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Growth Curve Models for Longitudinal Data:

Application for Psychiatric Research

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Growth Curve Models for Longitudinal Data: Application for Psychiatric Research

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Master of Science in Public Health
Rollins School of Public Health of Emory University
2013

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An abstract of the thesis submitted to the Faculty of the
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Abstract

Growth Curve Models for Longitudinal Data: Application for Psychiatric Research
By Sarah Chiodi

Background: Psychiatric researchers commonly use repeated measures ANOVAs to analyze longitudinal data with repeated measures, however growth curves provide different tests of efficacy that may be more relevant to study goals. This thesis compares these various analytical methods for establishing efficacy in the same dataset.

Methods: We utilized both complete case and available case ANOVA, as well as linear mixed model growth curves and piece-wise growth curves to determine efficacy of randomly assigned treatment.

Results: The results exhibited no significant group differences using ANOVA methods. In contrast, a significant difference was demonstrated in the added CBASP group in both the rate of change in phase two as well as the difference in slope between phases one and two, indicating both a more rapid decrease in symptomatology and a less significant slowing of the rate from phase one to phase two. This result was found when looking at only the second phase and when looking at both phases using a piece-wise growth curve model. Due to the CBASP and medications group being significantly different in both phases, one may believe it could be due to poor randomization rather than the efficacy of added CBASP.

Conclusions: Growth curve models, when accommodated (i.e. after demonstrating simple linear relationships) provide an advantage and should be the predominantly used method on longitudinal repeated measures data. When using multiple phases in a trial, piece-wise growth curve models should be the model of choice.

Keywords: Depression, Longitudinal, MMRM, repeated measures, growth curves

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Chapter 1

Introduction

1.1 Background

Depression is a debilitating disease that affects a large portion of the world population. Due to its high global impact, it is important to examine treatment options which allow patients to return to their daily lives and manage depression. Currently it has not been determined if medication, psychotherapy, or a combination of them both are the best method for treating depression. Kocsis and colleagues report that "approximately 50% of chronically depressed patients in a clinical trial fail to respond to a trial of psychotherapy or antidepressant medication (Harrison & Stewart, 1995). Along with the 50% of people who fail to respond, 20% do not obtain complete remission (Keller, et al., 1998; Thase, et al., 1996)" (Kocsis, et al., 2009).

When depression treatment using medication is not effective, one option for clinicians is to augment medication with psychotherapy. However, there is a lack of research on its benefits. A plethora of studies have been unable to find significant advantages for a combination of psychotherapy and medication compared to monotherapy for dysthymic patients (Markowitz, Kocsis, Bleiberg, Christos, & Sacks, 2005) along with patients with acute major depression (Manning, Markowitz, & Frances, 1992;Roth & Fonagy, 1996; Rush & Thase, Psychotherapies for depressive disorders: a review, 1999; Blom, et al., 2007). In

contrast, one large study by Keller et. al has determined that for chronically depressed patients a combined treatment is a better approach than monotherapy (Keller, et al., 2000).

Combination therapy is not often used in the treatment of depression. This may be due to the excess expenses that occur when psychotherapy is added onto medication treatment. A financially conservative approach would be for physicians to treat their patients with medication only first. If the patient has a poor or partial response to the medication only course of treatment, then psychotherapy may be used to augment the medication (Kocsis, et al., 2009). Several studies suggest that this approach is a useful substitute to multiple attempts of different pharmacotherapy regimens (Paykel, et al., 1999; Thase, et al., 2007).

The purpose of the REVAMP trial discussed in this thesis was to test whether therapy had an added benefit on top of medication. Comparisons of different statistical approaches to establishing efficacy were conducted in this thesis. Through statistical analyses, it can be shown whether or not adding psychotherapy at phase two increases the patient's rate of improvement. The different techniques used in this thesis will illustrate the different ways of establishing and will perhaps help shed some light on the best method to be used to analyze psychiatric data. Exploration of several different analytical methods and comparison of their results in improving efficacy were carried out.

Chapter 2

Review of Literature

2.1 The Statistical Problem

2.1.1 Repeated Measures ANOVA

One of the earliest solutions to analysis of repeated measures is to compare pre and post utilizing a 2-way (time by treatment group) ANOVA. However, this method requires a complete data set, i.e. no missing data. There are several methods which may be used to modify the data to create a complete set of data: delete all patients who having missing information (complete case) or use the last observation recorded on each subject to replace all of the missing single or multiple observations (LOCF). These methods give you different results and have different levels of bias and precision.

In order for complete case analysis to be correct (unbiased), the data must be missing completely at random (MCAR). MCAR means that the reason the data is missing is not related to the desired outcome or any of the variables that are being considered. MCAR is a subset of missing at random (MAR); MAR occurs when the data that is missing is not related to the desired outcome but may be related to the other variables that are being considered, a much easier requirement to meet. The complete case method further assumes that the people who are missing a visit are not different from the people who attended every visit.

This may be a flawed assumption. The deletion method also leads to decreased degrees of freedom and loss of possibly important information.

Another method to complete the data is the LOCF method. The LOCF method requires the data missing to be MAR. This method takes the last reported observation for the patient and carries it forward into all of the missing values after it (Mallinckrodt, Kaiser, Watkin, Molenberghs, & Carroll, 2004). The LOCF method may bias estimates of treatment effects in either direction and will underestimate the standard errors due to assuming all of the missed visits are identical to the last visit.

A repeated measures ANOVA can be run on the data once it is made complete by one of the methods mentioned above. One important fact about the repeated measures ANOVA is that both time and group are used as categorical variables, and the time points must be equally spaced. This model gives estimates of the desired outcome for each time point. Customized hypothesis tests can then be used to compare pre-post HAM-D scores across groups to establish efficacy. The 2-way ANOVA model is specified below:

$$y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + e_i$$

where i=group, j=time point, k=subject, μ= overall mean, α_i = group means, β_j = time means, γ_{ij} = group by time interaction, and $e_i \sim N(0, \sigma^2)$

Repeated measures ANOVA on a complete data set is still commonly used by clinicians due to its simplicity in both analysis and interpretations. The

biggest downside of this method is that it is missing possibly crucial information due to dropping out data or imputing data.

2.1.2 Mixed Models Repeated Measures ANOVA

The available-case linear mixed model (LMM) is referred to in clinical trials as the mixed models repeated measures ANOVA (MMRM). It uses all data that has been collected at all time points. This means that the method uses all randomized participants who have missed a few visits or have dropped out of the study which preserves the randomization process and decreases bias. Since there is missingness included in this model, there are often different numbers of participants depending on the time point, and relaxes the assumption that time points must be equally spaced due to the incorporation of random effects.

MMRM should be used when there is longitudinal dropout or subject specific effects. A subject specific effect occurs when it is expected that different subjects will exhibit different patterns. A benefit of MMRM is that it can be used when the missing data is classified as missing at random. The results of the pre-post by group test then can be used to test efficacy of treatment.

The MMRM model can include both patient-specific intercepts as well as time effects. This model incorporates the subject specific variance into the variance due to error. MMRM's mathematical representation is shown below.

For subject i:

$y_{ijk} = \beta_0 + \beta_{0i} + \beta_1 * \text{time} + b_{1i} * \text{time} + \beta_2 * \text{group} + \beta_3 * \text{time} * \text{group} + e_{jk}$

where j=time points (1, 2, 3,...), k=arm, the β's are parameter estimates,

and $e_{jk} \sim N(0, \sigma^2)$

MMRM method treats the time variable as a nominal number and is the industry standard. It is a better approach than the repeated measure ANOVA, but it essentially uses the same structure. The benefit of random effects is to allow for individual variation in the fit of intercept and slope rather than force the same pattern to all subjects. Similar comparisons of model estimates are then used to establish efficacy.

2.1.3 Growth Curve

The growth curve is a great tool for statisticians who would like to analyze rate of change over time. In order to use this method, the clinician must first plot the data and make sure a linear or curvilinear trend is a reasonable summary of the data. If time has a linear trend, then the clinician can use the group by time interaction model shown below.

For subject i:

$y_{ijk} = \beta_0 + \beta_{0i} + \beta_1 * \text{time} + b_{1i} * \text{time} + \beta_2 * \text{group} + \beta_3 * \text{time} * \text{group} + e_{jk}$

where j=time from start of study, k=arm, the β's are parameter estimates,

and $e_{jk} \sim N(0, \sigma^2)$

The growth curve method treats the time variable as continuous. This approach is very different from the ANOVA models previously discussed where

time was treated as a categorical variable. Since time is a continuous variable, the test for the significance of the time variable only involves one degree of freedom. Here time does not need to be equally spaced, but should represent the time it is suppose to represent accurately. This allows the results to be easily interpreted. For example, if visits occur at months two, four, six, and eight, then time should be two, four, six, and eight for those visits. This is simpler than the ANOVA models because there are no extra tests needed to determine the difference between multiple groups. If the data correctly fits a linear trend, a growth curve model may be a better approach to the problem and simpler to understand.

Sometimes a simple linear trend is not enough to model a complex data set. There are many growth curve adaptations that allow the researcher to create more complex models. One method is treating time not as a linear trend but as a parabolic or cubic trend. This requires modeling the time variable as $time^2$ or $time^3$respectively. The benefit of modeling time as non-linear is that it may be able to capture the trend of the data more accurately which leads to increased precision and decreased residual error.

2.1.4 Growth Curve with Piece-wise Linear Fit

Another adaptation of growth curves is to use a bent line and create knots. This is especially useful when there are at least two distinct time periods for which the slopes could be compared (for instance phases). This answers a different question about the data for establishing efficacy. More specifically, it can determine if the rate of recovery is altered by the added treatment. To test this, one needs to determine whether the slope in phase one is statistically

different than the slopes of phase two for each treatment group. In this approach, the time points where the change in slope should occur are called knots. Once those time points are decided, a new time variable can be created for each knot where for all time points before and at the knot the time variable is zero. For all points after the knot, the new time variable at each time point is defined as the time of that visit minus the time at the knot. When modeling this new variable, the different slopes per distinct time periods can be compared. The REVAMP trial design provides a unique opportunity to test these kinds of hypotheses.

2.2 The Clinical Problem

2.2.1 Disease, Symptoms, Causes

Major depressive disorder or major depression, prevents people from functioning normally and living their daily lives. According to the American Psychiatric Association, "17% of the United States will suffer with a major depressive episode at some point in their lives" (American Psychiatric Association, 2000). Although some people may experience only one episode in their life, it is more common that someone will experience many episodes over time. Common symptoms of depression are feelings of hopelessness, pessimism, guilt, worthlessness, or helplessness. Other symptoms may include irritability, restlessness, insomnia, early-morning wakefulness, excessive sleeping, overeating, appetite loss, fatigue, or decreased energy. People with depression usually report persistent sad, anxious, or empty feelings, and may have thoughts of suicide or suicide attempts. Depression may cause difficulty concentrating,

remembering details, making decisions, and enjoying activities once found pleasurable (including sex). Physical ailments such as aches or pains, cramps, headaches, or digestive problems may also be caused by depression. (American Psychiatric Association, 2000)

The most popular measure of the severity of depression is the Hamilton Depression Scale (HAM-D). This method is a 24 item survey originated in 1960 whose primary goal was to standardize the measurement of the severity of depression (Hamilton, 1960). Different from other depression rating surveys, the HAM-D is filled out by a nurse, doctor, or psychiatrist. It has been tested for inter-rater reliability and shows a higher level of accuracy than other depression scales such as Beck Depression Inventory. (Williams, 1988)

2.2.2 Medication

Antidepressants primarily work on neurotransmitters, specifically serotonin and norepinephrine. There are four types of antidepressants: Monoamine oxidase inhibitors (MAOIs), tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). It is thought that the cause of depression is either not having enough serotonin or norepinephrine, or the brain's inability to process these neurotransmitters. (Schatzberg, Cole, & DeBattista, 2010)

SSRIs are currently the first line of antidepressants. They block the reabsorption or reuptake of the neurotransmitter serotonin in the brain. SNRIs are newer and very similar to SSRIs; except that they block both serotonin and

norepinephrine reabsorption in the brain and are called dual reuptake inhibitors. SSRIs and SNRIs have fewer side effects than older tricyclics and MAOIs.

2.2.3 Counseling

There are several types of psychotherapy that can help people with mild or moderate depression. Most psychotherapy techniques occur face to face, either at the individual or group level. Some common types are interpersonal therapy (IPT) and cognitive-behavioral therapy (CBT). According to Jakobsen et. al, there is no statistical difference in the effectiveness of IPT and CBT (Jakobsen, Hansen, Simonsen, Simonsen, & Gluud, 2012).

IPT helps people work through their depression by determining and focusing on the root of their depression. The four main reasons for depression that IPT focuses on are unresolved grief, role transitions, role disputes, and interpersonal deficits.

CBT helps people restructure their negative thought patterns. This method teaches people a new, positive, and realistic way to interpret their environment and interactions. It can help people recognize what habits may be contributing to their depression. CBT can help change bad behaviors that make depression worse. Two therapies that fall within the CBT frame are cognitive behavioral analysis system of psychotherapy (CBASP) and brief supportive therapy (BSP).

CBASP focuses on a structured interpersonal problem solving algorithm. This method teaches the patient to realize negative thoughts or views are not valid but they may contribute to desired outcomes in interpersonal situations. CBASP uses

homework assignments to help teach their problem solving techniques. (McCullough, 2002) BSP emphasizes empathy, reflective listening, evoking affect, acknowledgement of patients' assets, and therapeutic optimism (Rogers, 1951; Frank & Emil, 1971).

2.2.4 Combination Therapy

For people with severe depression, psychotherapy alone may not be enough (Silva, et al., 2004). According to Hees et. al, IPT and medication outperformed a monotherapy of medication throughout clinical trials (Hees, Rotter, Ellermann, & Evers, 2013). Current research leads one to believe that combination therapy may be a better approach than monotherapy, but more research in this field is needed.

Chapter 3

Methodology

3.1 Clinical Methodology

The dataset used for this thesis, the REVAMP trial, was conducted between 2002 and 2006. The REVAMP trial had two twelve-week phases. Throughout the first phase, patients received antidepressant medication based on the pharmacotherapy algorithm. Response was evaluated throughout this phase and it was determined if the patient was a remitter, partial responder (PR), or non-responder (NR). Patients who achieved less than remission (NR, PR) were randomized into phase two. Remission criterion are met when the patient no longer meets the DSM-IV criteria for major depressive disorder for two consecutive visits occurring within weeks six through twelve, has a 24-item HAM-D total score less than eight, and has a greater than sixty percent reduction in their HAM-D total score.

Throughout phase two, all subjects (patients who did not show full response in phase one) received the next step treatment in the pharmacotherapy algorithm. Along with an augmentation to their medication, they were randomized into one of the three treatment cells in a 2:2:1 ratio. The first treatment group had CBASP added along with their medication. The second treatment group had BSP added along with their medication. The third treatment group continued taking medication alone.

The REVAMP trial was based at eight academic centers; patients were recruited through advertising and clinicians. To be included in the study, patients had to have depressive symptoms for more than two years without remission and a current major depression episode, defined by DSM-IV, for at least four weeks. Patients were between 18 and 75 years old, had scored at least 20 on the 24-item HAM-D at baseline, understood the requirements of the study, fluently spoke and understood English, and signed the informed consent.

The response algorithm used in this study was based on empirically created algorithms such as the Texas Medication Project (Crismon, et al., 1999) and other expert approaches (Thase & Rush, When at first you don't succeed: sequential strategies for antidepressant nonresponders, 1997; Rush & Thase, Strategies and tactics in the treatment of chronic depression, 1997; Depression Guideline Panel, 1993; American Psychiatric Association, 2000). This algorithm was closely related to the algorithms used in the STAR*D study (Fava, et al., 2003). The sequence included sertraline hydrochloride and escitalopram oxalate, two selective serotonin reuptake inhibitors (SSRIs), and newer substitutes to SSRIs such as venlafaxine and lithium.

CBASP and BSP were administered 16 to 20 sessions throughout phase two to the patients in their respective treatment groups. During the first four weeks, the psychotherapy was administered twice weekly. During weeks 5 through 12, the psychotherapy was administered weekly.

Patients in the REVAMP trial were evaluated every 2 weeks. At each visit, pharmacotherapists asked patients how well they adhered to the treatment and to

return unused pills. Patients were given packets of pills containing their daily dose for the two weeks between visits. If a patient was intolerant to a medication during the first four weeks of the trial, they could be moved to the next level of the sequence. The reasoning behind this was to lower attrition rates.

3.2 Modeling

The HAM-D scores at each visit were used as the random variable of interest. Two questions were considered in this research. The first question is if the combination of medication and therapy proves to be more effective than medication alone. The second question is if the addition of therapy onto medication changes the trajectory of depressive symptoms, i.e. does it increase the rate of remission. The second question is the topic of this thesis and also of interest to psychiatric researchers.

In our models, we consider time, group, and their interaction as the primary predictors. There are seven time points in phase one and seven time points in phase two, with an overlap where the last visit of phase one is the first visit of phase two. Group has three levels throughout both phases: CBASP and medication, BSP and medication, and medication alone. The difference between the models is how time is treated. The first four models will only look at phase two and the last model will consider the change in slope from phase one to phase two in order to compare the treatment groups.

The first two models that were run on phase two data were a repeated measures ANOVA. In order to use a repeated measures ANOVA, the data needs

to be made complete. For model one, all patients with missing data were deleted to make the complete case data set which was then used to run the analysis. For model two, the LOCF method was used to complete the data. Although this is a biased analysis, it is still often used and still currently approved by the FDA.

The third model run on the phase two data was a MMRM model using a random intercept; it is less biased because it uses all the data. This approach is the more recent clinical trials standard.

The fourth model used on the phase two data was a growth curve analysis using random intercept and random slope. This models time as a continuous variable and specifically tests the differences in slopes between groups as opposed to just comparing pre-post.

Phase one and phase two data were then used to answer the second question of whether the addition of psychotherapy to medication increases the rate of the improvement in the HAMD-D score. For this model, a piece-wise growth curve analysis was fit with a knot at twelve weeks using random intercept, random phase one slope, and random difference between phase two slope and phase one slope. Week twelve is the last visit of phase one and was considered baseline for phase two. This model allows the comparison of the slopes of the different groups before and after therapy was added.

The piecewise fit for our data would have a design matrix comprised of four columns (intercept, phase, time, and time-post); the current data resemble the following matrix:

$$\begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 2 & 0 \\ 1 & 1 & 4 & 0 \\ 1 & 1 & 6 & 0 \\ 1 & 1 & 8 & 0 \\ 1 & 1 & 10 & 0 \\ 1 & 1 & 12 & 0 \\ 1 & 2 & 14 & 2 \\ 1 & 2 & 16 & 4 \\ 1 & 2 & 18 & 6 \\ 1 & 2 & 20 & 8 \\ 1 & 2 & 22 & 10 \\ 1 & 2 & 24 & 12 \end{bmatrix}$$

Chapter 4

Results

The ANOVA methods did not demonstrate a significant difference between groups overall. In contrast, growth curve analysis shows a significant difference in the CSABP added group, evidenced by the higher rate of change (2.54 pts/month compared to 2.00 and 1.81). In addition, a direct test of the change in slope for phase two resulted in none of the three groups experiencing an increase in rate, which we had hypothesized. In fact, the data indicated that all three groups experienced a slowing down of the response in phase two, with the CBASP arm change significantly smaller than the other two groups. However, this was most likely due to the fact that they had an increased rate of recovery in phase one, which would not be expected, given the groups were randomized into phase two. In other words, the three groups ideally should have been similar in both severity and rate of change in phase one.

The slope estimates were significant in all models which ensure that the HAM-D scores did change significantly over time. Overall, HAM-D scores fell for all groups throughout all treatments as predicted by previous research on the efficacy of medication.

Both of the repeated measures ANOVAs did not find the variable group significant by itself or interacting with time. The complete case analysis did not find a large difference between the treatment groups. The complete case repeated measures model should not be used in the clinical research setting

because it deletes important information which may have led to the variable group being an important covariate.

The last observation carried forward method found a greater difference between the groups than the complete case method, but the difference was still not significant. The results of this method resembled the MMRM more than the complete case analysis method, implying that the approach taken to complete the data may give similar results for many cases. Similar to the last observation carried forward method; MMRM did not find the variable group significant by itself or interacting with time.

The growth curve model found the group by time interaction to be significant. This most likely occurred since time is now considered a continuous variable as it should be, due to its linearity. Growth curve analysis is a more sensitive test than pre-post comparisons. Growth curves should be the leading analysis tool (over repeated measures ANOVA and MMRM) when time can be treated as linear.

The ANOVA results, both complete case, last observation carried forward, and MMRM did not show significant group differences in efficacy as evidenced by pre post comparison.

Chapter 5

Conclusions

The piece-wise growth curve model answered the important question of whether adding therapy to medication decreases HAM-D scores in a patient. The piece-wise growth curve showed a difference between groups in rates of change when comparing phase two to phase one. The comparison of analyses indicated that growth curves, which assess changes in slope, can provide significantly different results, due to the more sensitive nature of changes in rate as opposed to overall change. However, the comparison of rates across phases did not result in increases in recovery rates as expected, but uncovered a possible flaw in randomization into phase two.

Using only phase two loses important data which may lead to different conclusions about the study. The piece-wise growth curve may be slightly more computationally difficult, but allows the researcher to answer important questions and can look at changes in rates of recovery between phases.

This research shows that although repeated measures ANOVA and MMRM are favored among psychology researchers, growth curve analyses should be considered often. Growth curve models allow time to be modeled not only as continuous but also as separate pieces (bent lines and knots), parabolic shapes, and cubic shapes. These adaptations allow the model to answer more complex questions of the data giving better and possibly significant results.

There is no evidence from this study that augmentation with therapy provides a therapeutic benefit. However, the study design which required both significant previous nonresponse to be eligible and an additional twelve weeks of treatment prior to the testing phase may have left little room for improvement due to the added treatments. Thus, it is still not clear from this study if the added treatment could provide a benefit either in more generalizable sample or in a much larger study where smaller effects would be detected.

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Tables and Figures:

Table 1: Phase 2 HAM-D Score

Group	Week							Model Estimates			
								Complete Case	LOCF	MMRM	Growth Curve
	0	2	4	6	8	10	12	Change in Phase 2	Change in Phase 2	Change in Phase 2	Rate of Change (points/ Month)
Meds Only Mean (SD)	(N=96) 18.28(7.94)	(N=92) 16.82(9.21)	(N=85) 15.27(9.46)	(N=80) 13.74(7.97)	(N=84) 13.71(8.54)	(N=79) 13.66(8.52)	(N=76) 12.28(8.44)	5.48	4.98	6.00	1.81
BSP + Meds Mean (SD)	(N=195) 19.45(8.30)	(N=181) 18.14(8.99)	(N=176) 17.24(8.04)	(N=170) 16.28(8.70)	(N=168) 15.08(8.26)	(N=163) 14.94(9.38)	(N=168) 12.77(8.45)	7.04	6.02	6.68	2.00
CBASP + Meds Mean (SD)	(N=189) 19.72(8.35)	(N=189) 17.61(8.13)	(N=183) 16.94(8.92)	(N=176) 14.85(8.57)	(N=173) 14.42(8.65)	(N=170) 13.18(8.36)	(N=174) 11.29(8.30)	7.94	7.50	8.43	2.54

Figure 1:

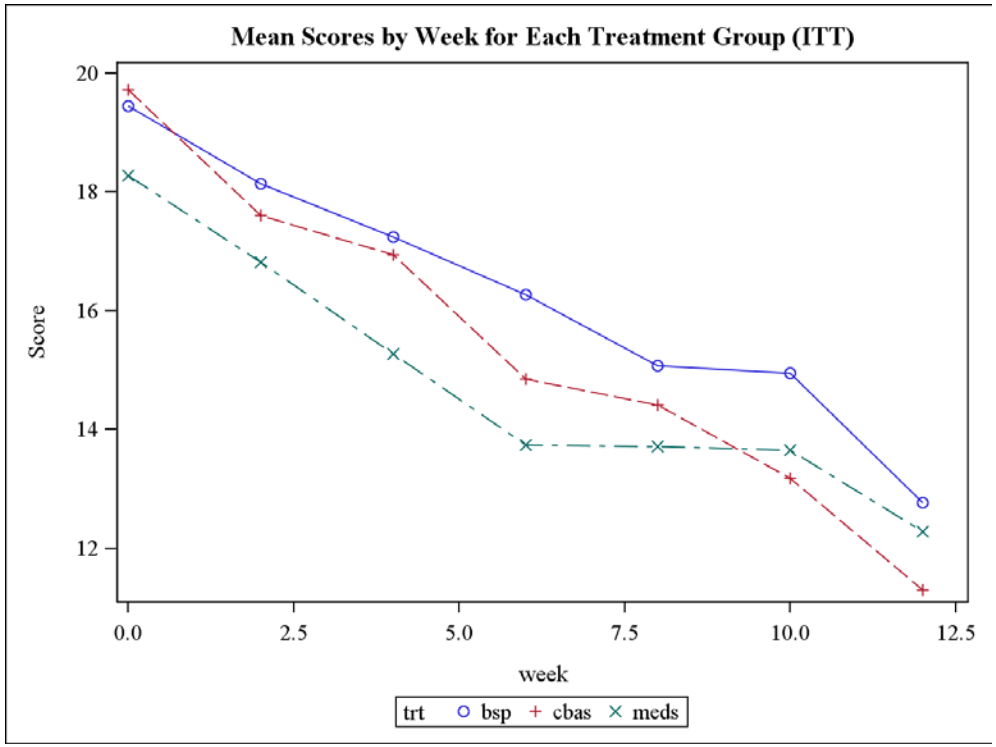
Mean Scores by Week for Each Treatment Group (ITT)
Score
20
18
16
14
12
0.0
2.5
5.0
7.5
10.0
12.5
week
trt
bsp
cbas
meds

Table 2: Model Results on Phase 2 data

Model	Group	Time	Group*Time
Complete Case Repeated Measures ANOVA	$F_{2,347}$=1.32 P=0.2697	$F_{6,2082}$=60.40 P<0.0001	$F_{12,2082}$=1.11 P=0.3473
LOCF Repeated Measures ANOVA	$F_{2,487}$=0.74 P=0.4762	$F_{6,2922}$=80.38 P<0.0001	$F_{12,2922}$=1.44 P=0.1395
MMRM	$F_{2,2568}$ =1.09 P=0.3363	$F_{6,2568}$ =78.07 P<0.0001	$F_{12,2568}$ =1.41 P=0.1556
Growth Curve	$F_{2,2107}$ =1.77 P=0.1698	$F_{1,476}$ =303.21 P<0.0001	$F_{2,2107}$ =3.54 P=0.0292

4.2 Comparisons of Treatment Groups Between Phases

Table 3: Phase 1 HAM-D Scores

Group	Week							Rate of decrease in HAMD (slope) (points/ month)	Change at 12 Weeks
	0	2	4	6	8	10	12		
Meds Only Mean (SD)	(N=79) 27.13 (5.38)	(N=96) 22.89(7.51)	(N=95) 20.40(7.09)	(N=95) 18.83(7.21)	(N=91) 17.86(7.53)	(N=68) 16.35(7.68)	(N=67) 15.34(6.93)	2.84	8.51
BSP + Meds Mean (SD)	(N=158) 28.11(5.93)	(N=192) 22.99(7.13)	(N=192) 21.54(7.78)	(N=188) 20.09(8.07)	(N=192) 19.07(7.79)	(N=149) 17.56(7.23)	(N=141) 16.82(7.78)	2.52	7.55
CBASP + Meds Mean (SD)	(N=160) 27.81(5.36)	(N=195) 22.87(5.36)	(N=194) 21.11(7.65)	(N=187) 19.19(7.07)	(N=193) 19.69(7.68)	(N=141) 17.51(7.33)	(N=138) 16.99(8.06)	2.32	6.94

Table 4: Phase 2 HAM-D Scores (Using Combined Phase Models)

Group	Week						Change in slope after phase 1 (points/ month)	Change in Phase 2
	14	16	18	20	22	24		
Meds Only Mean (SD)	(N=92) 16.82(9.21)	(N=85) 15.27(9.46)	(N=80) 13.74(7.97)	(N=84) 13.71(8.54)	(N=79) 13.66(8.52)	(N=76) 12.28(8.44)	1.82	3.05
BSP + Meds Mean (SD)	(N=181) 18.14(8.99)	(N=176) 17.24(8.04)	(N=170) 16.28(8.70)	(N=168) 15.08(8.26)	(N=163) 14.94(9.38)	(N=168) 12.77(8.45)	1.24	3.82
CBASP + Meds Mean (SD)	(N=189) 17.61(8.13)	(N=183) 16.94(8.92)	(N=176) 14.85(8.57)	(N=173) 14.42(8.65)	(N=170) 13.18(8.36)	(N=174) 11.29(8.30)	0.56	5.25

Figure 2:

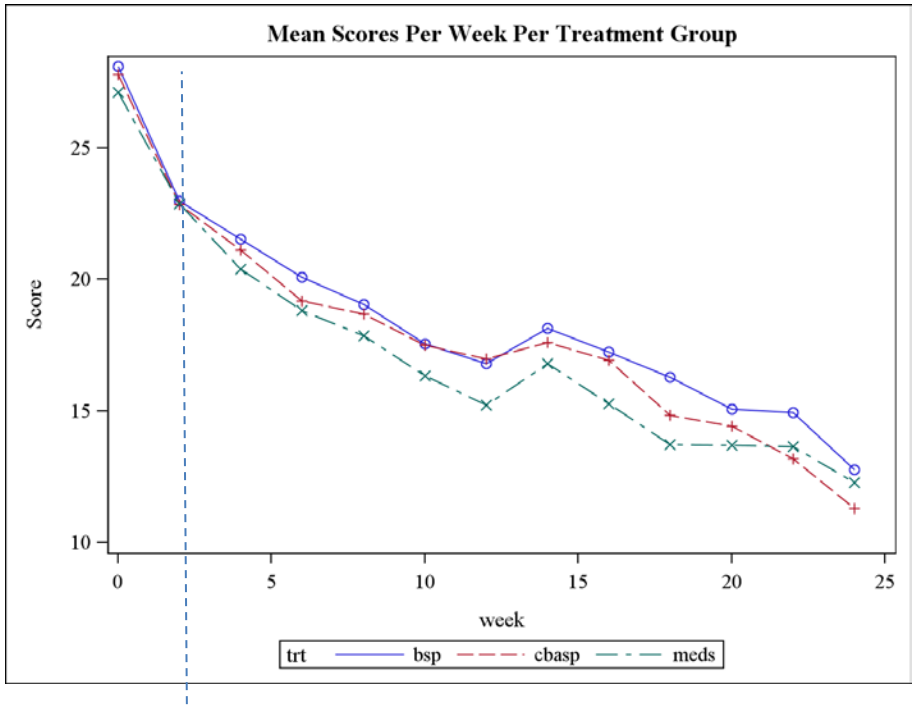

Table 5: Piece-wise Growth Curve Analysis Results

Variable	F Statistic	P-value
Group	0.55	0.5758
Time	607.48	<0.0001
Group*Time	1.89	0.1505
Time-post phase1	53.52	<0.0001
Group*time-post phase1	4.65	0.0096

Appendix:

SAS Code

```
*************************************************************************;
*
* Name: Sarah Chiodi
* Data: Thesis Data (Depression)
* Purpose: Cleaning the Data and Running analyses
* Created: 2/05/2013
* Edited: 4/22/2013
*
*************************************************************************;

libname raw "H:\Thesis\data";

*renaming the missing data to SAS missing variable;
data ham;
      set raw.ham;
      if score="-" then score=.;
run;

*creating a work dataset for randomization data;
data rand;
      set raw.rand;
run;

*combining HAMD data and randomization data;
data all;
      retain id phase arm;
      format outcome 3.;
      merge rand ham;
      by id;
      outcome=score;
run;

*creating a permanent data set;
/*data raw.all;*/
/*    set all;*/
/*run;*/

proc sort data=all; by id phase week; run;

*deleting all of phase 0 and keeping phase 2;
data phase2a;
      set all;
      by id phase week;
      if phase=0 then delete;
      last=last.phase;
      if (phase=1 and last.phase) then phase=2;
      if phase=2;
run;
```

```
proc sort data=phase2a; by id phase; run;

*creating the baseline for phase 2;
data phase2;
      retain id phase week;
      format time 2.;
      set phase2a;
      by id;
      if first.id then week=0;
      if arm=4 then delete;
      if score="-" then score=.;
      time=week*1;

run;

*creating the itt data set using the complete phase 2 data set;
data phase2itt;
      set phase2;
      if arm=. then delete;
run;

data raw.phase2itt;
      set phase2itt;
run;

*making data wide format to do summary statistics on;
data baselineitt;
      set phase2itt;
      format score1 3.;
      if week=0;
      score1=score;
      n=sum(id);
      keep id score1 arm phase week;
run;

data week1itt;
      set phase2itt;
      format score2 3.;
      if week=2;
      score2=score;
      keep id score2 arm phase week;
run;

data week2itt;
      set phase2itt;
      format score3 3.;
      if week=4;
      score3=score;
      keep id score3 arm phase week;
run;

data week3itt;
      set phase2itt;
      format score4 3.;
      if week=6;
      score4=score;
```

```
      keep id score4 arm phase week;
run;

data week4itt;
      set phase2itt;
      format score5 3.;
      if week=8;
      score5=score;
      keep id score5 arm phase week;
run;

data week5itt;
      set phase2itt;
      format score6 3.;
      if week=10;
      score6=score;
      keep id score6 arm phase week ;
run;

data week6itt;
      set phase2itt;
      format score7 3.;
      if week=12;
      score7=score;
      keep id score7 arm phase week;
run;

data phase2_wideitt;
      merge baselineitt(in=a) week1itt week2itt week3itt week4itt
week5itt week6itt rand;
      by id;
      if a;
      if (score2=. and score3=. and score4=. and score5=. and score6=.
and score7=.) then flag=1;
run;

*making the wide itt format permanent;
/*data raw.phase2_wideitt;*/
/*    set phase2_wideitt;*/
/*run;*/



***********Analyzing the means of each visit for phase 2************;
*creating the medication only group;
data med;
      set raw.phase2_wideitt;
      if arm=3;
run;

*finding the means per visit for the medication only group;
proc means data=med noprint;
      var score1 score2 score3 score4 score5 score6 score7;
      output out=medonlymeans mean=score1_m score2_m score3_m score4_m
score5_m score6_m score7_m;
run;
```

```
*creating the bsp and medication group;
data bsp;
      set raw.phase2_wideitt;
      if arm=1;
run;

*finding the means per visit for the bsp and medication group;
proc means data=bsp noprint;
      var score1 score2 score3 score4 score5 score6 score7;
      output out=bspmeans mean=score1_m score2_m score3_m score4_m
score5_m score6_m score7_m;
run;

*creating the cbasp and medication group;
data cbasp;
      set raw.phase2_wideitt;
      if arm=2;
run;

*finding the means per visit for the cbasp and medication group;
proc means data=cbasp noprint;
      var score1 score2 score3 score4 score5 score6 score7;
      output out=cbaspmeans mean=score1_m score2_m score3_m score4_m
score5_m score6_m score7_m;
run;

*transposing the data so it can be combined;
proc transpose data=medonlymeans out=meds_t;var score1_m score2_m
score3_m score4_m score5_m score6_m score7_m; run;
proc transpose data=bspmeans out=bsp_t; var score1_m score2_m score3_m
score4_m score5_m score6_m score7_m; run;
proc transpose data=cbaspmeans out=cbasp_t; var score1_m score2_m
score3_m score4_m score5_m score6_m score7_m;run;

*giving each new transposed data set a treatement;
data meds_t; set meds_t; trt='meds'; run;
data bsp_t ; set bsp_t; trt='bsp'; run;
data cbasp_t; set cbasp_t; trt='cbasp';  run;

*combining the mean scores for each group into a data set;
data arm (rename=(col1=Score));
      set meds_t bsp_t cbasp_t;
      by _Name_;
            if _Name_='score1_m' then week=0;
            if _Name_='score2_m' then week=2;
            if _Name_='score3_m' then week=4;
            if _Name_='score4_m' then week=6;
            if _Name_='score5_m' then week=8;
            if _Name_='score6_m' then week=10;
            if _Name_='score7_m' then week=12;
            drop _Name_;
run;
proc sort data=arm; by trt; run;

title "Mean Scores by Week for Each Treatment Group (ITT)";
proc sgplot data=arm;
      series x=week y=score/ group=trt;
```

```
      scatter x=week y=score/ group=trt;
run;

**********Complete Case Analysis**********;
*running a repeated measures ANOVA using complete case method;
title "Complete Case GLM";
proc glm data=raw.phase2_wideitt;
      class arm;
      model score1-score7=arm/ solution;
      repeated time;
run;

**********LOCF**********;
proc sort data=raw.phase2_wideitt out=locfitt; by id; run;

*creating a complete data set using the LOCF method;
data locfitt;
      set locfitt;
      if last.id and week=0 then delete;
      if score2=. then score2=score1;
      if score3=. then score3=score2;
      if score4=. then score4=score3;
      if score5=. then score5=score4;
      if score6=. then score6=score5;
      if score7=. then score7=score6;
run;

*running a repeated measures ANOVA using the LOCF method;
title "LOCF GLM";
proc glm data=locfitt;
      class arm;
      model score1-score7=arm/ solution;
      repeated time;
run;

**********Available Case Analysis**********;
*recoding the baseline for phase 2 as week 14, so it will be the
reference group;
data phase2itt;
      set raw.phase2itt;
      week2=week;
      if week2=0 then week2=14;
run;


*running a MMRM;
title "MMRM using random";
proc mixed data=phase2itt;
      class id week2 arm;
      model outcome=week2 arm week2*arm/s;
      random int/subject=id;
run;

**********Growth Curve Analysi**********;

*running the growth curve model;
title "Growth Curve Model (random interecept and random slope)";
```

```
proc mixed data=raw.phase2itt;
      class id arm;
      model outcome=time arm time*arm/s;
      random int time/ subject=id;
      estimate 'cbaspvbsp_int' arm 1 -1 0;
      estimate 'cbaspvbsp_slp' arm*time 1 -1 0;
      estimate 'cbaspvbsp' arm 1 -1 0 arm*time 1 -1 0;
run;

**********Both Phases: Plots**********;

*creating the data set for phase 1 and phase 2 for all ITT patients;
data all;
      retain id phase week;
      format time 2.;
      set raw.all;
      if phase=0 then delete;
      if phase=9 then delete;
      if arm=. then delete;
      time=week*1;
      if arm=4 then delete;
      if phase=2 then time=time+12;
run;

**********Plotting the means of the visits**********;
proc sort data=all; by time; run;

*creating the medication only group;
data med_all;
      set all;
      if arm=3;
run;
proc sort data=med_all; by id time; run;
proc transpose data=med_all out=meds_all;
by id;
id time;
var outcome;
run;

*creating the cbasp and medication group;
data cbasp_all;
      set all;
      if arm=2;
run;
proc sort data=cbasp_all; by id time; run;
proc transpose data=cbasp_all out=cbasps_all;
by id;
id time;
var outcome;
run;


*creating the bsp and medication group;
data bsp_all;
      set all;
      if arm=1;
run;
```

```
proc sort data=bsp_all; by id time ; run;
proc transpose data=bsp_all out=bsps_all;
by id;
id time;
var outcome;
run;

*finding the means for each visit for the medication only group;
proc means data=meds_all;
      var _0 _2 _4 _6 _8 _10 _12 _14 _16 _18 _20 _22 _24;
      output out=medallmeans mean=score0_m score2_m score4_m score6_m
score8_m score10_m score12_m score14_m score16_m score18_m score20_m
score22_m score24_m;
run;

*finding the means for each visit for the cbasp and medication group;
proc means data=cbasps_all print;
      var _0 _2 _4 _6 _8 _10 _12 _14 _16 _18 _20 _22 _24;
      output out=cbaspallmeans mean=score0_m score2_m score4_m score6_m
score8_m score10_m score12_m score14_m score16_m score18_m score20_m
score22_m score24_m;
run;

*finding the means for each visit for the bsp and medication group;
proc means data=bsps_all print;
      var _0 _2 _4 _6 _8 _10 _12 _14 _16 _18 _20 _22 _24;
      output out=bspallmeans mean=score0_m score2_m score4_m score6_m
score8_m score10_m score12_m score14_m score16_m score18_m score20_m
score22_m score24_m;
run;

*transposing data for all groups so they can be merged;
proc transpose data=medallmeans out=medsall_t;
var score0_m score2_m score4_m score6_m score8_m score10_m score12_m
score14_m score16_m score18_m score20_m score22_m score24_m;
run;

proc transpose data=bspallmeans out=bspall_t;
var score0_m score2_m score4_m score6_m score8_m score10_m score12_m
score14_m score16_m score18_m score20_m score22_m score24_m;
run;

proc transpose data=cbaspallmeans out=cbaspall_t;
var score0_m score2_m score4_m score6_m score8_m score10_m score12_m
score14_m score16_m score18_m score20_m score22_m score24_m;
run;

*giving each group their treatment names;
data medsall_t; set medsall_t; trt='meds'; run;
data bspall_t ; set bspall_t; trt='bsp'; run;
data cbaspall_t; set cbaspall_t; trt='cbasp'; run;
proc sort data=bspall_t; by _Name_; run;
proc sort data=cbaspall_t; by _Name_; run;
proc sort data=medsall_t; by _Name_; run;

*combining the data for all treatment groups;
data arm2 (rename=(col1=Score));
```

```
      set cbaspall_t medsall_t bspall_t;
      by _Name_;
            if _Name_='score0_m' then week=0;
            if _Name_='score2_m' then week=2;
            if _Name_='score4_m' then week=4;
            if _Name_='score6_m' then week=6;
            if _Name_='score8_m' then week=8;
            if _Name_='score10_m' then week=10;
            if _Name_='score12_m' then week=12;
            if _Name_='score14_m' then week=14;
            if _Name_='score16_m' then week=16;
            if _Name_='score18_m' then week=18;
            if _Name_='score20_m' then week=20;
            if _Name_='score22_m' then week=22;
            if _Name_='score24_m' then week=24;
            drop _Name_;
run;
proc sort data=arm2; by trt week; run;

title "Mean Scores Per Week Per Treatment Group";
proc sgplot data=arm2;
      series x=week y=score/ group=trt;
      scatter x=week y=score/ group=trt;
run;

***************Growth Curve with Spline for ITT****************;
*creating the data set to be used for piece-wise growth curve analysis;
data bothphases;
      set all;
      timepost=0;
      if time>12 then timepost=time-12;
run;

proc sort data=bothphases; by time; run;

*running a piece-wise growth curve model;
title "Growth Curve Model (just random intercept and slope with time)";
proc mixed data=bothphases;
      class id arm;
      model outcome=timepost time arm time*arm arm*timepost/s;
      random int time/ subject=id;
run;
```