ">6m", "depression longer than 6 months",
  "depression shorter than 6 months")) %>%
  mutate(treatment = ifelse(treatment == 0, "TAU", "BtheB")) %>%
  ggplot(aes(x = as.factor(month), y = level, color = treatment)) +
  geom_boxplot(width = 0.1)  +
  labs(y = "BDI level", x = "Month") + facet_wrap(~ length)  +
  stat_summary(aes(group = treatment), fun = mean, geom="line")+
```

```
  ggtitle("Treatment effect when drug = Yes")


#Individual trajectory plot
btheb_long %>%
  drop_na()%>%
  ggplot(aes(y = level, x = time, group = id,color = as.factor(treatment))) +
  facet_wrap(~ treatment) +
  geom_line() +
  labs(x = "time", y = "BDIlevel", color = "Treatment",
  caption = "Individual Trajectory Plot")


#model selection

#modeling without centering time
mod1 <- gls(level ~ treatment * month + dtherapy + length6m,
corr=corCompSymm(, form= ~ time | id),
weights = varIdent(form = ~ 1 | time), data = btheb_long)
summary(mod1) #Interaction can be dropped and will be tested later with method = "ML"

mod2 <- gls(level ~ treatment + month + dtherapy + length6m,
corr=corCompSymm(, form= ~ time | id), weights = varIdent(form = ~ 1 | time),
data = btheb_long)
summary(mod2) #treatment1 has estimate = -4.324902, p-value =   0.0339

#Likelihood test for the interaction
mod3 <- gls(level ~ treatment * month + dtherapy + length6m,
corr=corCompSymm(, form= ~ time | id), weights = varIdent(form = ~ 1 | time),
method = "ML", data = btheb_long)
summary(mod3)

mod4 <- gls(level ~ treatment + month + dtherapy + length6m,
corr=corCompSymm(, form= ~ time | id), weights = varIdent(form = ~ 1 | time),
method = "ML", data = btheb_long)
summary(mod4)
anova(mod3, mod4) #The model with no interaction fits better = mod4

mod5 <- gls(level ~ treatment * month + dtherapy + length6m + treatment*month2,
corr=corCompSymm(, form= ~ time | id),  weights = varIdent(form = ~ 1 | time),
method = "ML", data = btheb_long)
summary(mod5)
anova(mod5,mod3)

#Quad model with centered and add interaction terms
mod6 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corCompSymm(, form= ~ time | id),  weights = varIdent(form = ~ 1 | time),
method = "ML", data = bthebc)
summary(mod6)
anova(mod6, mod3)

# mod6 is the best, then we jump to the process for correlation structure

#Candidate models
```

```
#compound symmetry
mod6 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corCompSymm(, form= ~ time | id), weights = varIdent(form = ~ 1 | time),
data = bthebc)

#unstructured
mod7 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corSymm(form= ~ time| id), weights = varIdent(form = ~ 1 | time),
data = bthebc)

#toeplitz
mod8 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corARMA(form= ~ time| id, p= 1, q = 1), weights = varIdent(form = ~ 1 | time),
data = bthebc)

#AR1
mod9 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corAR1(form= ~ time| id), weights = varIdent(form = ~ 1 | time),
data = bthebc)

#exponential
mod10 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corExp(form= ~ time| id), weights = varIdent(form = ~ 1 | time),
data = bthebc)

#assess by AIC measure
AIC(mod6)
AIC(mod7) #smallest
AIC(mod8)
AIC(mod9)
AIC(mod10)

#final model
mod7 <- gls(level ~ dtherapy + length6m +treatment*monthc + treatment*monthcsq,
corr=corSymm(form= ~ time| id), weights = varIdent(form = ~ 1 | time),
data = bthebc)
summary(mod7) #coefficient summary

# predicted value confidence interval figure from mod7
predval <- predictSE(mod7, newdata = bthebc)
predupp <- predval$fit + 1.96*predval$se.fit
predlow <- predval$fit - 1.96*predval$se.fit
allpred <- data.frame(fit = predval$fit, predupp = predupp, predlow = predlow)
dentpred2 <- cbind(bthebc, allpred) %>%
  mutate(Treatment = ifelse(treatment == 0, "Treatment as usual", "Beating the blues"))

dentpred2 %>%
  filter(drug == "No" & length == "<6m") %>%
  ggplot(aes(x = month, y = fit)) +
  geom_ribbon(aes(ymin = predlow, ymax = predupp, fill = treatment), alpha = 0.1) +
  geom_line(aes(color = treatment))+
  labs(y = "BDI level", x = "Follow-up visits", color = "Treatment", fill = "Treatment")
```

```
# rate of change plot
x = seq(-4, 4, 0.1)
y1 = 0.12*x - 1.19
y2 = 0.48*x - 1.2
dat <- data.frame(x = x + 4, y1, y2)
dat %>%
  ggplot(aes(x = x, y = y1)) +
  geom_line(aes(x = x, y = y1, color = "TAU")) +
  geom_line(aes(x = x, y = y2, color = "BtheB"))+
  labs(y = "BDI level", x = "month")
```