Use of PROC MIXED in the Analysis of Repeated Measures Data from a Clinical Trial in Obsessive Compulsive Disorder

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I. Abstract

The subject of this paper is the analysis of data from a randomized, parallel group, multicenter clinical trial in patients with Obsessive Compulsive Disorder (OCD). The purpose of the study was to evaluate the efficacy and safety of three dose levels of Paxil™* (paroxetine HCl) versus placebo. The level of the patients' illness was measured using the Yale Brown Obsessive Compulsive Scale (YBOCS) at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12. The data set included data points which were missing due to skipped visits and patient dropouts.

PROC MIXED of the SAS System was used in two alternative approaches to the analysis of the data from this study. The first is a repeated measures analysis. Secondly, PROC MIXED was used in a random coefficient regression analysis. In this analysis the hypothesis of interest was the differences in slopes (rates of improvement) for the doses of Paxil and placebo.

II. Introduction

A clinical trial was conducted to establish the dose profile of Paxil in the treatment of patients with Obsessive Compulsive Disorder (OCD). The study evaluated three doses of Paxil (20mg, 40mg, and 60mg) and placebo in a 12 week, parallel group, multicenter study conducted in the United States. The primary measure of efficacy in the study was the Yale Brown Obsessive Compulsive Scale (YBOCS) which was measured at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12. The YBOCS is a psychometric scale which is used to determine the level of severity of the patient's OCD; it is a 10 item scale with each item measured on a 0-4 point scale resulting in a total score ranging from 0 to 40. The scale is typically analyzed as a change from baseline in total score, a negative value indicates an improving condition.

The typical analysis used in regulatory submissions and the literature includes univariate analysis of variance conducted at all timepoints with inferences based on the results from an a priori defined timepoint (week 12). Two datasets are analyzed, an extender (last observation carried forward) data set and a visit wise (observed cases) data set. The primary comparisons in the study were each active dose group against placebo; Dunnett's critical regions were used to maintain the overall alpha level of the study.

The results from the standard analysis demonstrate that both the 40mg and 60mg dose groups separate from placebo while the 20mg failed to separate from placebo. Therefore 40mg is considered the minimum effective dose for Paxil in OCD.

This paper presents two alternative approaches to the analysis through the use the PROC MIXED of SAS/STAT®. Both approaches used the restricted maximum likelihood (REML) algorithm. The first can be considered a repeated measures analysis of variance

* Paxil (paroxetine HCl) is a registered trademark of SmithKline Beecham.

approach. The second is a random coefficient regression approach which models each patient's change from baseline score as a function of time on treatment. Tests for treatment group differences in regression parameters are made.

The change from baseline in the YBOCS was assumed to be normally distributed. The missing observations were considered to be missing at random.

III. Modeling the Covariance Structure

The use of PROC MIXED requires the modeling of the within-patient covariance structure. Several structures are available in PROC MIXED. Four structures of the within-patient covariance were evaluated. The first was a 36 degree of freedom model which estimates an effect for each correlation between the 8 timepoints this is referred to as the Unstructured covariance model.

Three covariance structures were also evaluated which allow varying degrees of correlation dependent on the distance between observations. The Toeplitz model is an 8 degree of freedom model. Two single degree of freedom covariance models were also evaluated; the spatial covariance model which assumes a reduction in correlation in relation to the power of the distance between time points, and an autoregressive model was evaluated as well. Refer to the SAS technical Report P-229 for more detailed discussion.

Table 1 below evaluates the efficiency of the four covariance structures using the difference in -2 times the log likelihood from the "full" model (the 36 degree of freedom unstructured covariance model). The Toeplitz, spatial, and the autoregressive covariance models explained significantly less of the variation than did the unstructured model. Therefore the unstructured covariance matrix was used in the repeated measures analysis.

Table 1
Summary of Covariance Modeling
PAR116 - Intent to Treat Population

			Difference from Unstructured		
Covariance Structure	-2*log likelihood	cov-matrix df	-2*log likelihood	df	Chi-Square p-value
Unstructured	12477	36	- -	- -	- -
Toeplitz	12625	8	148	28	<0.01
Autoregressive	12666	1	189	35	<0.01
Spatial	12798	1	321	35	<0.01

IV. Repeated Measures

Displayed below in Table 2 is the analysis of variance table for this dose ranging study. The dose by investigator (or site) interaction was not significant (p=0.54) and was dropped from the model.

Figure 1 below is a graph of the Dose by Week least squares means generated by PROC MIXED. The significant Dose effect produced by PROC MIXED indicates differences between the 4 dose levels (0, 20, 40, and 60mg) averaged across weeks.

The graph reveals the source of the significant interaction; the dose levels exhibit different response profiles across time.

These results are similar to those generated by the univariate ANOVA performed at each timepoint. Table 3 contrasts the week 12 results from the univariate ANOVA and the results from PROC MIXED generated by a CONTRAST statement.

Table 2
Repeated Measures Analysis of Variance Table
Intent to Treat Population - PAR116

Effect	DF	Type III F	Pr > F
Dose	3	5.69	0.0007
Investigator	12	1.31	0.2077
Week	7	23.32	<0.0001
Dose by Week	21	2.50	0.0002

Figure 1 LS Means Generated from PROC MIXED

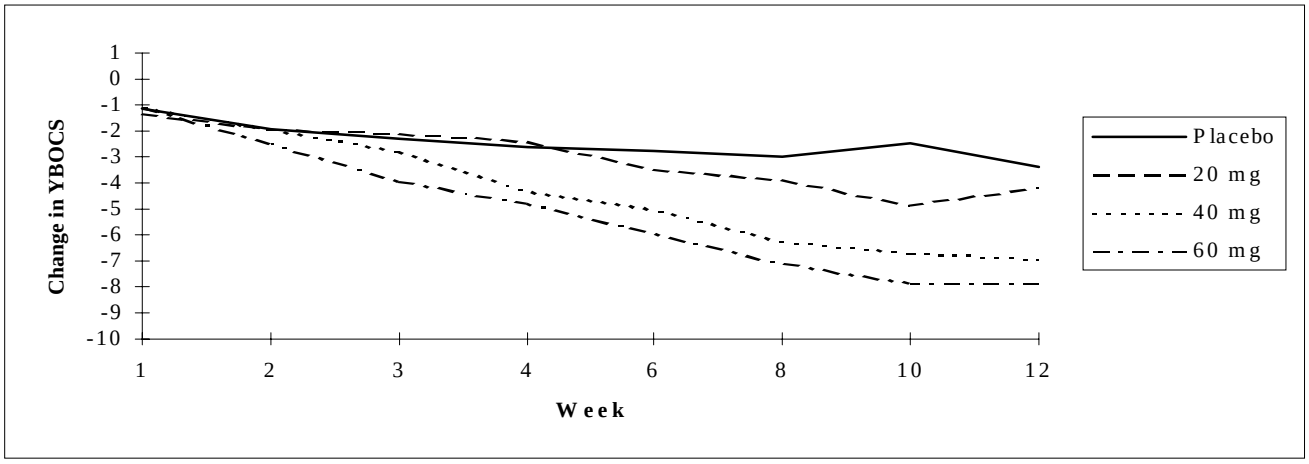


Table 3 Week 12 Results PROC MIXED AND PROC GLM

	Placebo N=88 mean (s.e.)	Paroxetine 20mg N=84 mean (s.e.)	Paroxetine 40mg N=83 mean (s.e.)	Paroxetine 60mg N=83 mean (s.e.)	P-values Dose	Linear
GLM	-3.36 (0.72)	-4.02 (0.74)	-6.33 (0.74) *	-7.27 (0.74)+*	<0.0001	<0.0001
MIX	-3.35 (0.78)	-4.16 (0.79)	-6.90 (0.82)+*	-7.88 (0.82)+*	0.0001	<0.0001

* Significantly different from placebo, + Significantly different from 20mg based on Dunnett's.

V. Random Coefficient Regression

These data were also analyzed via PROC MIXED using random coefficient regression. This allows separate response functions for each dose group to be modeled across time. The intra-subject regression coefficients were considered to be random. Time (week or visit) was considered to be continuous, an effect for time squared was included as well. The interest in this analysis is to test for differences in rates of improvement between dose groups. Also of interest are the parameter estimates for the response functions. Table 4 and 5 below summarize the results of this analysis.

The spatial covariance structure was used in this analysis and convergence was achieved. The structure has intuitive appeal in that the correlations between observations within a patient are modeled by a function of the distance between observations.

Table 4 displays the ANOVA table for the final model. Based on the repeated measures analysis and univariate ANOVA results an effect for the Dose by Investigator interaction was not included. The nonsignificant Dose effect is not surprising given that all dose groups began the study with zero change from baseline. The week and week squared effects were highly significant demonstrating that the change from baseline in the total YBOCS has a relationship which has a strong linear component with some curvature. What is especially noteworthy is the significant Dose by Week interaction which demonstrates that the 4 dose levels differ in their linear component. The marginally significant (p=0.0988) Dose by Week squared interaction indicates that the dose levels have slight differences in the degree of curvature in response function.

Table 4
Summary of the Full Model Used in the
Random Coefficient Regression Analysis

Source	df	Type III F-test	p-value
Dose	3	1.68	0.1688
Invest.	12	1.30	0.2120
Week	1	82.35	0.0001
$Week^2$	1	32.11	0.0001
Dose by Week	3	5.55	0.0009
Dose by Wk^2	3	2.90	0.0988

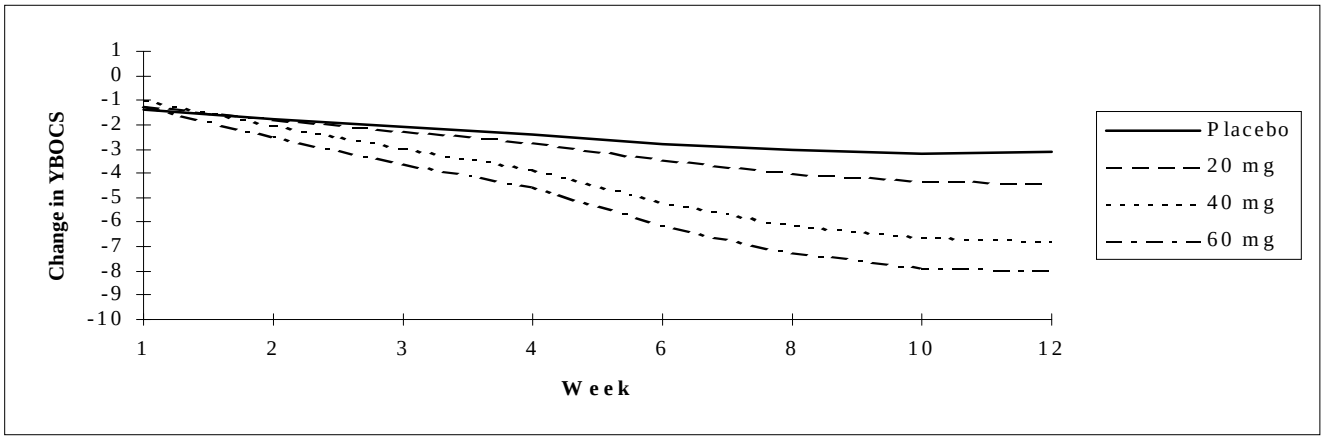
The parameter estimates and test of effects shown in Table 5 were generated from a no intercept model. The intercepts are not significantly different from zero or each other. The linear slope parameters were tested in a pairwise manner and the result is consistent with previous analyses in that the dose levels were ordered in effectiveness as 60mg, 40mg, 20mg, and 0mg with both the 40mg and 60mg dose group having significantly steeper slopes that the 0mg (placebo) dose group. The response functions are shown in graphical form in Figure 2. The rates of improvement tend to level off near the end of the study as reflected in the parameter estimates for the quadratic effect. The estimates for the quadratic parameters for the higher dose groups are numerically greater as the greater rate of initial improvement requires more curvature as the response begins to flatten.

Table 5
Summary of Random Coefficient Regression Analysis
Intent to Treat Population - PAR116

	Regression parameter estimates(se)		
Treatment	Intercept	Linear	Quadratic
Placebo	-0.994 (0.44)	-0.427 (0.20)	0.021(0.014)
20 mg	-0.651 (0.46)	-0.612 (0.20)	0.025 (0.014)
40 mg	0.121 (0.45)	-1.185 (0.20)	0.051 (0.014)
60 mg	0.162 (0.46)	-1.431 (0.21)	0.063 (0.014)
Pair-wise p-values			
pla v 20	- -	0.5070	- -
pla v 40	- -	0.0072*	- -
pla v 60	- -	0.0004*	- -
20 v 40	- -	0.0450	- -
20 v 60	- -	0.0044*	- -
40 v 60	- -	0.3981	- -

* Significant based on Dunnett's critical regions.

Figure 2 Graphical Display of the Improvement Function of Each Dose Group



VI Conclusion

PROC MIXED allows repeated measures analysis in the presence of missing values, assuming that the values are missing at random. The repeated measures analysis presented in this paper was valuable in establishing that the dose levels of Paxil exhibit different response profiles.

The random coefficient regression analysis is the preferred method for this study as it allows the testing of hypotheses relating to rates of improvement which have direct clinical relevance. Further, response functions are generated which can graphically depict the relationship between the four dose levels of Paxil.

References

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