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ORIGINAL PAPER

Improved statistical analysis of moclobemide dose effects on panic disorder treatment

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Abstract Clinical trials with several measurement occasions are frequently analyzed using only the last available observation as the dependent variable [last observation carried forward (LOCF)]. This ignores intermediate observations. We reanalyze, with complete data methods, a clinical trial previously reported using LOCF, comparing placebo and five dosage levels of moclobemide in the treatment of outpatients with panic disorder to illustrate the superiority of methods using repeated observations. We initially analyzed unprovoked and situational, major and minor attacks as the four dependent variables, by repeated measures maximum likelihood methods. The model included parameters for linear and curvilinear time trends and regression of measures during treatment on baseline measures. Significance tests using this method take into account the structure of the error covariance matrix. This makes the sphericity assumption irrelevant. Missingness is assumed to be unrelated to eventual outcome and the residuals are assumed to have a multivariate normal distribution. No differential treatment effects for limited attacks were found. Since similar results were obtained for both types of major attack, data for the two types of major attack were combined. Overall downward linear and negatively accelerated downward curvilinear time trends were found. There were highly significant treatment differences in the regression slopes of scores during treatment on baseline observations. For major attacks, all treatment groups improved over time. The flatter regression slopes, obtained with higher doses, indicated that higher doses result in uniformly lower attack rates regardless of initial severity. Lower doses do not lower the attack rate of severely ill patients to those achieved in the less severely ill. The clinical implication is that more severe patients require higher doses to attain best benefit. Further, the significance levels obtained by LOCF analyses were only in the 0.05–0.01 range, while significance levels of <0.00001 were obtained by these repeated measures analyses indicating increased power. The greater sensitivity to treatment effect of this complete data method is illustrated. To increase power, it is often recommended to increase sample size. However, this is often impractical since a major proportion of the cost per subject is due to the initial evaluation. Increasing the number of repeated observations increases power economically and also allows detailed longitudinal trajectory analyses.

Keywords Maximum likelihood · Analysis of covariance · Slope estimation · Panic disorder

Abbreviations

ANOVAR	Repeated measures analysis of variance
LOCF	Last observation carried forward

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Introduction

Klein and Ross [6] advocated that contrasting treatments by analysing the differences of post-treatment on pre-treatment slopes would detect whether initial severity affects degree of specific drug response. Simply testing for adjusted post-treatment mean differences when analyzing a clinical trial ignores this issue. It is usual that drug is clearly more beneficial than placebo in more severe cases. However, in less severe cases, drug is often equivalent to placebo. Therefore, if slope differences are not tested, the magnitude of drug effect is diluted. Simple analysis of variance should not be used if treatment groups have quite different slopes.

Even when observations are repeatedly taken after treatment initiation, the last obtained observation is frequently used as the sole dependent variable, despite the recognition that using all data is advisable. This practice is known as last observation carried forward (LOCF). Repeated measures analysis of variance (ANOVAR) methods that are limited to only those subjects with complete data have also been used. However, patients on placebo who can last the complete trial without dropping out, often have an atypically positive prognosis. This decreases the estimated magnitude of specific drug effect.

Traditional monoamine oxidase inhibitors (MAOIs), such as phenelzine and tranylcypromine have an established record of effectiveness in depression [15], particularly in atypical depression [11]. They also have been favored for anxiety disorder treatment, especially in Britain [13, 16]. Unfortunately, these compounds can have unacceptable adverse reactions [1, 10, 12], most seriously hypertensive crisis. This rare response results from drug induced failure to metabolize dietary tyramine (the cheese reaction). It has discouraged the use of these medications.

Moclobemide is the prototype of the new generation of reversible MAOIs. In doses as high as 1,200 mg/day its potentiation of tyramine effects is not clinically significant [3]. Tyramine competes effectively with the drug to be a substitute for the enzyme MAO. Moclobemide is a clearly effective treatment for depressive disorders [8, 10]. The evidence for its usefulness in social anxiety disorder is less uniformly positive [4, 5, 9, 14, 18]. Interestingly, an extensive search of several databases suggests that only a single small, placebo-controlled study of moclobemide in panic disorder has been published, showing no advantage over placebo [7].

To illustrate the maximum likelihood ANOVAR approach we reanalyzed a study, that used ANCOVA with LOCF, of the effects of several doses of moclobemide on panic attacks [17]. Only one other placebo controlled study of moclobemide in panic disorder has been published [7]. It showed no advantage over placebo.

The Institutional Review Board responsible for the ethical review of clinical studies at each of the original study sites approved the study. It was performed in accordance with the ethical standards laid down in 1961 Helsinki declaration. Potential candidates were selected based on a preliminary telephone interview. At the initial visit, each patient was informed in detail about the nature and procedures of the study. Any questions were answered. All persons gave written informed consent prior to being included in the study.

Patients were men and women older than the legal age of consent, generally 18 years meeting DSM-III-R criteria for panic disorder with or without agoraphobia. A score of at least 4 (moderate) on the 7-point Clinical Global Impression of panic disorder severity and at least one panic attack per week in each of the 4 weeks before baseline were required. Concurrent diagnoses of generalized anxiety disorder or social phobia (severity of less than 4) were permitted. Exclusion criteria included pregnancy or lactation, inadequate contraceptive measures, known hypersensitivity to MAOIs, any significant, unstable medical disorder; any organic psychiatric disorder, lifetime history of psychosis or bipolar disorder, obsessive–compulsive disorder, major depressive episode, or substance abuse or dependence within the past 6 months, positive drug screen (except benzodiazepines or alcohol), use of fluoxetine within 5 weeks of baseline or any other psychotropic medication within 2 weeks of baseline, and use of any investigational drug within 4 weeks of baseline. Patients taking benzodiazepines were tapered gradually to complete discontinuation. Patients were not randomized who showed more that mild improvement (score of 3 on the 7-point Clinical Impression of Change scale) after the run-in period.

Methods

All subjects with two or more observations may be used in maximum likelihood ANOVAR [1]. These computations take into account the structure of the error covariance matrix so that the sphericity assumption (that all within group variances are equal and all within groups correlations are equal) necessary for least squares analysis is obviated.

Time trends of treatment groups may be compared with respect to shape and location. As in analysis of covariance (ANCOVA), the analysis is enhanced by regressing during treatment data on initial severity level. This method and LOCF both assume that missing data are unrelated to potential outcome and that error components have a multivariate normal distribution.

Program 5 V in the BMDP package was used in the reanalysis [2]. In Uhlenhuth's [17] anaylsis, six treatment groups were collapsed into three. Placebo and 75 mg/day formed the low dose group; 150 and 300 mg/day formed the medium dose group; and 600 and 900 mg/day formed the high dose group.

Panic disorder is characterized by unexpected spontaneous attacks. Certain contexts, e.g. super markets, predispose to attacks, although their timing and even their occurrence are uncertain. Further, these attacks may be full, i.e. having a minimum of four symptoms, or limited, i.e. failing to reach the threshold of four symptoms. It is possible that the benefits of imipramine are limited to full attacks. Limited attacks may represent another process more closely related to anticipatory anxiety.

Uhlenhuth et al. did not separately analyze limited and full attacks but did separately analyze unexpected and situational attacks. The three group regression slopes of outcomes on initial severity were tested for significant differences; if there were none, the adjusted means were tested. The less steep the slope, the more efficacious the treatment for the more seriously ill patients. If all treatments have the same slope, the adjusted mean differences indicate a uniform treatment effect over the entire range of initial illness severity.

Uhlenhuth et al. found that for unexpected attacks, the low dose group had a significantly steeper slope than the high dose groups, indicating particular high dose benefit for the more severely afflicted. The medium dose group had a significantly lower adjusted mean than the low dose group. Therefore, medium doses benefited the entire range of pretreatment illness better than low dose. In both cases, the P values only equaled 0.04.

For situational attacks, the low dose group had a significantly steeper slope than both the high dose group and the medium dose group. The respective P values were 0.01 and 0.05. Particular benefit for the more severely afflicted was again indicated. Details are in Table 1.

Using maximum likelihood ANOVAR, we reanalyzed Uhlenhuth's data including intermediate observations to:

1. Study the course of improvement over time for the different treatments.
2. Illustrate the advantage of using both regression effects and multiple post-treatment observations in the analysis.
3. Retain all six original treatment groups.
4. It is clinically and heuristically useful to distinguish full unexpected attacks, limited unexpected attacks, full situational attacks, and limited situational attacks. These were analyzed separately using the number of attacks reported since the previous scheduled observation as the longitudinal dependent variable.

Table 1 Results from original analysis in Uhlenhuth et al.

Dose	Slope adjusted mean			
	Total unexpected attacks		Total situational attacks	
High	0.34	0.69	0.31	0.37
Medium	0.52	0.67	0.38	0.40
Low	0.57	0.85	0.55	0.51
Slope				
Total unexpected attacks			Total situational attacks	
Relevant significance tests				
Low versus high			Low versus high	
$P = 0.04$			$P = 0.01$	
Adjusted means			Slope	
Low versus medium			Low versus medium	
$P = 0.04$			$P = 0.05$	

The model is completely described in the "Appendix".

The design was fit hierarchically in the following order adjusting statistical testing for all preceding effects.

Effects	Degrees of freedom
Overall mean (or intercept)	1
Overall slope of post on pre scores	1
Adjusted treatment differences	5
Slope × treatment interactions	5
Overall linear trend of post scores over time	1
Overall hyperbolic trend of post scores over time	1
Linear trend × treatment interactions	5
Hyperbolic trend × treatment interactions	5

In each analysis, a reduced design was created using only the statistically significant parameters from the hierarchical testing. However, if slope × treatment interactions were significant, treatment effects were always included, even if not significant. The reduced model was tested against the full model. This indicates if anything was gained using the additional parameters.

Results

In preliminary analyses, there were no statistically significant treatment effects for either type of limited attack. Further, the results for the two types of full attack were quite similar. To simplify this presentation, we merged the full attacks data and reanalyzed.

Table 2 Analysis of variance of total full attacks

Test	*df*	χ^2	*P*
C|I	1	375.48	<0.00001
T|I,C	5	8.33	0.14
CxT|I,C,T	5	83.81	<0.00001
L|I,C,T,CxT	1	4.20	<0.00001
H|I,C,T,CxT,L	1	8.68	0.003
LxT|I,C,T,CxT,L,H	5	0.16	0.68
HxT|I,C,T,CxT,L,H,LxT	5	8.49	0.13

Test for difference between full design and (I, C, T, CxT, L, H) design is $\chi^2_{(10)} = 11.66$, $P = 0.31$

I Intercept, *C* baseline covariate, *T* treatments, *L* linear trend, *H* hyperbolic trend, | adjusted for

A model using only a common intercept, common linear and hyperbolic trends, and within treatment post on pre regression slopes fit adequately. Adding the linear and hyperbolic trend × treatment interactions did not significantly improve the fit. A square root transformation of the data to lessen positive skew yielded essentially equivalent results. Details of the raw data analysis are in Table 2.

The overall trend was towards decreasing severity during the study. Treatment main effects adjusted for regression were not significant, but there was a significant treatment × regression interaction. The highly significant overall regression on baseline effect and significant regression × treatment interactions show a general tendency for the treatments to be more effective for the most seriously afflicted patients. However, this varied between doses.

The slope for placebo is surprisingly low. Nevertheless, the slopes for the three lowest dose groups (placebo 75, 150 mg) were all steeper than the slopes for the three highest dose groups (300, 600, 900 mg.) A post hoc test for this contrast yielded $\chi^2_{(1)} = 78.19$, $P < 0.00001$. Details appear in Table 3. The significance levels of group slope differences are presented in Table 4.

Table 3 Analysis of post on pre regression slopes

Treatment	Slope
Placebo	0.62
75 mg	1.03
150 mg	0.80
300 mg	0.30
600 mg	0.45
900 mg	0.21

Contrast for mean (Placebo 75, 150 mg), mean (300, 600, 900 mg) $\chi^2_{(1)} = 78.19$, $P < 0.00001$

Table 4 Significance levels for pairwise contrasts of pre–post slopes of treatment groups

	Placebo	75 mg	150 mg	300 mg	600 mg
75 mg	0.0001				
150 mg	0.0418	0.0618			
300 mg	0.0000	0.0000	0.0000		
600 mg	0.0224	0.0000	0.0004	0.1141	
900 mg	0.0000	0.0000	0.0000	0.2836	0.0048

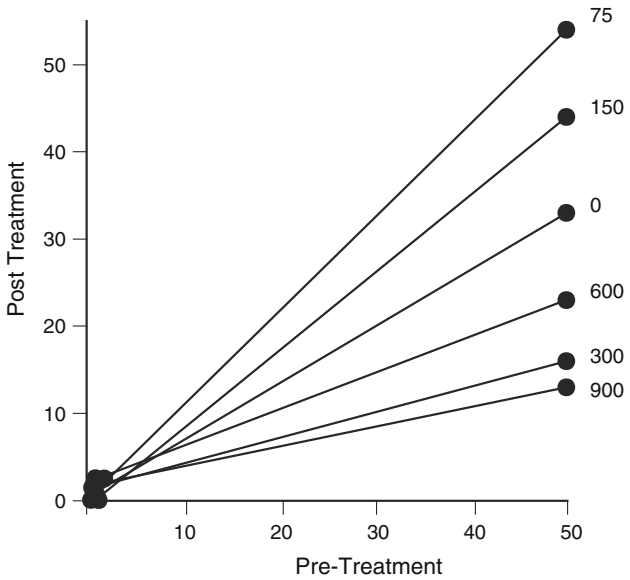

Fig. 1 Post initiation of treatment regression on pre-treatment scores

The regressions of post initiation of treatment scores on initial scores for each treatment group are presented in Fig. 1 and the common regression of post scores on time is presented in Fig. 2. The predicted score for an individual in any treatment group given the initial score and the week of treatment can be obtained from the sum of the two regressions.

Conclusions

For total full attacks, regardless of treatment, there is an overall improvement trend that includes a hyperbolic component. This indicates that degree of improvement was greatest early in treatment. However, the added contribution to the model fit is small compared to the linear trend ($\chi^2_{(1)} = 44.20$ vs. $\chi^2_{(1)} = 8.68$).

Treatment with 300 mg/day or more provides a statistically demonstrable improvement over placebo for the more seriously ill patients. There is no evidence of differential improvement over placebo for the 75 or 150 mg/day regimens.

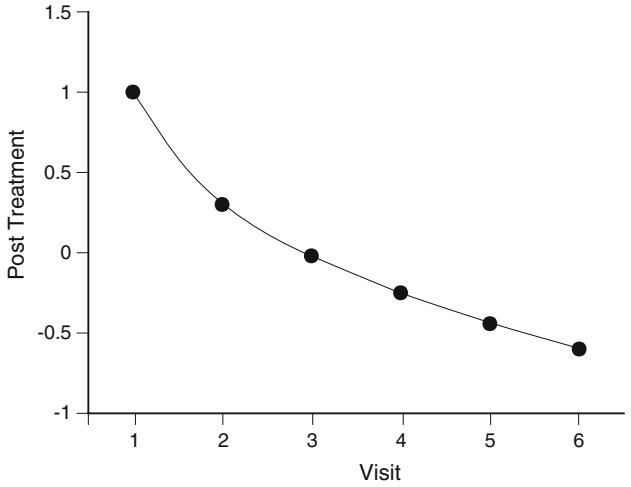

Fig. 2 Post initiation of treatment regression on visits

Discussion

In the original analysis, the most statistically significant results were at the 0.01 level. In contrast, this method found significance levels of 0.00001 illustrating the improved sensitivity obtained using all data points as well as regression effects, rather than just baseline measures and LOCF procedures.

This repeated measures approach may find general application in clinical trials since the increased power lessens the need for large samples. This need is usually met by having many sites with varying sample sizes. This substantially increases the administrative costs of site monitoring, training, personnel recruitment, etc. Further, requiring many sites increases the risk of the occasional aberrant biased site, incurring site by treatment interactions. These complicate exposition substantially and can raise doubts about the treatment having a simple indication.

Definitive proof of the superior power of this type of analysis over LOCF, or other methods, would require Monte Carlo studies. However, this paper illustrates highly enhanced power of LOCF analysis in a typical clinical trial.

Analysis of the treatment group slope differences is more informative than simple endpoint analysis. Inclusion of linear and curvilinear time trends reduces the error variance and thus improves the power of tests of other effects. There is no need to impute values for missing data and individual slopes are not estimated from partial data as is the case with random regression models.

A final scientific benefit may come from the detection of patient subsets differing in improvement trajectories as a function of treatment. It is generally believed that our syndromes are actually heterogeneous with regard to their pathophysiologies. Since the major psychotropic drugs have little effect on normal subjects (except to irrelevant toxicities) and it appears that their benefits are due to normalizing effects on pathophysiology. Differing trajectories of improvement over time may indicate differing pathophysiologies. Clearly, such analyses require detailed repeated measures for each subject.

Acknowledgments Hoffmann-LaRoche and Quintiles graciously supplied the full database from protocol #N3676A. Principal investigators are listed in Uhlenhuth et al.

Appendix

Let g index group (treatment),
i index individual,
t index time (observation).
y_{git} the post-treatment score of the ith individual in group g for post-treatment observation t
Then, the complete design tested was
$y_{git} = \mu + \alpha_g + \beta x_{gi} + \phi_g x_{gi} + \lambda l_t + \eta h_t + \gamma_g l_t + \delta_g h_t + \varepsilon_{git}$,
where
μ the overall mean (or intercept when a regression or trend is included in the design),
α_g the intercept of group g,
β the overall slope of post-treatment scores on pre-treatment scores.
x_{gi} the pre-treatment score of the ith individual in group g,
ϕ_g the slope of post-treatment scores on pre-treatment scores for group g.
λ the coefficient for the overall linear trend over the six post-treatment observations,
l_t the linear constant for observation t (scored 5, 3, 1, −1, −3, −5),
η the coefficient for the overall hyperbolic trend over the six post-treatment observations,
h_t the hyperbolic constant for observation t (scored 213, 23, −27, −57, −75, −87),
γ_g the coefficient for the linear trend for group g,
δ_g the coefficient for the hyperbolic trend for group g,
ε_{git} the random error component of the y_{git} observation.

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