Efficacy of emotional exposure therapy (EET) for Fibromyalgia in Randomized Clinical Trial

UMID last 4-digits : 9609

ABSTRACT

Fibromyalgia (FM) is a chronic disorder that causes widespread musculoskeletal pain, fatigue, and tenderness. Since the conventional interventions, which target behaviors and cognition, have limited efficacy, a 2-site, 3-arm, allegiance-controlled randomized clinical trial (RCT) for FM investigated the benefit of emotional exposure therapy (EET). In order to test the efficacy of EET compared to Cognitive-behavioral therapy (CBT) and FM Education (EDU), a linear spline generalized estimating equation (GEE) was applied to the clinical trial dataset. The GEE model showed that the efficacy of EET was beneficial to 3 months follow-up (*p-value* < 0.001) compared to the EDU (*p-value* = 0.007), but there was no difference between EET and CBT (*p-value* = 0.530).

INTRODUCTION

More than 3 million Americans per year suffer from Fibromyalgia (FM), which is a disorder accompanied by widespread muscle pain, tenderness and fatigue and therefore, affect people's mood. FM cannot be cured, and conventional approaches to FM have only targeted relief of behaviors and cognition symptoms. According to the updated pain definition [1], the pain is defined as a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components. Moreover, it has been shown that psychological interventions help to manage patients' chronic pain [2]. Thus, it is important to consider psychological treatment for mitigation of the chronic pain for FM. The previous smaller studies suggest that the techniques involving emotional exposure and processing are efficacious for FM. However, these components had not been combined into a theoretically integrated emotional

exposure therapy (EET) and the efficacy of EET had not been tested in a controlled, clinical trial. Therefore, a multi-site randomized clinical trial (RCT) [3] examined the efficacy of EET, which targets psychological treatment for reducing stress, compared to the conventional interventions, cognitive-behavioral therapy (CBT) and FM education (EDU). The EET encouraged patients to disclose stressful experiences and increase expression of emotions through weekly sessions and homework. CBT focused on cognitive and behavioral exercises to manage FM symptoms rather than the emotional factor. EDU provided knowledge about FM in terms of its definition, diagnoses, medications and research methods in order to increase patient's understanding and thus, decrease uncertainty and reduce defensiveness. Through RCT, the main interest of outcome was pain reduction following treatments.

METHODS

This clinical trial design was a 2-site, 3-arms, allegiance-controlled RCT. At the Wayne State University and the University of Michigan, participants were recruited and evaluated through screening processes by inclusion and exclusion criteria from the trial protocol. A total of 230 adults (94% female, n = 216, mean age of females = 49.5) with FM were assigned randomly to small groups. Each group provided one of three treatments, EET, CBT, and EDU. Through eight weekly small-group sessions, the three treatments were compared on key health outcomes, such as clinical and psychophysical pain testing, subjective disability and objective physical activity, fatigue, mood, and sleep problems at baseline, 3- and 9-month follow-up evaluation. Since the research question was to compare the efficacy of EET compared to CBT and EDU in terms of pain relief, the primary outcome measurement was the subjective clinical pain evaluated from the Brief Pain Inventory (BPI; 162), which assess current pain and highest, lowest, and average pain during the past week. Each BPI has scale from 0 to 10, and the lower scale is, the less pain occurs. The pain score from the four items was averaged in order to combine all the pain severity. Since the depressive symptoms and anxiety symptoms were collected for secondary outcome measures,

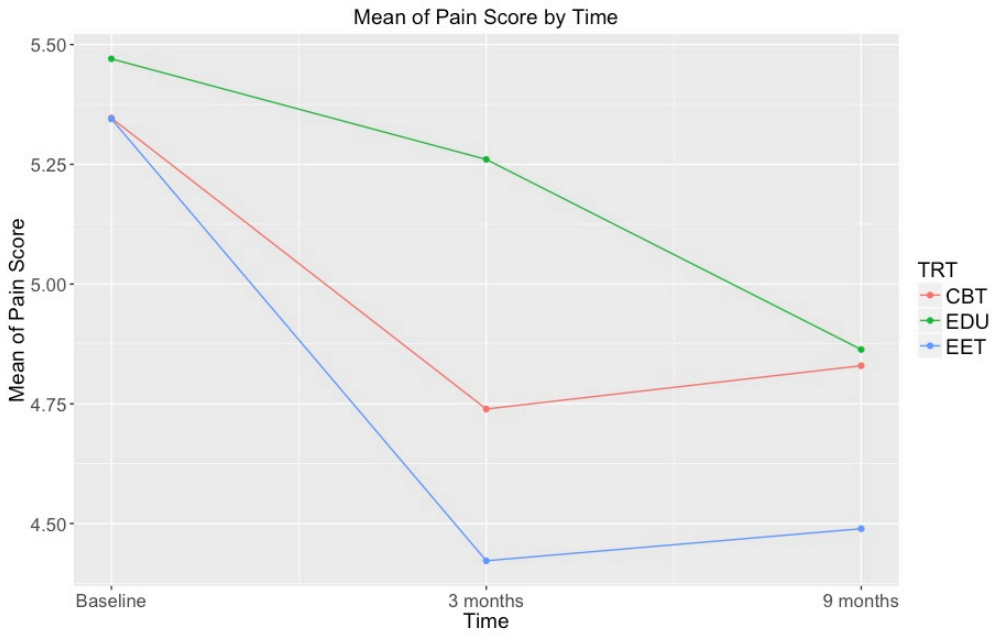
they were not included in this analysis in order to address the main research question. Demographic variables were collected, including age, gender, body mass index (BMI), ethnicity, race, highest educational level, total tender points, fibromyalgianess, and a score of symptoms evaluated by Complex Medical Symptoms Inventory. In order to check the validity of randomization, the demographic variables at baseline were compared across three treatments. For continuous variables, one-way ANOVA test and Kruskal-Wallis test were conducted respectively if the data followed normal and non-normal distributions in order to compare the means across treatments. In the case of categorical/binary variables, the Chi-square test and Fisher's exact test were applied to test the difference in proportions between treatments. If the randomization was valid and there were no other risk factors, such as a site effect, then it would guarantee that the treatments are the only factor to contribute to the outcome, pain score in a longitudinal analysis model. Since a generalized estimating equation (GEE) enables to analyze the repeated measurements in a marginal level, the data was modeled with a spline GEE model based on a mean trend plot and the validity of randomization. When it comes to modeling, a covariance structure for repeated outcome measurements was determined based on the form of unstructured covariance for the values. With the specified covariance structure, coefficients from the fitted GEE model were estimated and tested by comparing two nested models. Finally, residuals from the fitted GEE model were used to do diagnostics. For missing values, the percentages of missingness were evaluated, which implicated how to deal with the missingness in this dataset. The longitudinal analysis was conducted in R and specifically the 'geepack' package[4] was used to fit GEE models.

RESULTS

At baseline, each demographic variable were examined across treatments in order to check the validity of randomization. According to Appendix Table A1, FM patients were randomly assigned to each treatment arm. Moreover, the effect of different site was tested across treatment

arms and there was no evidence to say that interventions were different from sites (p-value = 0.2). This implied that the stratification was not necessary in modeling process. Figure 1 suggests that a linear spline pattern for each treatment over time, therefore, the linear spline GEE model was selected to model the dataset. Based on the validity of randomization and the spline pattern for the repeated measurements of pain score, the linear spline GEE model was fitted to the dataset.

Figure 1. Mean trend plots of the pain score for three treatments (EET, CBT and EDU)



The mean trend plots for treatments suggest a linear spline GEE model for the RCT. Time (Baseline, 3 months and 9 months) indicates that baseline, post-treatment and 6 months follow-up, respectively. EET and CBT show decreasing first and increasing again over time, whereas EDU shows decreasing pattern over time.

The fitted linear spline GEE model was expressed in the following marginal model for the pain score:

$$E(Pain_{ij}) = \beta_1 + \beta_2 * Time_{ij} + \beta_3 * (Time_{ij} - 3)_+ + \beta_4 * Time_{ij} * I(CBT_i) + \beta_5 * (Time_{ij} - 3)_+ * I(CBT_i) + \beta_6 * Time_{ij} * I(EDU_i) + \beta_7 * (Time_{ij} - 3)_+ * I(EDU_i)$$

In order to make easy interpretations, EET was chosen to be a reference treatment. For a covariance structure, an exchangeable covariance structure was selected based on empirical correlation matrix of pain scores over time. The 'geeglm' function from 'geepack' package in R was applied to estimate parameters with its standard error based on a sandwich variance estimator, which are shown in Table 1.

Table 1. Parameter estimates and standard errors (based on sandwich variance estimator) from marginal regression model for the pain score.

Variable	Estimate	SE	Chi-square statistic	Wald 95% CI	*p-value*
(Intercept)	5.39	0.11	2520.99	(50.00 , 50.42)	$< 0.001^*$
Time	-0.31	0.07	19.10	(-4.51 , -4.23)	$< 0.001^*$
$(\text{Time} - 3)_+$	0.22	0.06	13.62	(3.58 , 3.81)	$< 0.001^*$
Time × CBT	0.10	0.09	1.21	(0.93 , 1.28)	0.271
$(\text{Time} - 3)_+ \times$ CBT	-0.06	0.08	0.68	(-0.98 , -0.67)	0.411
Time × EDU	0.26	0.09	8.27	(2.70 , 3.05)	0.004^*
$(\text{Time} - 3)_+ \times$ EDU	-0.23	0.08	9.34	(-3.20 , -2.91)	0.002^*

Since the three treatments were randomly assigned at baseline, the treatment effect was not included in the linear spline GEE model.
(Intercept) indicates that the EET effect at baseline.
$(x)_+ = x$ if $x > 0$, 0 otherwise.
SE : sandwich variance estimator.
Estimated scale parameter: $\hat{\phi} = 3.21$. Estimated working correlation: $\hat{\alpha} = 0.57$.

In Table 1, the first three estimates are the common estimates of the mean pain score, comparing both CBT and EDU to EET, since EET was a reference treatment. The rest of estimates were interpreted as the mean difference of pain score in each treatment (CBT and EDU) compared to EET at 3 months and 6 months follow-up. For example, the expected mean pain score at baseline in EET is 5.39 (se = 0.11). The estimate for Time variable (-0.31, se = 0.07) is the expected mean change of pain score comparing 3 months follow up to baseline, in EET. On the other hand, the estimate for Time × CBT (0.10, se = 0.09) is the expected mean difference of pain score

comparing CBT to EET at 3 months follow-up. In detail, the parameter of the marginal model for comparison was summarized as Table A2 in Appendix. By the way, Table 1 also addresses that the EET has significant effect to the pain score at baseline, 3 months and 6 months follow-up (*p-values* < 0.001). In order to test the efficacy of EET comparing both CBT and EDU to EET, the estimates of slope changes over time were summarized in Table 2 and the comparison of efficacy of EET to others was tested with nested GEE models. In Table 2, the slope for each treatments change over time, which demonstrated consistent patterns in Figure 1, and EET has the most sharp decreasing pattern in the pain score from baseline to 3 months follow-up (-0.31) and it recovered faster than other treatments to 9 months follow-up (0.22). Finally, the efficacy of EET compared to CBT was not significant (*p-value* = 0.530), but it was significant to EDU (*p-value* = 0.007).

Table 2. Estimated slope change and the test for efficacy of CBT and EDU treatments to EET.

Treatment	**The change of slope**		**EET vs. Treatment**
	Baseline to 3 months	**3 months to 9 months**	***p-value***
EET	-0.31	0.22	-
CBT	-0.21	0.15	0.530
EDU	-0.05	-0.01	0.007*

For diagnostics, the mean model assumption was checked through residual analysis, which were shown in Appendix Figure A1. Moreover, the percentages of missingness were calculated for each variable and they were assumed to be no pattern in the missingness in order to apply the GEE model.

DISCUSSION

The linear spline GEE analysis concluded that EET was beneficial to reduce the chronic pain for FM from the baseline to post-treatment, but the efficacy disappeared at 6 months follow-up. Moreover, the efficacy of EET did not show a significant difference to CBT, however, showed the significant difference to EDU.

There were multiple limitations in this longitudinal analysis. Firstly, the follow-up period was not long and repeated measures were only collected twice. If the longer periods of observations were available, then it would give more reliable results. Secondly, there would be a selection bias that might come from the nature of the RCT design. Since the patients were filled up each treatment group according to first-come first-serve way, it could possibly contaminate the structure of correlated measurements and thus, randomization might be threatened. Even though the RCT would try to recruit more patients or increase the number of groups in order to remove the possible selection bias, there would be trade-off between the two ways due to the limit of budgets or the decrease of analysis power. Besides, it is possible to exist unobserved confounders. During the 8 therapy sessions, patients could be affected from other environmental components, which were not controlled by this RCT. Lastly, subjective ratings for the symptoms are not robust and therefore, it would be good to incorporate the individual's susceptibility variable in the model in order to compensate the individual variations.

Not only the limitation in the dataset, but also there were two concerns in the analysis. From the property of the GEE, using the sandwich estimator may lose the statistical power if the covariance was correctly specified. Secondly, FM symptoms were dependent to individuals and within-subject variations could be large. But, the marginal model, like GEE, did not consider subject's level variation.

FM is a significant quality of life issue for people suffering from the chronic pain. In this study, I found that the emotional factor helped to reduce patients' pain in a short-term period and the

better efficacy than the EDU therapy. Longer follow-up and incorporating other risk factors can confirm the durability of these findings.

References

[1] Williams & Craig, (2016). Updating the definition of pain. Pain. 157, 2420-2423

[2] Roditi, D., & Robinson, M. E. (2011). The role of psychological interventions in the management of patients with chronic pain. Psychology Research and Behavior Management, 4, 41–49. http://doi.org/10.2147/PRBM.S15375

[3] Lumley, M. & Williams, D.A. (2013?). R01 AR057808 A1: Emotional Exposure and Cognitive Behavioral Therapies for Fibromyalgia

[4] Søren Højsgaard, (2016). 'geepack' packages of version 1.2-1 in R to solve generalized estimating equation.

Acknowledgment

I would like to thank Kristen Herold from SPH Writing Lab for her suggestions on the writing of this report.

Appendix

Table. A1. Demographic information at baseline for three treatments

			EET (n = 79)	CBT (n = 75)	EDU (n = 76)	p-value
Age (year)		mean (sd)	49.0 (11.7)	48.1 (12.5)	50.3 (12.5)	0.55[1]
BMI (kg/m^2)		mean (sd)	29.2 (6.6)	30.2 (7.7)	31.5 (6.4)	0.07[2]
Gender		# (%)				0.08[3]
	Female		73 (92.4%)	68 (90.7%)	75 (98.7%)	
	Male		6 (7.6%)	7 (9.3%)	1 (1.3%)	
Ethnicity		# (%)				0.70[3]
	Hispanic or Latino		2 (2.6%)	2 (2.7%)	4 (5.3%)	
	Not Hispanic or Latino		76 (97.4%)	71 (97.3%)	72 (94.7%)	
Race		# (%)				0.20[3]
	American Indian or Alaskan Native		1 (9.1%)	1 (1.3%)	0 (0.0%)	
	Native Hawaiian or Other Pacific Islander		0 (0.0%)	0 (0.0%)	1 (1.3%)	
	Black or African American		8 (72.7%)	15 (20.0%)	18 (23.7%)	
	White		2 (18.2%)	57 (76.0%)	54 (71.1%)	
	Multi-Racial or Other		0 (0.0%)	2 (2.7%)	3 (3.9%)	
Educational Level		# (%)				0.30[3]
	11th grade		1 (1.3%)	1 (1.3%)	0 (0.0%)	
	High school graduate or GED		6 (7.6%)	13 (17.3%)	7 (9.2%)	
	Some college, no AA		20 (25.3%)	12 (16.0%)	18 (23.7%)	
	Technical degree or AA		12 (15.2%)	16 (21.3%)	23 (30.3%)	
	College degree (BA/BS)		26 (32.9%)	21 (28.0%)	20 (26.3%)	
	Masters (MS, MA)		5 (6.3%)	6 (8.0%)	2 (2.6%)	
	Professional degree (PhD, MD)		9 (11.4%)	6 (8.0%)	6 (7.9%)	
Relationship Status		# (%)				0.90[3]
	Married		43 (54.4%)	39 (52.0%)	43 (56.6%)	
	Separated		2 (2.5%)	3 (4.0%)	1 (1.3%)	
	Divorced		9 (11.4%)	13 (17.3%)	13 (17.1%)	
	Widowed		4 (5.1%)	3 (4.0%)	1 (1.3%)	
	Never Married		14 (17.7%)	14 (18.7%)	14 (18.4%)	
	Living with a partner in a committed relationship		7 (8.9%)	3 (4.0%)	4 (5.3%)	

			EET (n = 79)	CBT (n = 75)	EDU (n = 76)	p-value
Number of Household		mean (sd)	2.8 (1.8)	2.8 (1.6)	2.9 (1.4)	0.60[2]
Number of Child		mean (sd)	0.7 (1.3)	0.76 (1.2)	0.67 (1.2)	0.80[2]
Employment Status		# (%)				0.20[3]
	Homemaker		13 (16.5%)	7 (9.3%)	7 (9.2%)	
	Unemployed		6 (7.6%)	8 (10.7%)	9 (11.8%)	
	Retired		10 (12.7%)	10 (13.3%)	13 (17.1%)	
	On disability		16 (20.3%)	16 (21.3%)	9 (11.8%)	
	On leave of absence		1 (1.3%)	0 (0.0%)	2 (2.6%)	
	Full-time employed		13 (16.5%)	20 (26.7%)	20 (26.3%)	
	Part-time employed		19 (24.1%)	10 (13.3%)	9 (11.8%)	
	Full-time student only		1 (1.3%)	4 (5.3%)	6 (7.9%)	
	Missing		0 (0.0%)	0 (0.0%)	1 (1.3%)	
Household Income		# (%)				0.20[3]
	< $10,000		3 (3.8%)	5 (6.7%)	7 (9.2%)	
	$10,000 to $14,999		4 (5.1%)	6 (8.0%)	3 (3.9%)	
	$15,000 to $24,999		11 (13.9%)	15 (20.0%)	12 (15.8%)	
	$25,000 to $34,999		4 (5.1%)	4 (5.3%)	9 (11.8%)	
	$35,000 to $49,999		12 (15.2%)	13 (17.3%)	9 (11.8%)	
	$50,000 to $74,999		25 (31.6%)	11 (14.7%)	12 (15.8%)	
	$75,000 to $99,999		8 (10.1%)	6 (8.0%)	11 (14.5%)	
	$100,000 to $149,999		8 (10.1%)	8 (10.7%)	11 (14.5%)	
	$150,000 to $1999,999		2 (2.5%)	2 (2.7%)	0 (0.0%)	
	> $200,000		0 (0.0%)	3 (4.0%)	0 (0.0%)	
	Missing		2 (2.5%)	2 (2.7%)	2 (2.6%)	
Health Insurance Status		# (%)				0.20[3]
	Yes		9 (12.0%)	9 (11.8%)	4 (5.1%)	
	No		66 (88.0%)	67 (88.2%)	75 (94.9%)	
Total tender points		mean (sd)	14.7 (2.8)	14.6 (3.0)	14.8 (2.5)	1.00[2]
Fibromyalgianess		mean (sd)	21.0 (4.4)	20.3 (4.7)	20.6 (4.7)	0.70[2]
Complex Medical Symptoms Inventory		mean (sd)	37.3 (11.7)	34.0 (11.7)	38.8 (12.9)	0.05[2]

[1]: One-way ANOVA, [2]: Kruskal-Wallis test, [3]: Fisher's Exact test

Table. A2. Parameters of the marginal linear spline GEE model for the pain score.

Treatment Group	Time	$E(Pain_{ij})$	$\widehat{E}(Pain_{ij})$
EET (Reference)	Baseline	β_1	5.39
	3 months	$\beta_1 + \beta_2$	5.08
	9 months	$\beta_1 + \beta_2 + \beta_3$	5.29
CBT vs. EET	Baseline	β_1	5.39
	3 months	$(\beta_1 + \beta_2) + \beta_4$	5.18
	9 months	$(\beta_1 + \beta_2 + \beta_3) + \beta_4 + \beta_5$	5.33
EDU vs. EET	Baseline	β_1	5.39
	3 months	$(\beta_1 + \beta_2) + \beta_6$	5.34
	9 months	$(\beta_1 + \beta_2 + \beta_3) + \beta_6 + \beta_7$	5.32

The model is the following: $E(Pain_{ij}) = \beta_1 + \beta_2 * Time_{ij} + \beta_3 * (Time_{ij} - 3)_+ + \beta_4 * Time_{ij} * I(CBT_i) + \beta_5 * (Time_{ij} - 3)_+ * I(CBT_i) + \beta_6 * Time_{ij} * I(EDU_i) + \beta_7 * (Time_{ij} - 3)_+ * I(EDU_i)$

Figure A1.1 Diagnostics for the fitted spline GEE model.

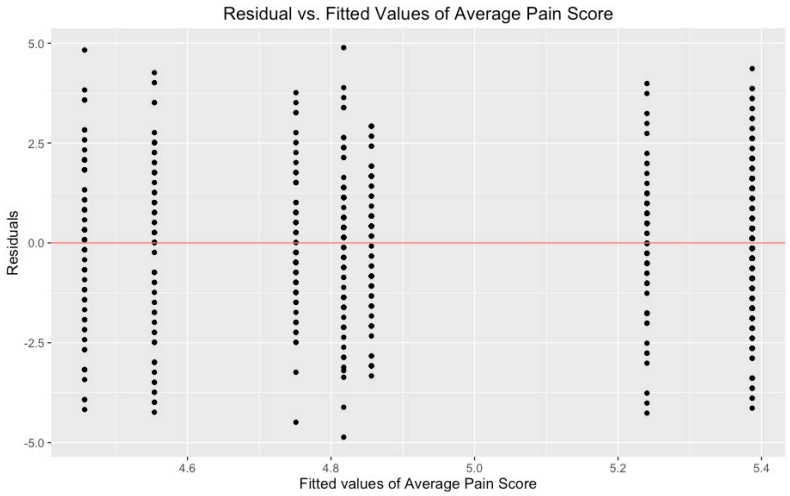


Figure A1.2 Q-Q plot for residuals at baseline.

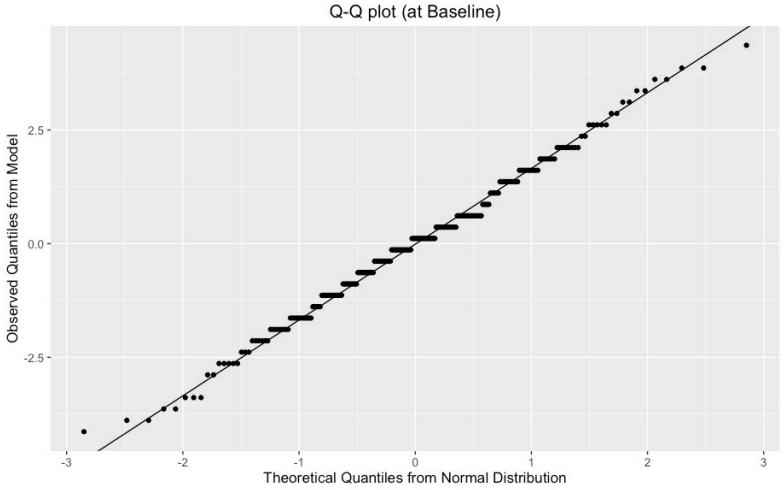


Figure A1.3 Q-Q plot for residuals at 3 months follow-up.

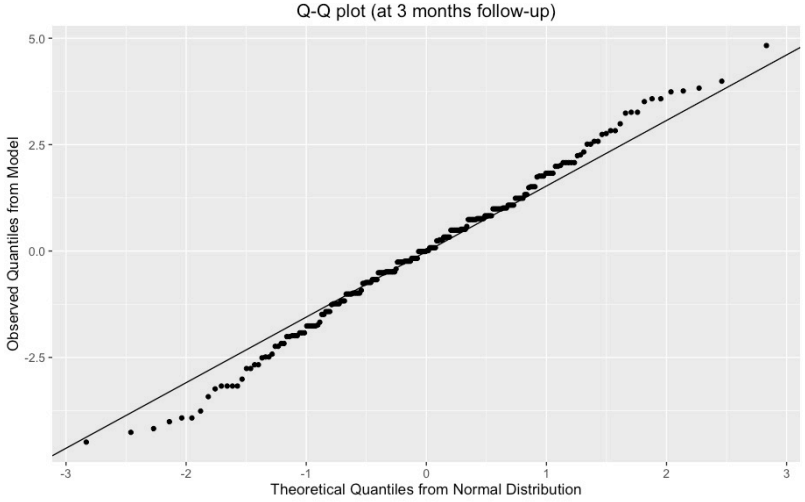
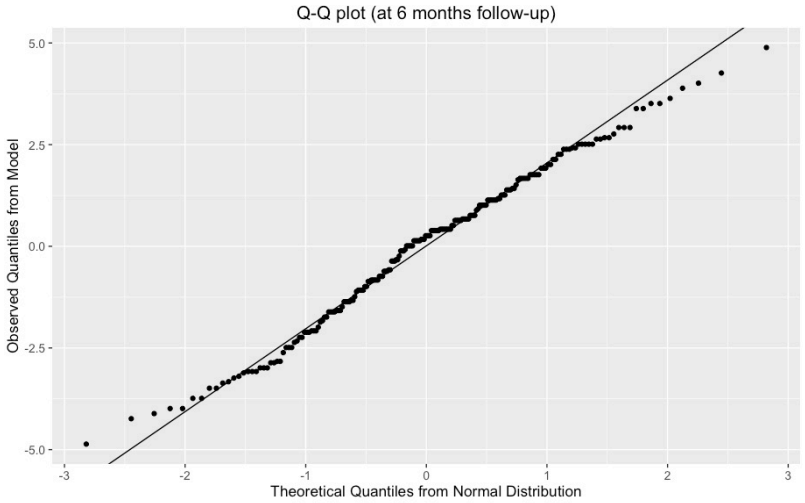


Figure A1.4 Q-Q plot for residuals at 6 months follow-up.



<R code>

```
##### Data import -----
library(gdata) # read csv file
library(reshape2) # melt (wide -> long format)
library(ggplot2) # plot
library(geepack) # fit GEE model
library(plyr) # ddply
library(BaylorEdPsych) # test MCAR
library(mvnmle) # test MCAR


df <- read.table("./Data/DataforBIOS699.csv", header = TRUE, sep =",")
# https://www.r-bloggers.com/read-excel-files-from-r/
head(df)
str(df)

# check missing data
M <- sapply(df, function(x) sum(is.na(x)))
M[M>0]


##### wide to long format -----
df1 <- subset(df, select = c(pid, condition, grpnbr, numsessions, therapysite,
                        yearfmonset, yearfmdiagnosed,
                        BPI_PainSeverity_V2, BPI_PainSeverity_V3, BPI_PainSeverity_V4,
                        CESD_TOT_V2, CESD_TOT_V3, CESD_TOT_V4,
                        GAD7TOTAL_V2, GAD7TOTAL_V3, GAD7TOTAL_V4,
                        AGE, sex, ethnic, race, bmi,
                        tptotal, acr_fmness, CMSI_Total,
                        highesteduc, relationstatus, numberhousehold, numberchildren,
                        currentemployment, hhincome, healthinsurance))

colnames(df1) <- c('PID', 'TRT', 'gp', 'session', 'site', 'onset','diagnosed',
                '2.pain', '3.pain', '4.pain',
                '2.dep', '3.dep', '4.dep',
                '2.anx', '3.anx', '4.anx',
                'age', 'gender', 'ethnic', 'race', 'bmi', 'tptotal', 'fmness', 'symptom',
                'edu', 'relation', 'num_hh', 'numchild', 'empl', 'hh_income', 'health_ins')

df1$PID <- as.character(df1$PID)

# nominal factor
cols <- c("gp", "session", "gender", "ethnic", "race",  "relation", "empl", "health_ins")
df1[cols] <- lapply(df1[cols], factor)

# ordered factor
missing.edu <- sapply(df1$edu, function(x) sum(is.na(x)))
missing.edu[missing.edu>0]

df1$edu <- factor(df1$edu, labels = c(11,12,13,14,16,18,20), ordered=TRUE)
```

```
missing.hh_income <- sapply(df1$hh_income, function(x) sum(is.na(x)))
missing.hh_income[missing.hh_income>0]

df1$hh_income <- factor(df1$hh_income, labels = c(1,2,3,4,5,6,7,8,9,10), ordered=TRUE)

# http://stackoverflow.com/questions/23945350/reshaping-wide-to-long-with-multiple-values-
columns
df2 <- reshape(df1, direction='long',
       varying=c('2.anx', '2.dep', '2.pain',
                 '3.anx', '3.dep', '3.pain',
                 '4.anx', '4.dep', '4.pain'),
       timevar='visitnum',
       times=c('2', '3', '4'),
       v.names=c('pain', 'dep', 'anx'),
       idvar='PID')

df2 <- df2[order(df2$PID, df2$visitnum),]
rownames(df2) <- seq(length=nrow(df2))

# add Time column (0 = visitnum 2, 3 = visitnum 3, 9 = visitnum 4)
df2$Time <- sapply(df2$visitnum, function(x) ifelse(x == 2, 0, ifelse(x == 3, 3, 9)))

head(df2) # long format
head(df1) # wide format

# test MCAR for fitting GEE ------
colnames(df2)[2:23]

MCAR.test <- LittleMCAR(df2[, c(2:23)])
MCAR.test$amount.missing  # less than 10% in each variables -> ignore missing values



##### EDA -----
g <- ggplot(df2, aes(x=as.numeric(visitnum), y=pain)) +
  geom_line(aes(group = PID)) +
  geom_smooth(method='loess') +
  facet_grid(~TRT) +
  labs(title = "Average Pain Score by Treatments", y = 'Average Pain Score') +
  scale_x_continuous('Times', breaks=seq(2,4,1),labels=c('Baseline', '3 months', '9 months')) +
  theme_set(theme_grey(base_size = 13)) +
  theme(axis.text.x = element_text(angle = 60, hjust = 1))
g

df2.mean <- ddply(df2,~TRT,summarise,mean=mean(pain, na.rm=TRUE))

g1 <- ggplot(df2, aes(x=pain)) +
  geom_histogram(binwidth=.5, colour="black", fill="white") +
  facet_grid(~TRT) +
  ggtitle("Histogram for Average Pain Score by Treatment") +
  ylab('Frequency') +
```

```
  geom_vline(data=df2.mean, aes(xintercept=mean), linetype="dashed", size=1, colour="red")
g1

# 1) TRT-wise demographic &  information -----
## continuous : age, bmi, tptotal, fmness, symptom
## categorical : gender, ethnic, race, edu, relation, num_hh, numchild, empl, hh_income,
health_ins
## primary outcome : pain
## secondary outcome : dep, anx

# 1.1 for conti :
# - test normality, and compare means for each TRT gps
# - if normal, one-way ANOVA anova
# - if not, Kruskal-Wallis test
# 1.2 for categorical :
# - make a table and check sparsity, and compare proportions for each TRT gps
# - if not sparse, Chi-square test
# - if sparse, fisher'x exact test

# Demographic Table -------
# total
table(df2[which(df2$visitnum == "2"), 'TRT'])
# age
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(age, na.rm = TRUE),
sd=sd(age, na.rm = TRUE))
# bmi
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(bmi, na.rm = TRUE),
sd=sd(bmi, na.rm = TRUE))
# gender
tbl1 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'gender'],
exclude = NULL)
colnames(tbl1) <- c("Female", "Male", "Missing")
tbl1
# ethnic
tbl2 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'ethnic'],
exclude = NULL)
colnames(tbl2) <- c("Hispanic or Latino", "Not Hispanic or Latino", "Missing")
tbl2
# race
tbl3 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'race'], exclude
= NULL)
colnames(tbl3) <- c("American Indian or Alaskan Native", "Native Hawaiian or Other Pacific
Islander",
                    "Black or African American", "White", "Multi-Racial or Other", "Missing")
tbl3
# edu
tbl4 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'edu'], exclude
= NULL)
colnames(tbl4) <- c("11th grade", "High school graduate or GED", "Some college, no AA",
"Technical degree or AA", "College degree (eg. BA/BS)", "Masters (MS, MA)", "Professional
degree (eg. PhD, MD)", "Missing")
```

```
tbl4
# relation
tbl5 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'relation'],
exclude = NULL)
colnames(tbl5) <- c("Married", "Separated", "Divorced" , "Widowed" , "Never Married" , "Living
with a partner in a committed relationship", "Missing")
tbl5
# num_hh
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(num_hh, na.rm =
TRUE), sd=sd(num_hh, na.rm = TRUE))
table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'num_hh'], exclude =
NULL)

# numchild
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(numchild, na.rm =
TRUE), sd=sd(numchild, na.rm = TRUE))
table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'numchild'], exclude =
NULL)

# empl
tbl8 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'empl'],
exclude = NULL)
colnames(tbl8) <- c("Homemaker", "Unemployed", "Retired", "On disability", "On leave of
absence", "Full-time employed", "Part-time employed", "Full-time student only", "Missing")
tbl8

# hh_income
tbl9 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'hh_income'],
exclude = NULL)
colnames(tbl9) <- c("< $10,000", "$10,000 to $14,999", "$15,000 to $24,999", "$25,000 to
$34,999", "$35,000 to $49,999",
"$50,000 to $74,999", "$75,000 to $99,999", "$100,000 to $149,999", "$150,000 to $1999,999",
"> $200,000", "Missing")
tbl9
t(tbl9)
# health_ins
tbl10 <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'health_ins'],
exclude = NULL)
colnames(tbl10) <- c("Yes", "No", "Missing")
t(tbl10)
# tptotal
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(tptotal, na.rm =
TRUE), sd=sd(tptotal, na.rm = TRUE))
# fmness
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(fmness, na.rm =
TRUE), sd=sd(fmness, na.rm = TRUE))
# symptom
ddply(df2[which(df2$visitnum == "2"), ], .(TRT), summarise, mean=mean(symptom, na.rm =
TRUE), sd=sd(symptom, na.rm = TRUE))
```

```
# normality check for continuous variables (H0 : samples are from normal dist'n) -----
# age : follows normal
with(df2[which(df2$visitnum == 2),],tapply(age,list(TRT),function(x) if (length(unique(x))==1)
NA else shapiro.test(x)))
# bmi : not follow normal
with(df2[which(df2$visitnum == 2),],tapply(bmi,list(TRT),function(x) if (length(unique(x))==1)
NA else shapiro.test(x)))
# tptotal : not follow normal
with(df2[which(df2$visitnum == 2),],tapply(tptotal,list(TRT),function(x) if
(length(unique(x))==1) NA else shapiro.test(x)))
# fmness : not follow normal
with(df2[which(df2$visitnum == 2),],tapply(fmness,list(TRT),function(x) if
(length(unique(x))==1) NA else shapiro.test(x)))
# symptom : follow normal
with(df2[which(df2$visitnum == 2),],tapply(symptom,list(TRT),function(x) if
(length(unique(x))==1) NA else shapiro.test(x)))

# anova test for age : no difference
g.age <- ggplot(df2[which(df2$visitnum == 2),], aes(x=TRT, y=age)) +
  geom_boxplot(aes(fill=TRT)) +
  labs(x="") +
  theme_bw() +
  theme(strip.background=element_rect(fill="black")) +
  theme(strip.text=element_text(color="white", face="bold")) +
  ggtitle("Age at Baseline for each Treatment")
g.age

g<-lm(df2[which(df2$visitnum == 2),'age']~df2[which(df2$visitnum == 2),'TRT'])
anova(g) # H0 : same means across gps

# Kruskal-Wallis test for bmi : no difference
g.bmi <- ggplot(df2[which(df2$visitnum == 2),], aes(x=TRT, y=bmi)) +
  geom_boxplot(aes(fill=TRT)) +
  labs(x="") +
  theme_bw() +
  theme(strip.background=element_rect(fill="black")) +
  theme(strip.text=element_text(color="white", face="bold")) +
  ggtitle("BMI at Baseline for each Treatment")
g.bmi
kruskal.test(df2[which(df2$visitnum == 2),'bmi']~df2[which(df2$visitnum == 2),'TRT']) # H0 :
same means across gps

# Kruskal-Wallis test for tptotal : no difference
g.tptotal <- ggplot(df2[which(df2$visitnum == 2),], aes(x=TRT, y=tptotal)) +
  geom_boxplot(aes(fill=TRT)) +
  labs(x="") +
  theme_bw() +
  theme(strip.background=element_rect(fill="black")) +
  theme(strip.text=element_text(color="white", face="bold")) +
  ggtitle("Total Tender Points at Baseline for each Treatment")
g.tptotal
```

```
kruskal.test(df2[which(df2$visitnum == 2),'tptotal']~df2[which(df2$visitnum == 2),'TRT']) # H0
: same means across gps

# Kruskal-Wallis test for fmness : no difference
g.fmness <- ggplot(df2[which(df2$visitnum == 2),], aes(x=TRT, y=fmness)) +
  geom_boxplot(aes(fill=TRT)) +
  labs(x="") +
  theme_bw() +
  theme(strip.background=element_rect(fill="black")) +
  theme(strip.text=element_text(color="white", face="bold")) +
  ggtitle("fmness Tender Points at Baseline for each Treatment")
g.fmness
kruskal.test(df2[which(df2$visitnum == 2),'fmness']~df2[which(df2$visitnum == 2),'TRT']) # H0
: same means across gps

# Kruskal-Wallis test for symptom : no difference (boundary)
g.symptom <- ggplot(df2[which(df2$visitnum == 2),], aes(x=TRT, y=symptom)) +
  geom_boxplot(aes(fill=TRT)) +
  labs(x="") +
  theme_bw() +
  theme(strip.background=element_rect(fill="black")) +
  theme(strip.text=element_text(color="white", face="bold")) +
  ggtitle("symptom Tender Points at Baseline for each Treatment")
g.symptom
kruskal.test(df2[which(df2$visitnum == 2),'symptom']~df2[which(df2$visitnum == 2),'TRT']) #
H0 : same means across gps

g1<-lm(df2[which(df2$visitnum == 2),'symptom']~df2[which(df2$visitnum == 2),'TRT'])
anova(g1) # H0 : same means across gps

# num_hh : no difference
kruskal.test(df2[which(df2$visitnum == 2),'num_hh']~df2[which(df2$visitnum == 2),'TRT']) #
H0 : same means across gps

tbl.num_hh <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'num_hh'])
fisher.test(tbl.num_hh, workspace=2e9)

# numchild : no difference
kruskal.test(df2[which(df2$visitnum == 2),'numchild']~df2[which(df2$visitnum == 2),'TRT']) #
H0 : same means across gps

tbl.numchild <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'numchild'])
fisher.test(tbl.numchild)


# same proportionality check for categorical variables (H0 : same proportios) -----
# gender : no difference
tbl.gender <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'gender'])
```

```
fisher.test(tbl.gender)

# ethnic : no difference
tbl.ethnic <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'ethnic'])
fisher.test(tbl.ethnic)

# race : no difference
tbl.race <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'race'])
fisher.test(tbl.race)

# edu : no difference
tbl.edu <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'edu'])
fisher.test(tbl.edu, workspace=2e9)

# relation : no difference
tbl.relation <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'relation'])
fisher.test(tbl.relation)

# empl : no difference
tbl.empl <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'empl'])
fisher.test(tbl.empl, workspace=2e9)

# hh_income : no difference
tbl.hh_income <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'hh_income'])
fisher.test(tbl.hh_income, workspace=2e9)

# health_ins : no difference
tbl.health_ins <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum ==
2),'health_ins'])
fisher.test(tbl.health_ins)

#####  check the site effect -----
# site effect check -> no difference
tbl.site <- table(df2[which(df2$visitnum == 2),'TRT'], df2[which(df2$visitnum == 2),'site'])
tbl.site
fisher.test(tbl.site)

##### GEE fitting -----
# TRT : EET, CBT, EDU
cor(df1[,c('2.pain', '3.pain', '4.pain')], use = "complete.obs")  # exchangeable covariance structure

df2$TRTn <- as.numeric(df2$TRT)  # 1 = CBT, 2 = EDU, 3 = EET
df2$Time.CBT <- df2$Time*(df2$TRTn == 1)
df2$Time.EDU <- df2$Time*(df2$TRTn == 2)
df2$Time.CBT.EDU <- df2$Time*I(df2$TRTn != 3)

df2$Time.knot3 <- sapply(df2$Time, function(x) ifelse(x > 3 , x, 0))
df2$Time.CBT.knot3 <- df2$Time.knot3*(df2$TRTn == 1)
df2$Time.EDU.knot3 <- df2$Time.knot3*(df2$TRTn == 2)
```

```
head(df2[, c('TRT', 'Time', 'Time.knot3', 'Time.CBT', 'Time.CBT.knot3', 'Time.EDU',
'Time.EDU.knot3')], 20)

# spline GEE -----
m.spline <- geeglm(pain ~ Time + Time.knot3 + Time.CBT + Time.CBT.knot3 + Time.EDU +
Time.EDU.knot3, family = gaussian, data = df2, id = PID, corstr = "exch", std.err = "san.se")
summary(m.spline)

m.spline.EET <- geeglm(pain ~ Time + Time.knot3, family = gaussian, data = df2, id = PID,
corstr = "exch", std.err = "san.se")
summary(m.spline.EET)

m.spline.CBT <- geeglm(pain ~ Time + Time.knot3 + Time.CBT + Time.CBT.knot3, family =
gaussian, data = df2, id = PID, corstr = "exch", std.err = "san.se")
summary(m.spline.CBT)

m.spline.EDU <- geeglm(pain ~ Time + Time.knot3 + Time.EDU + Time.EDU.knot3, family =
gaussian, data = df2, id = PID, corstr = "exch", std.err = "san.se")
summary(m.spline.EDU)

anova(m.spline.EET, m.spline) # at least one is not zero.

# ad-hoc : which trt is different from EET?
anova(m.spline.EET, m.spline.CBT)  # CBT = EET
anova(m.spline.EET, m.spline.EDU)  # EDU =/= EET



# different parameterization - same as the above ------
df2$TRTn1 <- sapply(df2$TRT, function(x) ifelse(x == "EET" , "0", ifelse(x == "CBT", "1",
"2")))
m.1 <- geeglm(pain ~ Time + Time * TRTn1, family = gaussian, data = df2, id = PID, corstr =
"exch", std.err = "san.se")
summary(m.1)

# different parameterization with spline - same as the above
m.2 <- geeglm(pain ~ Time + Time.knot3 + Time * TRTn1 + Time.knot3 * TRTn1, family =
gaussian, data = df2, id = PID, corstr = "exch", std.err = "san.se")
summary(m.2)



##### 'gee' package ------
install.packages("gee")
library(gee)
m.lm <- glm(pain ~ Time + Time.CBT + Time.EDU, data = df2, family = gaussian)

m.gee <- gee(pain ~ Time + Time.CBT + Time.EDU, family = gaussian, data = df2, id = PID,
corstr = "exchangeable", b = m.lm$coefficients)
summary(m.gee)

m.lm.spline <- glm(pain ~ Time + Time.knot3 + Time.CBT + Time.CBT.knot3 + Time.EDU +
Time.EDU.knot3, data = df2, family = gaussian)
```

```
m.gee.spline <- gee(pain ~ Time + Time.knot3 + Time.CBT + Time.CBT.knot3 + Time.EDU +
Time.EDU.knot3, family = gaussian, data = df2, id = PID, corstr = "exchangeable", b =
m.lm.spline$coefficients)
summary(m.gee.spline)

# Robust S.E. in gee = Std.err in geepack
# (Robust z)^2 in gee = Wald in geepack

# plot(m.lm)


##### diagnostic -----
install.packages("boot")
library(boot)

# spline GEE -----
# residual vs. fitted values
non.missing.idx.spline <- as.numeric(rownames(as.data.frame(m.spline$residuals)))
non.missing.TRT.spline <- df2[as.numeric(rownames(df2)) %in% non.missing.idx, 'TRT']
non.missing.Time.spline <- df2[as.numeric(rownames(df2)) %in% non.missing.idx, 'Time']

df3.spline <- as.data.frame(cbind(non.missing.TRT.spline, non.missing.Time.spline,
m.spline$residuals, m.spline$fitted.values))
colnames(df3.spline) <- c("TRT", "Time", "resids", "fitted")

# overall residuals : should be randomly scattered around zero
ggplot(data = df3.spline, aes(x=fitted, y=resids, colors = TRT)) +
  geom_point() +
  geom_hline(aes(yintercept=0, colour = "red")) +
  labs(title = "Residual vs. Fitted Values of Average Pain Score") +
  xlab("Fitted values of Average Pain Score") +
  ylab("Residuals") +
  theme(legend.position="none")

# q-q plot
# reg : http://stackoverflow.com/questions/4357031/qqnorm-and-qqline-in-ggplot2
qqplot.data <- function (vec, timeline){
  # following four lines from base R's qqline()
  y <- quantile(vec[!is.na(vec)], c(0.25, 0.75))
  x <- qnorm(c(0.25, 0.75))
  slope <- diff(y)/diff(x)
  int <- y[1L] - slope * x[1L]

  d <- data.frame(resids = vec)

  ggplot(d, aes(sample = resids)) + stat_qq() +
    geom_abline(slope = slope, intercept = int) +
    labs(title = paste("Q-Q plot (at ", timeline, ")", sep="")) +
    xlab("Theoretical Quantiles from Normal Distribution") +
    ylab("Observed Quantiles from Model")
}
```

```
time.char <- c("Baseline", "3 months follow-up", "6 months follow-up")
qqplot.data(df3.spline[which(df3.spline$Time == 0),'resids'], time.char[1])
qqplot.data(df3.spline[which(df3.spline$Time == 3),'resids'], time.char[2])
qqplot.data(df3.spline[which(df3.spline$Time == 9),'resids'], time.char[3])

##### -----
# with(df2[which(df2$visitnum == "4"),],tapply(pain,list(TRT),function(x) mean(x, na.rm =
TRUE)))

stats <- rbind(cbind(summary.stat.2, visitnum = rep(2,3)), cbind(summary.stat.3, visitnum =
rep(3,3)), cbind(summary.stat.4, visitnum = rep(4,3)))

# with CI
ggplot(stats,aes(x=visitnum,y=mean,color=TRT)) +
  geom_errorbar(aes(ymin=mean-sd, ymax=mean+sd), width=.1) +
  geom_line() +
  geom_point() +
  scale_x_continuous(breaks=c(2,3,4), labels=c("Baseline", "3 months", "9 months")) +
  labs(title = "Mean of Pain Score by Time", x = "Time", y = "Mean of Pain Score") +
  theme(plot.title = element_text(face="bold", color="black", size=rel(1.5))) +
  theme(axis.text.x = element_text(size=15), axis.text.y = element_text(size=15)) +
  theme(axis.title.x = element_text(size = rel(1.5))) +
  theme(axis.title.y = element_text(size = rel(1.5)))


# w/o CI
ggplot(stats,aes(x=visitnum,y=mean,color=TRT)) +
  geom_line() +
  geom_point() +
  scale_x_continuous(breaks=c(2,3,4), labels=c("Baseline", "3 months", "9 months")) +
  labs(title = "Mean of Pain Score by Time", x = "Time", y = "Mean of Pain Score") +
  theme(plot.title = element_text(face="bold", color="black", size=rel(1.5))) +
  theme(axis.text.x = element_text(size=15), axis.text.y = element_text(size=15)) +
  theme(axis.title.x = element_text(size = rel(1.5))) +
  theme(axis.title.y = element_text(size = rel(1.5)))
```