Longitudinal Data Analysis by Example

Fares Qeadan, Ph.D

Department of Internal Medicine

Division of Epidemiology, Biostatistics, & Preventive Medicine
University of New Mexico Health Sciences Center

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- Longitudinal Data Analysis

  - Definitions: *Longitudinal vs. Time series*
  - Data Structure
  - Properties of Longitudinal Data
  - Graphical visualization
  - Modeling strategies
  - Mixed Effects Modeling
  - Model selection

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- Example: Beating the Blues

    - Background
    - Research Questions
    - Selecting the Covariance Structure
    - Analysis for Research Questions
    - Pitfalls
    - Inference on Individuals

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Longitudinal Studies:

Studies in which subjects' outcomes and possibly treatments or exposures are measured at multiple follow-up times and thus their statistical analysis constitutes an analysis of intra- and inter-individual variation [1].

- Results generalize across the population from which the sample of subjects was drawn

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Time Series Studies:

Studies that pertain to the sequential behavior of a single subject (or any unitary entity) and thus their statistical analysis constitutes an analysis of intra-individual variation [2].

- Results do not generalize across some population of subjects but instead generalize across the time domain.

Example: Studying the number of Upper Urinary Tract Stones among adults in New Mexico over time.

Standard plot from Longitudinal data: Spaghetti plot of individual patient-specific longitudinal relationships between Hamilton Depression Scores (HD) and time for each subject[1].

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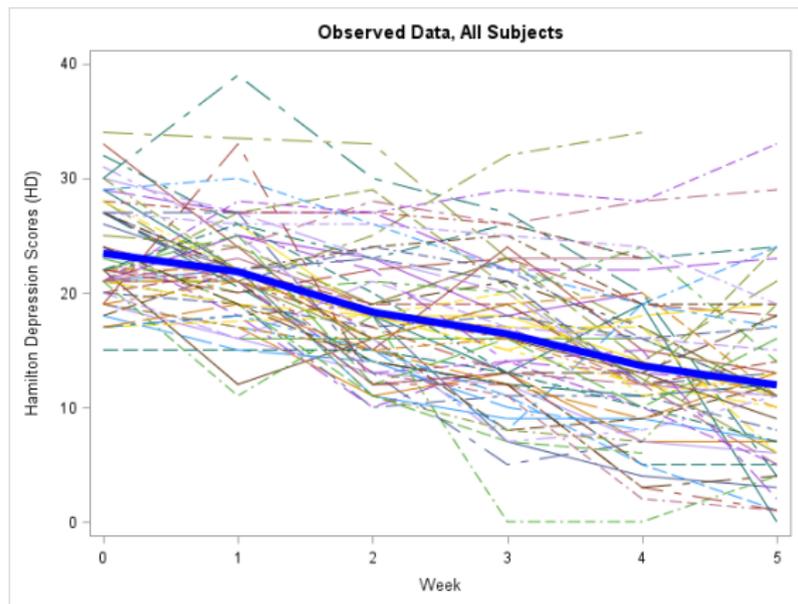
[1]This figure was generated from a data set taken from [3].

Standard plot from a Time Series data: Plot of the number of Upper Urinary Tract Stones by time for adults in New Mexico through the UNM network[2].

Smoothed Trend for Stones

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Data Structure for Longitudinal Studies: Longitudinal data files have two types of structure (Long and Wide). However, usually wide (broad) format (one row per subject) are converted to long format (one row for each time point by subject combination)[5].

"long" data structure

Data for subject 1

ID	Y	time	X_4
1	3.5	1	1
1	3.7	2	1
1	3.9	3	1
1	3.0	4	1
1	3.2	5	1
1	3.2	6	1
2	4.1	1	1
2	4.1	2	1
.			
.			
N	5.0	5	2
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"broad" data structure

ID	Y_{t1}	Y_{t2}	Y_{t3}	Y_{t4}	Y_{t5}	Y_{t6}	X_4
1	3.5	3.7	3.9	3.0	3.2	3.2	1
2	4.1	4.1	4.2	4.6	3.9	3.9	1
3	3.8	3.5	3.5	3.4	2.9	2.9	2
4	3.8	3.9	3.8	3.8	3.7	3.7	1
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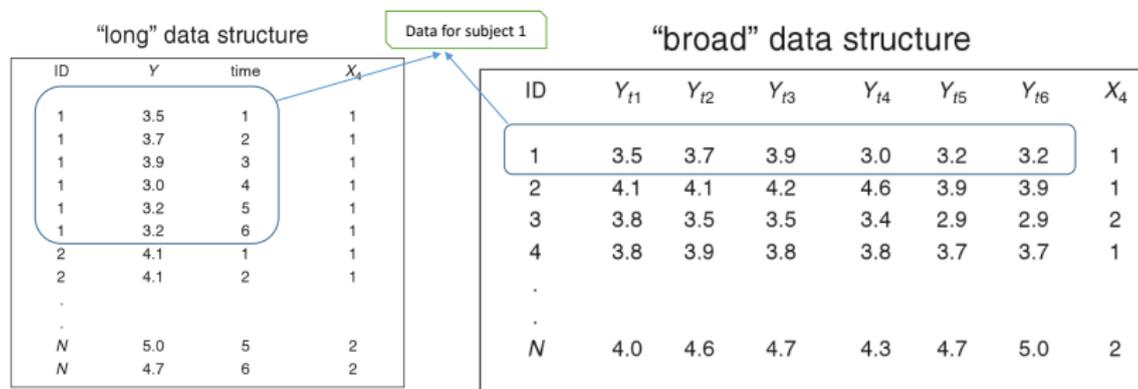
Remark 1. Longitudinal data, that follow one subject's changes over the course of time make a time series.

Remark 2. Longitudinal data generally are associated with a limited number of time points whereas time series data can entail a large number of repetitive occasions [6].

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- Robust to missing data and irregularly spaced measurement occasions (only if Mixed effect modeling was used) [8]

Graphical visualization of Longitudinal Data:

- Spaghetti plots (overall, by treatment or other covariates of interest)
- Box-plots by time (overall, by treatment or other covariates of interest)
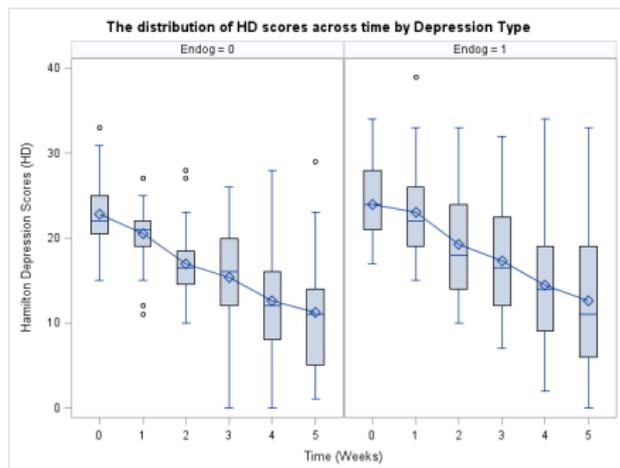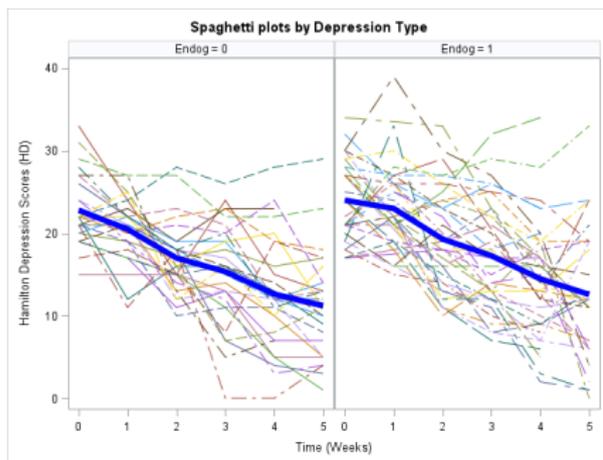
Graphical visualization of Longitudinal Data (continued):

- Mean profiles (overall, by treatment or other covariates of interest)
- Scatterplot Matrix of the response at the different time points.

Mean Profiles for Depression Types

Scatterplot Matrix of HD scores at the different time points
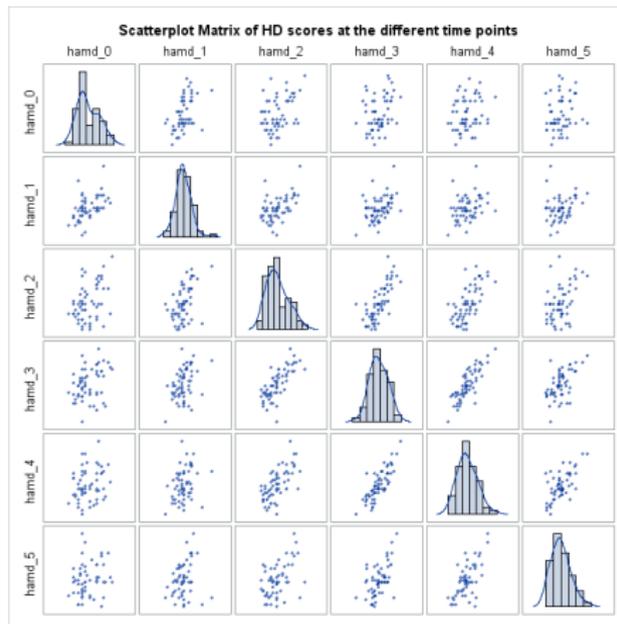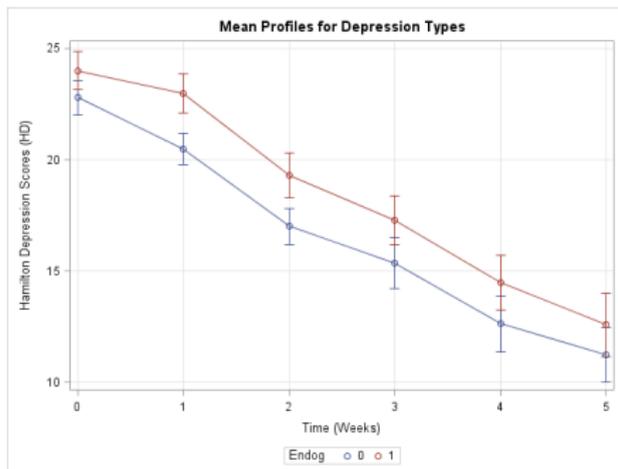
Modeling strategies:

Traditional Methods:

- ANCOVA (adjusting for baseline differences).
- Repeated-measures ANOVA (Univariate approach)
- MANOVA (Multivariate approach)

Newer Methods:

- Generalized Estimating Equations (GEE) Models.
- Structural Equations Models.
- Transition Models.
- Mixed-effects Models

Comparing Mixed-effects Models with Traditional ones [3]:

Table 1. Comparison of Traditional and Mixed-Effects Approaches for the Analysis of Repeated-Measures Data

	End-Point Analysis	rANOVA	rMANOVA	Mixed-Effects Analysis
Complete data required on every subject	Yes	No*	Yes	No
Possible effect of omitting subjects with missing values	Sample bias	Sample bias	Sample bias	Not applicable†
Possible effects of imputation of missing data	Estimation bias	Estimation bias	Estimation bias	Not applicable†
Subjects measured at different time points	Yes	No	No	Yes
Description of time effect	Simple	Flexible	Flexible	Flexible
Estimation of individual trends	No	No	No	Yes
Restrictive assumptions about correlation pattern	Not applicable	Yes	No	No
Time-dependent covariates	No	Yes	No	Yes
Ease of implementation	Very easy	Easy	Easy	Hard
Computational complexity	Low	Low	Medium	High

Abbreviations: rANOVA, univariate repeated-measures analysis of variance; rMANOVA, multivariate repeated-measures analysis of variance.
*Subjects with missing data are often omitted from the analysis.
†It is not necessary to omit subjects with missing values from the analysis or to impute missing values.

[3] This Table was taken from [9].

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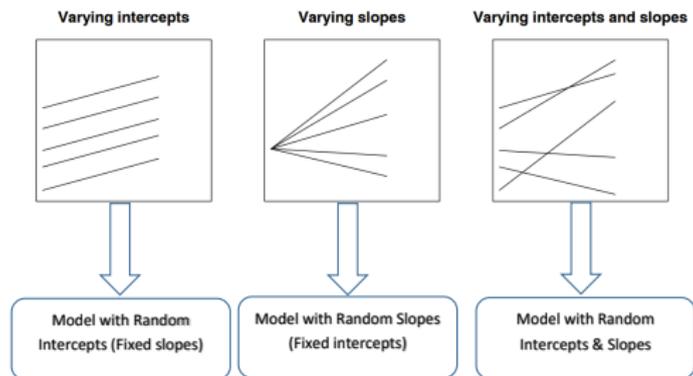
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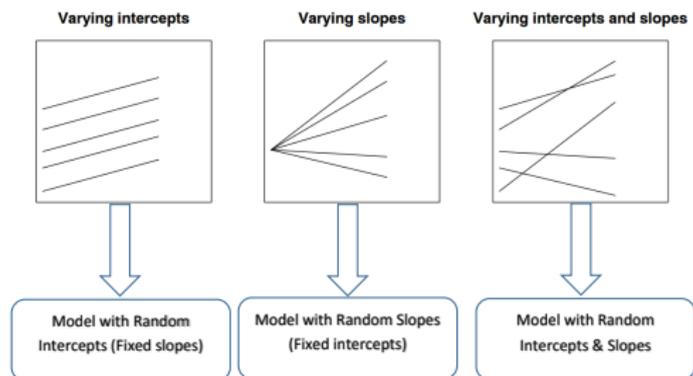
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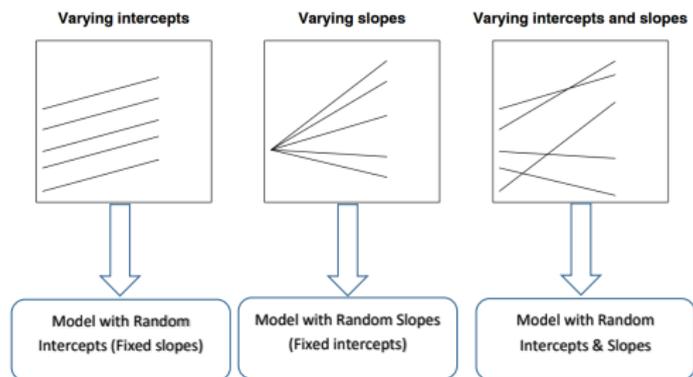
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2. To determine the best model among the above three: use the restricted likelihood ratio test (G^2) assuming the selected covariance structure in (1). The three possible mixed-effect models (random intercepts, random slopes, random intercepts & slopes) are always nested.

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- Beating the Blues is a self-help eight-session program that combines computerized cognitive models with softer science in order to engage the depression patients in a unique form of therapy. Patients work through modules designed to aid in behavior modification to help treat different depression symptoms, taking into account everything from sleeping habits to task breakdown to problem solving skills.

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- Characteristics of Participants

		Total			Beating The Blues (BtB)			Treatment as Usual (TaU)		
		N	%	C.I. (95%)	N	%	C.I. (95%)	N	%	C.I. (95%)
Total		100	100%	NA	52	52%	(42.0-62.0)	48	48%	(38.0-58.0)
Prescribed Drug	Yes	44	44%	(34.1-53.9)	30	30%	(20.9-39.1)	14	14%	(7.1-20.9)
	No	56	56%	(46.1-65.9)	22	22%	(13.7-30.3)	34	34%	(24.5-43.4)
Length of Illness	Less Than 6 months	49	49%	(39.0-59.0)	26	26%	(17.2-34.7)	23	23%	(14.6-31.4)
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3. Do the effects of BtB (and TaU) differ in patients who did or did not receive the drugs?
4. Do the patterns of change over time differ in the BtB (and TaU) group by drug therapy?
5. Do the patterns of change over time differ in the BtB (and TaU) group by length of illness and drug therapy?

Selecting the Covariance Structure: To select the covariance structure, we compare the saturated model with different covariance patterns. The saturated model includes all covariate variables as well as the corresponding interaction terms:

$$
\begin{aligned}
(1) \quad E(BDI) = {} & drug + length + drug*length + month + month*drug + month*length \\
& + month*drug*length + treatment + treatment*drug + treatment*length \\
& + treatment*drug*length + month*treatment + month*treatment*drug \\
& + month*treatment*length + month*treatment*drug*length
\end{aligned}
$$

| Covariance Pattern Model	-2(REML) Log-Likelihood	AIC
UN (15 parameters)	2428.8	2458.8
CS (2 parameters)	2461.8	2465.8
CSH (6 parameters)	2457.2	2469.2
AR(1) (2 parameters)	2462.8	2466.8
ARH(1) (6 parameters)	2454.2	2466.2

Table 1: Covariance Pattern Model

Covariance models	G^2 (nested)	Df (nested)	p-value (nested)	Best model (nested)	Lowest AIC (non-nested)
UN vs. CS	33	15-2=13	0.001704	UN	
UN vs. CSH	28.4	15-6=9	0.0008176	UN	
UN vs. AR(1)	34	15-2=13	0.0012036	UN	
UN vs. ARH(1)	25.4	15-6=9	0.0025591	UN	
CS vs. CSH	4.6	6-2=4	0.3308542	CS	
CS vs. AR(1)					CS
CS vs. ARH(1)					CS
CSH vs. AR(1)					AR(1)
CSH vs. ARH(1)					ARH(1)
AR(1) vs. ARH(1)	8.6	6-2=4	0.0719134	AR(1)	

Table 2: Covariance Models' Comparisons

The **unstructured** covariance model was found to be most adequate.

1. Do BtB and TaU differ in their effects on depression?
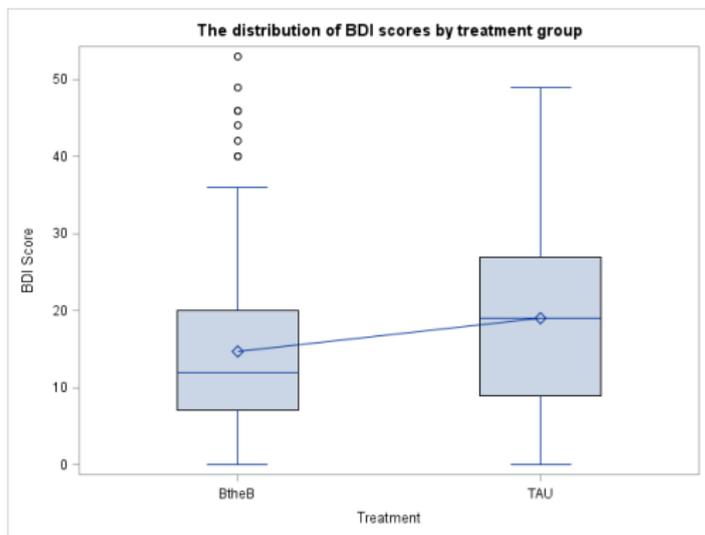
The distribution of BDI scores by treatment group

Model:

$$E(BDI) = drug + length + month + treatment$$

| Type 3 Tests of Fixed Effects | | | | | | |
|---|---|---|---|---|---|
| Effect | Num DF | Den DF | Chi-Square | F Value | Pr > ChiSq | Pr > F |
| Drug | 1 | 279 | 1.07 | 1.07 | 0.3012 | 0.3021 |
| Length | 1 | 279 | 3.46 | 3.46 | 0.0630 | 0.0641 |
| month | 1 | 279 | 115.16 | 115.16 | <.0001 | <.0001 |
| Treatment | 1 | 279 | 4.83 | 4.83 | 0.0280 | 0.0288 |

1. We will favor the model with random varying intercepts (p-value=0.142) and without interaction effect (model selection p-value=0.403).

2. So, there is strong evidence (p-value=0.029) to suggest that BtB and TaU differ in their effects on depression, as reflected by the BDI score.

Remark 5. Null and alternative hypotheses for model selection:

H_0: Model with random intercepts is adequate
H_1: Model with random intercepts and slopes is adequate

H_0: Model without interaction is adequate
H_1: Model with interaction is adequate

2. Do the patterns of change over time differ in the two treatment groups? Does one treatment show results more quickly?
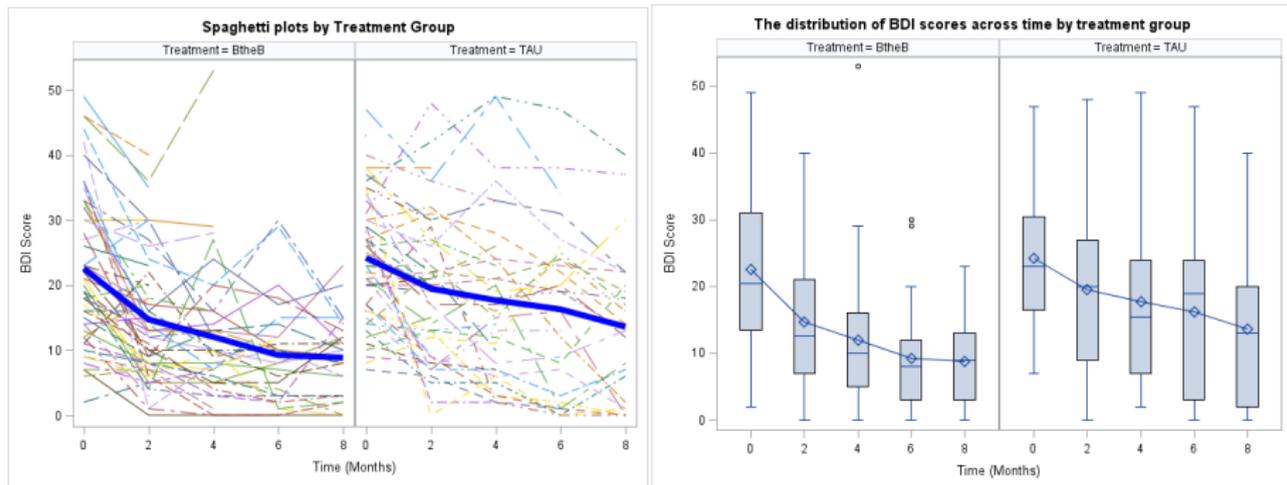

Remark 6. We observe a decreasing variance across time for the BtB treatment but not for the TaU.

Remark 7. We observe a general linear decline over time for both treatments.

(continued)

Mean Profiles for BtB and TAU treatment groups
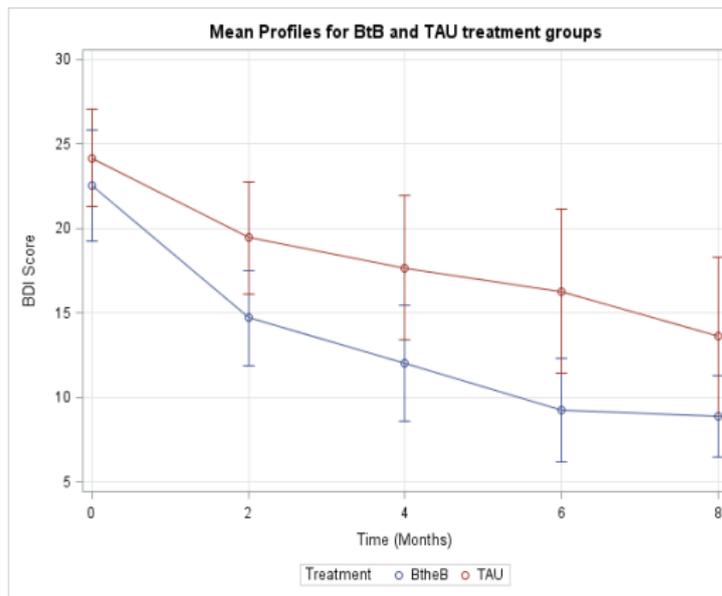
Model:

$$E(BDI) = drug + length + month + treatment + treatment * month$$

| Type 3 Tests of Fixed Effects						
Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
Drug	1	278	1.03	1.03	0.3101	0.3110
Length	1	278	3.22	3.22	0.0726	0.0737
month	1	278	113.67	113.67	<.0001	<.0001
Treatment	1	278	3.04	3.04	0.0812	0.0823
month*Treatment	1	278	0.67	0.67	0.4119	0.4126

1. We will favor the model with random varying intercepts (p =0.135). Even though a model without interaction effect is more adequate (model selection p =0.403) we will include the interaction term to examine this particular research question.

2. So, there is no evidence of difference (p =0.413) in the pattern of change of BDI score between subjects receiving BtB and TaU over time. Even though the BDI score mean plot reveals that BtB shows results more quickly than TaU, there is no statistical significance to infer such a thing.

3. Do the effects of BtB (and TaU) differ in patients who did or did not receive the drugs?

The distribution of BDI scores by treatment group and drug therapy
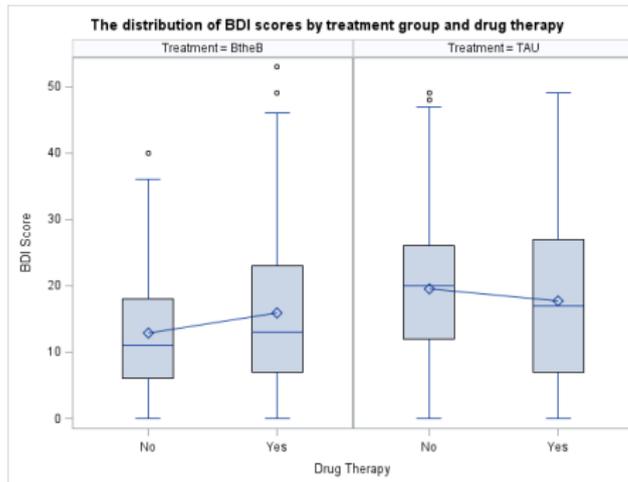
Model:

$$E(BDI) = drug + length + month + treatment + treatment * drug$$

Type 3 Tests of Fixed Effects						
Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
Drug	1	279	0.83	0.83	0.3622	0.3630
Length	1	279	3.32	3.32	0.0683	0.0693
month	1	279	114.34	114.34	<.0001	<.0001
Treatment	1	279	3.96	3.96	0.0467	0.0477
Treatment*Drug	1	279	0.57	0.57	0.4519	0.4526

1. We will favor the model with random varying intercepts (p =0.165). Even though a model without interaction effect is more adequate (model selection p =0.741) we will include the interaction term to examine this particular research question.

2. So, there is no evidence (p =0.453) that the effect of BtB (or TaU) is different in patients who did or did not receive drug. However, the pattern of change of BtB (or TaU) effect is different in patients who did or did not receive drug as illustrated in the next research question (p-value=0.0508)

4. Do the patterns of change over time differ in the BtB (and TaU) group by drug therapy?
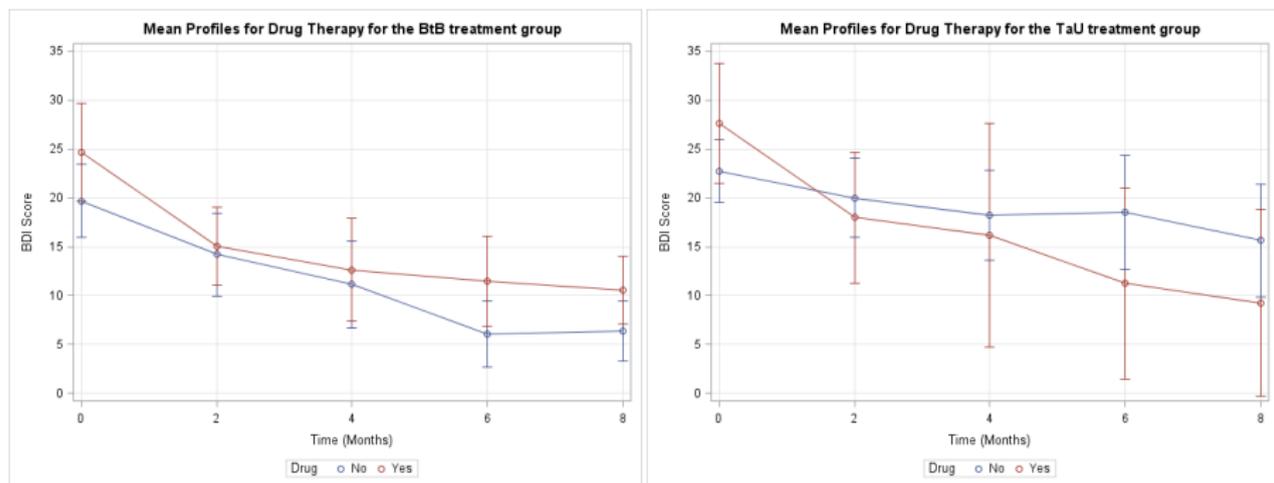
Remark 8. We observe a positive effect between Drug Therapy and TaU treatment (being in Drug therapy with TaU treatment gives lower mean BDI scores).

Remark 9. We observe a negative effect between Drug Therapy and BtB treatment (being in Drug therapy with BtB treatment gives higher mean BDI scores).

(continued)

Model:

$$E(BDI) = drug + length + month + treatment + treatment*drug + month*drug + month*treatment + month*treatment*drug$$

Type 3 Tests of Fixed Effects						
Effect	**Num DF**	**Den DF**	**Chi-Square**	**F Value**	**Pr > ChiSq**	**Pr > F**
Drug	1	276	2.70	2.70	0.1003	0.1015
Length	1	276	3.50	3.50	0.0614	0.0624
month	1	276	121.06	121.06	<.0001	<.0001
Treatment	1	276	3.60	3.60	0.0579	0.0590
Treatment*Drug	1	276	0.00	0.00	0.9909	0.9909
month*Drug	1	276	4.84	4.84	0.0279	0.0287
month*Treatment	1	276	0.00	0.00	0.9688	0.9688
month*Treatment*Drug	1	276	3.85	3.85	0.0498	0.0508

1. We will favor the model with random varying intercepts (p =0.407). A model with 3-way interaction effect is more adequate (model selection p =0.0134).

2. So, at the 10% significance level, there is evidence (p =0.0508) that the pattern of change of BtB (or TaU) effect is different in patients who did or did not receive drug.

Remark 10. The use of BtB treatment in CBT brings significant clinical improvement in anxiety and depression as compared to TaU. While there was no interaction of BtB with Drug therapy over time, there was an interaction of TaU with Drug therapy, which was found to be marginally statistically significant (p=0.0508). This indicates that TaU brings about a feeling of relaxation more swiftly in patients receiving Drug therapy than those who are not. **Note that this result was ignored by Proudfoot.**

5. Do the patterns of change over time differ in the BtB (and TaU) group by length of illness and drug therapy?

Model:

$$E(BDI) = drug \mid length \mid month \mid treatment$$

Type 3 Tests of Fixed Effects						
Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
Drug	1	272	2.58	2.58	0.1081	0.1092
Length	1	272	3.00	3.00	0.0831	0.0843
Drug*Length	1	272	0.88	0.88	0.3485	0.3493
month	1	272	119.95	119.95	<.0001	<.0001
month*Drug	1	272	3.67	3.67	0.0553	0.0564
month*Length	1	272	0.03	0.03	0.8722	0.8723
month*Drug*Length	1	272	1.33	1.33	0.2484	0.2495
Treatment	1	272	3.69	3.69	0.0546	0.0557
Treatment*Drug	1	272	0.00	0.00	0.9603	0.9603
Treatment*Length	1	272	0.18	0.18	0.6683	0.6686
Treatmen*Drug*Length	1	272	0.23	0.23	0.6307	0.6311
month*Treatment	1	272	0.07	0.07	0.7982	0.7984
month*Treatment*Drug	1	272	2.87	2.87	0.0903	0.0914
month*Treatme*Length	1	272	0.75	0.75	0.3878	0.3885
mont*Trea*Drug*Lengt	1	272	0.82	0.82	0.3644	0.3652

1. We will favor the model with random varying intercepts (p =0.472). A model with 4-way interaction effect is adequate (model selection p =0.0003).

2. Results from this model should be interpreted with cautions due to the possibility of over-fitting.

High Order Interaction Terms: To make a reliable statistical inference from compound interaction terms, the sample size of the subgroups due interaction must be reasonably large. Separation tables could be used for this purpose such that cell sizes less than 10 are usually an indication for poor results and possible over-fitting.

TaU treatment group:			
Drug	Length	month	Frequency
No	<6m	0	15
No	<6m	2	15
No	<6m	4	15
No	<6m	6	15
No	<6m	8	15
No	>6m	0	19
No	>6m	2	19
No	>6m	4	19
No	>6m	6	19
No	>6m	8	19
Yes	<6m	0	8
Yes	<6m	2	8
Yes	<6m	4	8
Yes	<6m	6	8
Yes	<6m	8	8
Yes	>6m	0	6
Yes	>6m	2	6
Yes	>6m	4	6
Yes	>6m	6	6
Yes	>6m	8	6

BtB treatment group:			
Drug	Length	month	Frequency
No	<6m	0	9
No	<6m	2	9
No	<6m	4	9
No	<6m	6	9
No	<6m	8	9
No	>6m	0	13
No	>6m	2	13
No	>6m	4	13
No	>6m	6	13
No	>6m	8	13
Yes	<6m	0	17
Yes	<6m	2	17
Yes	<6m	4	17
Yes	<6m	6	17
Yes	<6m	8	17
Yes	>6m	0	13
Yes	>6m	2	13
Yes	>6m	4	13
Yes	>6m	6	13
Yes	>6m	8	13

Inference on Individuals versus Population:

Model for the population (the intercept is the same for all individuals):

$$E\left(BDI_i\right) = \beta_0 + \beta_1 \, drug + \beta_2 \, length + \beta_3 \, month + \beta_4 \, treatment$$

$$E\left(BDI_i\right) = 21.22 + 2.07 drug + 3.52 length - 1.36 month - 4.32 treatment$$

Model for the individuals (the intercept differs from individual to another):

$$E\left(BDI_i\right) = \beta_0 + \beta_{0i} + \beta_1 \, drug + \beta_2 \, length + \beta_3 \, month + \beta_4 \, treatment$$

$$E\left(BDI_i\right) = 21.22 + \beta_{0i} + 2.07 drug + 3.52 length - 1.36 month - 4.32 treatment$$

Solution for Fixed Effects

Effect	Treatment	Drug	Length	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				21.2152	1.9009	96	11.16	<.0001
Drug		Yes		2.0696	2.0397	279	1.01	0.3112
Drug		No		0	.	.	.	.
Length			>6m	3.5182	1.9402	279	1.81	0.0709
Length			<6m	0	.	.	.	.
month				-1.3558	0.1268	279	-10.70	<.0001
Treatment	BtheB			-4.3249	2.0096	279	-2.15	0.0322
Treatment	TAU			0	.	.	.	.

Solution for Random Effects

Effect	ID	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	1	-9.4758	3.6647	279	-2.59	0.0102
Intercept	2	4.3221	3.1914	279	1.35	0.1767
Intercept	3	0.4588	4.3396	279	0.11	0.9159
Intercept	4	-0.3508	3.2105	279	-0.11	0.9131

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Thank you.
For questions, Email: FQeadan@salud.unm.edu