STAT 36900: Homework 3

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1 Introduction

The data for this problem are from the Riesby *et al.*, article that we have discussed in class. This study examined the relationship in depressed inpatients between the drug plasma levels—the antidepressant imipramine (IMI) and its metabolite desimipramine (DMI)—and clinical response as measured by the Hamilton Depression Rating Scale (HDRS). In class, we noted that there was a significant relationship across time between the drug plasma levels (specifically, desimipramine) and depression. What I would like you to do for this assignment is examine the degree to which this posited relationship is influenced by the variance-covariance structure (of the dependent measure across time) that characterizes different statistical models of the data. The dataset `RIESBYT4.dat` is available on the class website and contains the following variables:

- **field 1: Patient ID**
- **field 2: HDRS change from baseline score**
- **field 3: a field of ones (is "one" the loneliest variable?) — *ignore this variable***
- **field 4: Week — from 0 (Week 2) to 3 (Week 5)**

- **field 5: sex (0 = male, 1 = female) — *ignore this variable***
- **field 6: diagnostic group (0 = non-endogenous, 1 = endogenous)**
- **field 7: Imipramine (IMI) plasma levels (in $\ln$ units)**
- **field 8: Desimipramine (DMI) plasma levels (in $\ln$ units)**

For this problem (as in Problem Set 2), I would like you to combine the drug plasma levels into one variable—the natural log ($\ln$) of the ratio of DMI to IMI (*i.e.,* $\ln(DMI) - \ln(IMI)$). Let's denote this variable as LDIM. For this problem set do the following.

2 Question 1

Consider a model with fixed effects of $Week$, $Week^2$, $LDIM$, $ENDOG$, and the interaction of $ENDOG$ by $LDIM$. Decide on either ML or REML estimation and then perform a covariance structure selection using ideas discussed in class. What covariance structure do you settle upon (note: you may want to consider a few models with random effects, and covariance pattern models)? What criteria do you use to make this selection? What is your interpretation of the covariance structure and fixed effects in your model? Summarize your findings.

Below, we consider seven different models, each with the above fixed effects, but with varying variance-covariance structures. In particular, we consider: (1) a covariance pattern model (CPM) with an unstructured conditional variance-covariance matrix, (2) a CPM with Toeplitz-structured conditional variance-covariance matrix, (3) a CPM with AR(1)-structured conditional variance-covariance matrix, (4) a CPM with compound symmetry (exchangeable)-structured conditional variance-covariance matrix, (5) a mixed effects model with random intercepts, random linear time trends, and random quadratic time trends, (6) a mixed effects model with random intercepts and random linear time trends, and (7) a mixed effects model with random intercepts only. Since we are using the same set of fixed effects in each model (and will not be performing any feature selection in this assignment), we use REML estimation to estimate each model.[1] Since each of models (2) – (7) are nested within model (1), we begin by comparing the results of each to model (1) using a likelihood ratio test, which tests the null hypothesis that a given model's variance-covariance parameters are equal to those of the unstructured model. Following the code output below, we summarize our model comparisons and select our final variance-covariance structure.

```
. infile id deltaHDRS one week sex endog lnimi lndmi ///
> using RIESBYT4.DAT.txt, clear
(250 observations read)
. generate ldim = lndmi - lnimi
. generate week2 = week * week
```

[1] See, e.g., Hedeker & Gibbons, *Longitudinal Data Analysis*, page 79.

```
. generate endog_ldim = endog * ldim
.
. **** CPMs ****
.
. * Unstructured
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id:, noconstant residuals(unstructured, t(week)) reml

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -823.47875  (not concave)
Iteration 1:  Log restricted-likelihood =  -772.3285  (not concave)
Iteration 2:  Log restricted-likelihood = -749.89491
Iteration 3:  Log restricted-likelihood =  -741.4163
Iteration 4:  Log restricted-likelihood = -740.03598
Iteration 5:  Log restricted-likelihood = -740.01044
Iteration 6:  Log restricted-likelihood = -740.01042

Computing standard errors ...

Mixed-effects REML regression                   Number of obs     =        250
Group variable: id                              Number of groups  =         66
                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4
                                                Wald chi2(5)      =      76.64
Log restricted-likelihood = -740.01042          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.816709    .698125    -2.60   0.009    -3.185009   -.4484094
       week2 |  -.0955102    .231607    -0.41   0.680    -.5494516    .3584311
        ldim |  -2.934276   .8798424    -3.34   0.001    -4.658736   -1.209817
       endog |  -.0960678   1.423923    -0.07   0.946    -2.886906    2.694771
  endog_ldim |   2.249897   1.090696     2.06   0.039     .1121728    4.387621
       _cons |  -3.990768    1.08406    -3.68   0.000    -6.115487   -1.866049
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id:                   (empty) |
-----------------------------+------------------------------------------------
Residual: Unstructured       |
```

```
                     var(e0) |    27.0619   4.927703      18.93926    38.66817
                     var(e1) |   40.89945   7.267527      28.87123    57.93881
                     var(e2) |    50.3589   8.973552      35.51394    71.40909
                     var(e3) |   65.71428   12.42943       45.3587    95.20484
                  cov(e0,e1) |   23.93392     5.2706      13.60374    34.26411
                  cov(e0,e2) |   24.62381   5.658714      13.53293    35.71469
                  cov(e0,e3) |   22.54808   6.176021       10.4433    34.65285
                  cov(e1,e2) |     37.006   7.336985      22.62577    51.38622
                  cov(e1,e3) |   34.89225   8.115213      18.98672    50.79777
                  cov(e2,e3) |   41.47041   9.230715      23.37854    59.56228
------------------------------------------------------------------------------
LR test vs. linear model: chi2(9) = 166.94                Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
. estimates store m_ustr
.
. * Toeplitz Structure
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id:, noconstant residuals(toeplitz, t(week)) reml
Note: time gaps exist in the estimation data

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -823.47875  (not concave)
Iteration 1:  Log restricted-likelihood =   -762.709
Iteration 2:  Log restricted-likelihood = -756.35328
Iteration 3:  Log restricted-likelihood = -750.84317
Iteration 4:  Log restricted-likelihood = -750.79718
Iteration 5:  Log restricted-likelihood = -750.79717

Computing standard errors ...

Mixed-effects REML regression                     Number of obs    =    250
Group variable: id                                Number of groups =     66
                                                  Obs per group:
                                                               min =      3
                                                               avg =    3.8
                                                               max =      4
                                                  Wald chi2(5)     =  65.27
Log restricted-likelihood = -750.79717            Prob > chi2      = 0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
```

```
        week |  -1.896708   .7103483    -2.67   0.008    -3.288965   -.5044507
       week2 |  -.0332847    .218917    -0.15   0.879    -.4623541    .3957848
        ldim |  -2.817754   .9452552    -2.98   0.003    -4.670421   -.9650882
       endog |  -.2258519   1.645142    -0.14   0.891    -3.450271    2.998567
  endog_ldim |   1.854722   1.221844     1.52   0.129    -.5400473    4.249492
       _cons |  -3.885164   1.288989    -3.01   0.003    -6.411536   -1.358792
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id:                   (empty) |
-----------------------------+------------------------------------------------
Residual: Toeplitz(3)         |
                         cov1 |   33.98607   6.196691      21.84078    46.13136
                         cov2 |   28.66788   6.188242      16.53915    40.79661
                         cov3 |   22.97221   6.519901      10.19344    35.75098
                       var(e) |   45.54594   6.252983      34.80075    59.60886
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 145.36                Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
. estimates store m_tplz
.
. * AR(1) Structure
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id:, noconstant residuals(ar 1, t(week)) reml
Note: time gaps exist in the estimation data

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -823.47875
Iteration 1:  Log restricted-likelihood = -790.45356
Iteration 2:  Log restricted-likelihood = -783.74379
Iteration 3:  Log restricted-likelihood = -752.62618
Iteration 4:  Log restricted-likelihood = -752.22005
Iteration 5:  Log restricted-likelihood = -752.21791
Iteration 6:  Log restricted-likelihood = -752.21791

Computing standard errors ...

Mixed-effects REML regression                     Number of obs    =    250
Group variable: id                                Number of groups =     66
                                                  Obs per group:
```

```
                                                                  min =      3
                                                                  avg =    3.8
                                                                  max =      4
                                                  Wald chi2(5)      =  54.71
Log restricted-likelihood = -752.21791            Prob > chi2       = 0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.901453   .7476908    -2.54   0.011      -3.3669   -.4360059
       week2 |  -.0138859   .2290022    -0.06   0.952    -.4627219    .4349502
        ldim |  -2.856637   .9348441    -3.06   0.002    -4.688898   -1.024376
       endog |  -.2641485   1.611308    -0.16   0.870    -3.422255    2.893958
  endog_ldim |   1.880018   1.211681     1.55   0.121    -.4948336    4.254869
       _cons |  -3.905709   1.277423    -3.06   0.002    -6.409411   -1.402007
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id:                   (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .7484652   .0388256      .6620363    .8152482
                      var(e) |   45.67472   6.098593      35.15778    59.33763
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 142.52                Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
. estimates store m_ar1
.
. * Compound Symmetry (Exchangeable) Structure
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id:, noconstant residuals(exchangeable) reml

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -823.47875
Iteration 1:  Log restricted-likelihood =  -758.7839
Iteration 2:  Log restricted-likelihood = -758.62337
Iteration 3:  Log restricted-likelihood = -758.62301
Iteration 4:  Log restricted-likelihood = -758.62301

Computing standard errors ...
```

```
Mixed-effects REML regression                   Number of obs     =        250
Group variable: id                              Number of groups  =         66
                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4
                                                Wald chi2(5)      =      98.32
Log restricted-likelihood = -758.62301          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.873642   .7758398    -2.41   0.016     -3.39426   -.3530242
       week2 |  -.0595028   .2486557    -0.24   0.811     -.546859    .4278533
        ldim |  -2.522739   .9474043    -2.66   0.008    -4.379617   -.6658605
       endog |  -.1980272   1.660912    -0.12   0.905    -3.453356    3.057301
  endog_ldim |     1.8113   1.223937     1.48   0.139    -.5875729    4.210173
       _cons |  -4.041376   1.286034    -3.14   0.002    -6.561957   -1.520794
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id:                   (empty) |
-----------------------------+------------------------------------------------
Residual: Exchangeable       |
                     var(e) |   45.36494   6.253955       34.6238    59.43824
                     cov(e) |   30.42837    6.16292      18.34926    42.50747
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 129.71                Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
. estimates store m_exch
.
. **** MRMs ****
.
. *Random Intercept, Linear Trend, and Quadratic Trend
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id: week week2, covariance(unstructured) reml

Performing EM optimization ...
```

```
Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -741.64731
Iteration 1:  Log restricted-likelihood = -741.43049
Iteration 2:  Log restricted-likelihood = -741.41765
Iteration 3:  Log restricted-likelihood = -741.41765

Computing standard errors ...

Mixed-effects REML regression                   Number of obs     =        250
Group variable: id                              Number of groups  =         66
                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4
                                                Wald chi2(5)      =      72.37
Log restricted-likelihood = -741.41765          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.987592   .7074295    -2.81   0.005    -3.374128   -.6010556
       week2 |  -.0173368   .2364558    -0.07   0.942    -.4807816    .4461079
        ldim |   -2.87861   .8749024    -3.29   0.001    -4.593387   -1.163833
       endog |  -.1149569   1.420532    -0.08   0.936    -2.899149    2.669235
  endog_ldim |   2.258326    1.08784     2.08   0.038     .1261979    4.390454
       _cons |  -3.987186   1.080156    -3.69   0.000    -6.104253    -1.87012
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   10.49073   7.101934       2.78334    39.54081
                  var(week2) |   1.297415   .7779641      .4005679    4.202248
                  var(_cons) |   18.93163   5.076942       11.1923    32.02262
             cov(week,week2) |    -3.1631   2.271402     -7.614967    1.288766
             cov(week,_cons) |    6.00222   4.037048     -1.910249    13.91469
            cov(week2,_cons) |   -1.53584   1.295138     -4.074265    1.002584
-----------------------------+------------------------------------------------
               var(Residual) |   8.166725   1.517299      5.674177     11.7542
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 164.12                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
. estimates store m_rand1
```

```
.
. * Random Intercept and Linear Trend
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id: week, covariance(unstructured) reml

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -746.14846
Iteration 1:  Log restricted-likelihood = -746.14641
Iteration 2:  Log restricted-likelihood = -746.14641

Computing standard errors ...

Mixed-effects REML regression                   Number of obs     =        250
Group variable: id                              Number of groups  =         66
                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4
                                                Wald chi2(5)      =      69.01
Log restricted-likelihood = -746.14641          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.947951   .6862916    -2.84   0.005    -3.293057   -.6028438
       week2 |   -.033572    .211014    -0.16   0.874    -.4471518    .3800079
        ldim |   -2.89187   .8836062    -3.27   0.001    -4.623706   -1.160033
       endog |  -.0837397   1.496605    -0.06   0.955    -3.017032    2.849553
  endog_ldim |   2.163195   1.124785     1.92   0.054    -.0413424    4.367732
       _cons |   -3.96952   1.144086    -3.47   0.001    -6.211887   -1.727153
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.829319   .9698712      1.445093    5.539467
                  var(_cons) |   21.90875   5.427638      13.48162    35.60351
              cov(week,_cons) |   1.433916   1.622509     -1.746144    4.613975
-----------------------------+------------------------------------------------
                var(Residual) |   10.42497   1.366588      8.062927    13.47898
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 154.66                Prob > chi2 = 0.0000
```

```
Note: LR test is conservative and provided only for reference.
. estimates store m_rand2
.
. * Random Intercept
. mixed deltaHDRS week week2 ldim endog endog_ldim, ///
>       || id:, reml

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log restricted-likelihood = -758.62301
Iteration 1:  Log restricted-likelihood = -758.62301

Computing standard errors ...

Mixed-effects REML regression                   Number of obs     =        250
Group variable: id                              Number of groups  =         66
                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4
                                                Wald chi2(5)      =      98.32
Log restricted-likelihood = -758.62301          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
   deltaHDRS | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |  -1.873642   .7758398    -2.41   0.016     -3.39426   -.3530243
       week2 |  -.0595028   .2486556    -0.24   0.811    -.5468589    .4278532
        ldim |  -2.522739   .9474045    -2.66   0.008    -4.379617   -.6658602
       endog |  -.1980274   1.660913    -0.12   0.905    -3.453357    3.057302
  endog_ldim |     1.8113   1.223937     1.48   0.139     -.587573    4.210173
       _cons |  -4.041375   1.286035    -3.14   0.002    -6.561957   -1.520794
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |   30.42839   6.162926      20.45868    45.25642
-----------------------------+------------------------------------------------
               var(Residual) |   14.93657   1.569504      12.15649    18.35242
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 129.71        Prob >= chibar2 = 0.0000
```

```
. estimates store m_rand3
.
. **** LR Tests ****
.
. * Stage 1: Compared to Unstructured CPM
. lrtest m_ustr m_tplz

Likelihood-ratio test
Assumption: m_tplz nested within m_ustr

 LR chi2(6) =  21.57
Prob > chi2 = 0.0014

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
. lrtest m_ustr m_ar1

Likelihood-ratio test
Assumption: m_ar1 nested within m_ustr

 LR chi2(8) =  24.41
Prob > chi2 = 0.0020

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
. lrtest m_ustr m_exch

Likelihood-ratio test
Assumption: m_exch nested within m_ustr

 LR chi2(8) =  37.23
Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
. lrtest m_ustr m_rand1
```

```
Likelihood-ratio test
Assumption: m_rand1 nested within m_ustr

 LR chi2(3) =   2.81
Prob > chi2 = 0.4211

Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
. lrtest m_ustr m_rand2

Likelihood-ratio test
Assumption: m_rand2 nested within m_ustr

 LR chi2(6) =  12.27
Prob > chi2 = 0.0562

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
. lrtest m_ustr m_rand3

Likelihood-ratio test
Assumption: m_rand3 nested within m_ustr

 LR chi2(8) =  37.23
Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
.
. # Stage 2: Compare viable candidates
Unknown #command
. lrtest m_rand1 m_rand2

Likelihood-ratio test
Assumption: m_rand2 nested within m_rand1

 LR chi2(3) =   9.46
Prob > chi2 = 0.0238
```

```
Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects
      specification is identical for both models.
.
```

Model No.	Model	Log Restricted-Likelihood	LR χ^2 Test $d.f$ vs. (1)	LR χ^2 Statistic vs. (1)	LR χ^2 Test p-value vs. (1)
(1)	CPM: Unstructured	-740.01042	N/A	N/A	N/A
(2)	CPM: Toeplitz	-750.79717	6	21.57	0.0014
(3)	CPM: AR(1)	-752.21791	8	24.41	0.0020
(4)	CPM: Compound Symmetry	-758.62301	8	37.23	< 0.001
(5)	MRM: Random Intercept, Linear Trend, & Quadratic Trend	-741.41765	3	2.81	0.4211
(6)	MRM: Random Intercept & Linear Trend	-746.14641	6	12.27	0.0562
(7)	MRM: Random Intercept	-758.62301	8	37.23	< 0.001

All of the likelihood ratio tests performed and summarized in the table above are conservative relative to a chi-bar-squared likelihood ratio test, meaning that the p-values reported are slightly higher than the "true" p-values for these comparisons. As shown, models (2), (3), (4), and (7) yield estimates that are statistically significantly different (at the $\alpha = 0.05$ level) than those yielded by model (1). Given that our likelihood ratio tests are conservative, we can be confident that each of these models are significantly different than model (1), and we reject them.

Moreover, model (5) yields estimates that are clearly not significantly different from those of model (1), making it a candidate for our final model. Model (6) yields estimates that are "on the margin" of being significantly different from those of model (1), as we recover a p-value of $0.0562 \approx 0.05$ from our likelihood ratio test. Since our likelihood ratio tests are conservative, it is entirely plausible that the "true" p-value is below 0.05, in which case this model would be significantly different from model (1). Nevertheless, in an effort to check all plausible models, we also consider model (6) as a candidate for our final model. Since model (6) is nested within model (5), we use a likelihood ratio test to compare the two (as shown at the bottom of the Stata output above). This comparison yields a χ^2 statistic of 9.46 and a corresponding p-value of $0.0238 < 0.05$, meaning that models (5) and (6) yield significantly

different estimates from one another. Since we wish to select a variance-covariance structure that yields estimates that are *not* significantly different from those of the unstructured CPM model, but that use as few parameters as possible, we select model (5) as our final model.

That is, our final model is as follows:

Within-Subjects Model:

$$\Delta HDRS_{ij} = b_{0i} + b_{1i} \cdot Week_{ij} + b_{2i} \cdot Week_{ij}^2 + b_{3i} \cdot LDIM_{ij} + \varepsilon_{ij}$$

where:

- $i = 1, \ldots, 66$ individuals, and
- $j = 1, \ldots, n_i$ observations ($3 \leq n_i \leq 4$) for patient i,

and:

- b_{0i} is patient i's change in HDRS score from her baseline score as of Week 2, given that her DMI and IMI plasma levels are equal (so that $LDIM_{ij} = 0$),
- b_{1i} is patient i's average weekly linear incremental (i.e., from the previous week) change in HDRS score,
- b_{2i} is patient i's average weekly quadratic incremental (i.e., from the previous week) change in HDRS score, and
- b_{3i} is the average incremental change in patient i's HDRS score associated with a one-unit increase in the log of the ratio of her DMI to IMI plasma levels.

Between-Subjects Model:

$$\begin{aligned} b_{0i} &= \beta_0 + \beta_4 \cdot ENDOG_i + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \\ b_{2i} &= \beta_2 + \upsilon_{2i} \\ b_{3i} &= \beta_3 + \beta_5 \cdot ENDOG_i \end{aligned}$$

where:

- β_0 is the average change in HDRS score from baseline as of Week 2 among patients with non-endogenous depression, given that DMI and IMI plasma levels are equal (so that $LDIM = 0$),
- β_4 is the difference in average HDRS change scores as of Week 2 between patients with endogenous and non-endogenous depression, given that DMI and IMI plasma levels are equal (so that $LDIM = 0$),
- υ_{0i} is individual i's deviation from the average change in HDRS score from baseline as of Week 2,

- β_1 is the average weekly linear incremental change in HDRS score across all patients,
- υ_{1i} is patient i's deviation from the average weekly linear incremental change in HDRS score,
- β_2 is the average weekly quadratic incremental change in HDRS score across all patients,
- υ_{2i} is patient i's deviation from the average weekly quadratic incremental change in HDRS score,
- β_3 is the average incremental change in HDRS score associated with a one unit increase in the log of the ratio of a patient's DMI to IMI plasma levels among patients with non-endogenous depression, and
- β_5 is the difference between the average incremental changes in HDRS score associated with a one-unit increase of $LDIM$ between patients with endogenous and non-endogenous depression.

So,

- $\beta_0 + \beta_4$ is the average change in HDRS score from baseline as of Week 2 among patients with endogenous depression, and
- $\beta_3 + \beta_5$ is the average incremental change in HDRS score associated with a one unit increase in the log of the ratio of a patient's DMI to IMI plasma levels among patients with endogenous depression.

3 Question 2

Suppose Researcher A says "covariance structure, my foot! If compound symmetry is good enough for my hairstyle, it's good enough for me!" and decides to do an analysis using the same fixed effects as above, but only allowing for a CS structure on the dependent variable across time. Is Researcher A likely to report any dubious findings with regards to the fixed effects in the model?

In general, the choice of variance-covariance structure does not substantially affect the estimates of fixed effects, but can have a significant effect on the standard errors of those fixed effects estimates.[2] In the table below, we compare each covariate's fixed effects estimates, their standard errors, and their p-values between our final model (model (5), with random intercepts, linear time trends, and quadratic time trends) and a model with compound symmetry (CS) structure (model (4)). First, notice that the coefficient estimates are not too different between each model. More importantly, notice that the CS model gives higher standard errors for every coefficient estimate than our final model. This means that the CS model's confidence intervals for coefficient estimates are wider than our final model's, and p-values are larger. In other words, Researcher A is prone to Type II errors, or "missing

[2] See, e.g., Hedeker & Gibbons, *Longitudinal Data Analysis*, page 129.

out" on identifying statistically significant fixed effects. In fact, this actually happens: while we recover a p-value on the $ENDOG \times LDIM$ fixed effect of $0.038 < 0.05$, Researcher A recovers a fixed effect with p-value $0.139 > 0.05$. This means that he fails to find that the effect of $LDIM$ on HDRS change scores differs between patients with non-endogenous and endogenous depression—even though our analysis showed that this underlying relationship exists.

	Final			**CS**		
Regressor	Coef.	Std. Err.	p-value	Coef.	Std. Err.	p-value
Intercept	-3.987	1.080	< 0.001	-4.041	1.286	0.002
$Week$	-1.988	0.707	0.005	-1.874	0.776	0.016
$Week^2$	-0.017	0.236	0.942	-0.060	0.249	0.811
$LDIM$	-2.879	0.875	0.001	-2.523	0.947	0.008
$ENDOG$	-0.115	1.421	0.936	-0.198	1.661	0.905
$ENDOG \times LDIM$	2.258	1.088	0.038	1.811	1.224	0.139

4 Question 3

Suppose Researcher B says "covariance structure, my eye! If unstructured is good enough for my closet, it's good enough for me!" and decides to do the same analysis, but using an unstructured covariance structure for the dependent variable across time. Is Researcher B likely to report any dubious findings with regards to the fixed effects in the model?

In the table below, we compare each covariate's fixed effects estimates, their standard errors, and their p-values between our final model (model (5), with random intercepts, linear time trends, and quadratic time trends) and a model with an unstructured variance-covariance matrix (model (1)). Once again, the coefficient estimates produced by the two models are fairly similar. This time, however, the standard errors of these coefficient estimates are also very similar across the two models. This means that the unstructured model's confidence intervals for coefficient estimates are about as wide as the corresponding confidence intervals in our final model, so that both models should have similar findings regarding the statistical significance (or lack thereof) of different covariates' effects. Indeed, as shown below, the p-values for each coefficient estimate reported by the two models are very similar, and in some cases are even identical. This means that—at the $\alpha = 0.05, 0.01$, or 0.001 levels—when our model finds a statistically significant relationship between a covariate and HDRS change scores, so does Researcher B's model, and when our model finds that a coefficient estimate is not statistically significant, so does Researcher B's model. In short, since her coefficient estimates and corresponding p-values are both very close to our own, Researcher B is unlikely to report any dubious findings with regard to fixed effects.

	Final			Unst.		
Regressor	Coef.	Std. Err.	p-value	Coef.	Std. Err.	p-value
Intercept	-3.987	1.080	< 0.001	-3.991	1.084	< 0.001
$Week$	-1.988	0.707	0.005	-1.817	0.698	0.009
$Week^2$	-0.017	0.236	0.942	-0.096	0.232	0.680
$LDIM$	-2.879	0.875	0.001	-2.934	0.880	0.001
$ENDOG$	-0.115	1.421	0.936	-0.096	1.424	0.946
$ENDOG \times LDIM$	2.258	1.088	0.038	2.250	1.091	0.039

5 Question 4

Summarize your feelings regarding covariance structure selection, and its place in statistical modeling of longitudinal data.

Covariance structure selection plays multiple important roles in the statistical analysis of longitudinal data. Firstly, understanding the covariance structure of repeated measures—as well as estimating the corresponding variance and covariance parameters—is often important in its own right. For example, to determine whether a medical intervention should be one-time or recurring (e.g., should a patient receive just one session of hypotherapy, or monthly sessions?), researchers may want to understand how much a patient's health levels at one point in time are correlated with their health levels at another point in time, as well as if this correlation tapers off over greater gaps in time. This is precisely the kind of information that can be gleaned through the covariance structure selection process.

Moreover, even if a researcher is not specifically interested in estimating covariance parameters, selecting an appropriate covariance structure is crucial for proper inference regarding fixed effects. As we saw in Question 2 above, failure to properly specify a model's covariance structure can alter coefficient estimates, and even worse, can increase the risk of Type II errors (failing to find a statistically significant relationship when one is actually there). As such, it is always important for a researcher to do her due diligence in specifying a covariance structure for longitudinal data.

My feelings about covariance structure selection are positive! I have never given much thought to estimating variance and covariance parameters before, as my focus has always been on fixed effects estimates/β's. Our survey of covariance structure selection techniques has given me a greater appreciation for the other kinds of relationships that can exist within data. It is also striking how coefficient estimates and standard errors can be so sensitive to the choice of covariance structure, even when the estimation procedure (e.g., maximum likelihood, REML, least squares) is held the same. This has definitely piqued my interest in understanding the mechanics of parameter estimation.