**DPET 831 Exercise 2, Spring 2016, Solutions**

Migraine is a common cause of chronic pain and is the most prevalent neurologic disorder, affecting 16% of adult women and 7% of adult men. Abortive therapies for migraine have improved treatment options substantially, but their cost and side effects limit their use in many individuals. Preventative therapies, such as topiramate have offered some benefit albeit incomplete. Hence, additional therapeutic approaches have been eagerly awaited.

The following data was collected from 90 migraine sufferers attending local neurology clinics, some with episodic migraine (<15 headaches per week) and others with chronic migraine (15 or more headaches per week). Individuals were included if they had documented migraine for at least 2 years, with or without prior head injury, but without other definable causes of headache. Inclusion and exclusion criteria are listed below.

|  |  |
| --- | --- |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • 18 years of age or older  • Either gender • Meets 2004 ICHD-II\* criteria for Migraine • Headache history: > 2 years leading up to study meeting migraine criteria • Willing to complete a headache diary  • Under care of a physician for headaches • Able to read and communicate in English | • Marked depression, anxiety or psychosis.  • Pregnancy or anticipated pregnancy  • Active treatment for a major medical illness, such as malignancy, autoimmune, immune deficiency disorder, etc. • History of head/neck surgery within the past 3 years • History of subarachnoid or intra-cerebral hemorrhage or subdural hematoma • History of nervous system infection such as meningitis or encephalitis within the preceding 5 years • History of vasculitis, intracranial mass, clotting disorder • Cognitive dysfunction that would prevent informed consent |

In this small, exploratory study, individuals were randomized to receive either the investigational drug or a placebo in addition to usual care for their headaches for 12 weeks. They were also randomized to receive a standard preventative therapy (Topiramate) vs. placebo. They were asked to avoid making any other changes in their therapy, except as recommended by their physicians. Data collected before and after the trial (Week 0 and Week 12) included:

1. The number of headaches in the past 4 weeks
2. The average severity of headaches in the past 4 weeks
3. The Headache Impact Test (HIT-6)—a validated headache-specific quality-of-life measure.

Demographic data (age, sex, race) was collected at baseline.

Your task is to examine the dataset for distributions and missing data and to answer the following questions, based on the data:

1. Large amounts of missing data in a clinical trial can have a marked effect on the results. How might missing data in this dataset impact the results? Are people with missing data markedly different from people without missing data?

Six people were missing data for headache severity at the end of the trial (missing coded as 99) and four were missing data for headache frequency with a total of 8 with missing data. We recode those variables to missing and then create a missing variable indicator:

**Data dpet831b.extwo;**

**set dpet831b.extwo;**

**if hasevpst = 99 then hasevpsta=.;**

**else hasevpsta=hasevpst;**

**if hafrqpst = 99 then hafrqpsta=.;**

**else hafrqpsta=hafrqpst;**

**if hasevpst =99 then mispst = 1;**

**Else if hafrqpst=99 then mispst=1;**

**else mispst=0;**

**run;**

**proc freq data = dpet831b.extwo;**

**tables mispst\*male;**

**tables mispst\*newrx;**

**tables mispst\*topir;**

**tables mispst\*raceth;**

**tables mispst\*hasevpre;**

**run;**

**proc means data = dpet831b.extwo;**

**class mispst;**

**var age hafrqpre hit6pre;**

**run;**

Then we can examine the distribution across the missing variable indicator. People with missing data are a bit older (mean 38 vs. 36) and have a higher baseline HIT-6 (63.7 vs. 61.7). In addition, they are less likely to be in the new drug group and more likely to be in the topiramate group.

If the variables with missing data were important in your analysis, you could use multiple imputation techniques to estimate the results. Multiple imputation uses the existing data to predict a range of possible values for the data that is missing. Special techniques are applied to estimate the result, increasing the standard deviation for the outcome based on the additional variability associated with the imputation. Multiple imputation relies on an assumption that the missing data is missing at random, that it can be predicted based on non-missing variables in the dataset.

In a clinical trial, for an intention-to-treat analysis, some form of imputation is always used—either multiple imputation or single imputation (last value carried forward). Both methods require some untestable assumptions. Multiple imputation results in preserved effect size estimates at the expense of increased variance and single imputations reduced effect size estimates (closer to the null), but with variances that are probably too small.

1. Even when randomized, a small trial can result in marked imbalances in baseline characteristics across levels of the exposure variable. Are there any imbalances across the new preventative medication or topiramate in the current trial?

Best to create a table for this one:

**Table 1. Distribution of baseline characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | New drug | Not on new drug | Topiramate | No Topiramate |
| HA severity >6 (%) | 16 | 20 | 16 | 20 |
| Male (%) | 24 | 33 | 18 | 39 |
| On topiramate (%) | 44 | 53 |  |  |
| On new drug |  |  | 45 | 54 |
| Race (%) |  |  |  |  |
| NHW | 38 | 56 | 45 | 48 |
| NHB | 40 | 22 | 30 | 33 |
| Other\* | 22 | 22 | 25 | 20 |
| Mean age (SD) | 36.5 (9.3) | 36.1 (8.9) | 35.3 (9.8) | 37.3 (8.3) |
| Mean baseline HA freq. (SD) | 21.3 (8.0) | 21.4 (7.7) | 20.4 (7.5) | 22.2 (8.1) |
| Mean baseline HIT-6 (SD) | 61.6 (5.3) | 62.2 (4.0) | 62.2 (4.3) | 61.6 (5.1) |

\*Other race includes Hispanics/Latinos, Asians, and American Indians

You might also have created a variable that defined each drug alone, both drugs, and neither drug and examined the distribution across those categories.

**Data bothdrugs;**

**set dpet831b.extwo;**

**if newrx = 1 and topir = 1 then both = 3;**

**else if newrx = 0 and topir = 1 then both = 2;**

**else if newrx = 1 and topir = 0 then both = 1;**

**else both=0;**

**if hasevpre in(8,9,10) then sevpre=1;**

**else if hasevpre < 8 then sevpre=0;**

**run;**

**Proc freq data = bothdrugs;**

**tables male\*both/norow nopct;**

**tables raceth\*both/norow nopct;**

**tables sevpre\*both/norow nopct;**

**run;**

**proc means data = bothdrugs;**

**class both;**

**var age hafrqpre hit6pre;**

**run;**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Neither  N=21 | New drug only  N=25 | Topiramate only  N=24 | Both drugs  N=20 |
| HA severity >3 (%) | 19 | 20 | 21 | 10 |
| Male (%) | 48 | 32 | 21 | 15 |
| Race |  |  |  |  |
| NHW | 57 | 40 | 54 | 35 |
| NHB | 14 | 48 | 29 | 30 |
| Other | 29 | 12 | 17 | 35 |
| Mean age (SD) | 33.7 (9.8) | 36.7 (9.7) | 38.2 (7.6) | 36.2 (9.1) |
| Mean baseline HA freq. (SD) | 22.2 (8.2) | 22.2 (8.2) | 20.5 (7.9) | 20.4 (4.6) |
| Mean baseline HIT-6 (SD) | 61.7 (4.0) | 61.6 (6.0) | 62.7 (4.1) | 61.6 (4.6) |

In both tables, we see that the distribution across race is a bit off. That may mean nothing, but we might consider controlling for race in our analyses.

1. Analysis of data at two time points often relies on methods that control for the correlation between the pre-measure and the post-measure. What is the magnitude of the correlation coefficient between the pre-and post-measure for the HIT-6? Is it statistically significant at the 0.05 alpha level?

Here the correlation is smaller than you might expect from a pre-post measure at 0.26 (usually 0.5 or higher). This correlation was statistically significant at the 0.05 level. You need this information for doing sample size estimates for a repeated measures study. It is something your statistician may ask you to find.

1. How large is the pre-post difference in headache frequency (and HIT-6) for the active treatment group? For the control group? Remember to include a confidence interval with your answer.

Let’s look at this for both of the continuous outcome variables:

**Table 2. Clinical Outcomes by New Drug**

|  |  |  |  |
| --- | --- | --- | --- |
|  | New Drug  N=45 | Placebo  N=45 | Between group |
| Mean Headache frequency pre (SD) | 21.3 (8.0) | 21.4 (7.7) |  |
| Mean Headache frequency post (SD) | 21.1 (8.0) | 22.0 (7.4) |  |
| Difference (95% CI) | 0.27 (-1.8, 2.3) | -0.48 (-2.4, 1.5) | 0.91 (-2.3, 4.2) |
|  |  |  |  |
| Mean HIT-6 pre (SD) | 61.6 (5.3) | 62.2 (4.0) |  |
| Mean HIT-6 post (SD) | 52.5 (6.9) | 59.2 (6.1) |  |
| Difference (95% CI) | -9.1 (-11.7, -6.5) | -3.0 (-4.4, -1.5) | 6.7 (4.0, 9.5) |

Because of some violations of normality and the relatively modest sample size, you could consider using nonparametric tests for headache frequency.

1. Examine an independent sample t-test for the between-group mean difference for the HIT-6 post-test. How does this between-group difference compare with a simple linear regression using the HIT-6-post as the endpoint and group assignment (*newrx*) as the independent variable?

You get exactly the same answer. The idea here was to show you that the two statistical procedures are related to one another. See the between-group stats in Table 2.

1. Some of the individuals in the trial were randomized to another preventative medication for their migraines. Please evaluate the main effects of the use of each medication plus their interaction on the *change in the HIT-6* using a factorial (2-way) ANOVA.

Controlling for topiramate use, the main effects of the use of the new drug was a drop in the HIT-6 by 5.2 points (95% CI: -9.1, -1.4). Controlling for new drug use, topiramate users had an increase in the HIT-6 of 2.7 points (95% CI: -1.2, 6.6). There did not appear to be a significant interaction between the two drugs: they were neither synergistic nor antagonistic.

1. One of the most common applications of ANCOVA in clinical trials is to control for the baseline value of the primary endpoint. For example, because of regression to the mean, individuals with a high HIT-6 at baseline are more likely to have a bigger decrease in HIT-6 over time. Run an ANCOVA regression model with HIT-6\_post as the endpoint and HIT-6\_pre as the covariate. Repeat the analysis, also controlling for topiramate use. Is topiramate an important confounding variable in the analysis?

Table 3. **Adjusted mean difference**

|  |  |  |  |
| --- | --- | --- | --- |
|  | New Drug  N=45 | Placebo  N=45 | Between group  difference |
| Mean HIT-6 pre (SD) | 61.6 (5.3) | 62.2 (4.0) |  |
| Adjusted Mean HIT-6 post (SD) | 52.6 (6.9) | 59.1 (6.1) | 6.5 (3.9, 9.2) |

Note that the confidence interval is a bit narrower, adjusting for the baseline. There was no evidence for confounding by whether or not we controlled for topiramate (as we expected in this randomized study).

1. You might also be interested in what patient characteristics predict a higher HIT-6 at baseline. Include as predictors all other variables measured at baseline (age, sex, race, baseline headache frequency, baseline headache severity). Drop any variables that do not make independent contributions to the model.

The best predictor of the baseline HIT-6 is the headache severity in the thirty days before the trial. Individuals with an increase in headache severity by one point had a 1.7 (1.3, 2 2) point increase in the HIT-6. You might have noticed that the model diagnostics looked OK (not perfect). There were a few studentized residuals that were greater than 2 or less than -2 and a few spikes on the Cook’s D analysis. But the residuals were normally distributed around 0 and the model diagnostics for the model where headache frequency was included were just a little better. The Cook’s d looks OK for both models, too. And none of the values are out of range or implausible. You could choose to report either model. (this is a print-out for the predicted values, jackknife residuals, and Cook’s d for the model with both frequency and severity).

| **Obs** | **hit6pre** | **hasevpre** | **hafrqpre** | **sfprob** | **sfjack** | **sfcook** |
| --- | --- | --- | --- | --- | --- | --- |
| **1** | 50 | 4 | 6 | 57.4390 | -2.24873 | 0.12513 |
| **2** | 76 | 10 | 20 | 69.6163 | 1.92211 | 0.10209 |
| **3** | 50 | 2 | 30 | 55.9621 | -1.78008 | 0.07582 |
| **4** | 58 | 8 | 15 | 65.5272 | -2.22998 | 0.05717 |
| **5** | 62 | 4 | 5 | 57.3489 | 1.38631 | 0.05396 |
| **6** | 61 | 8 | 30 | 66.8784 | -1.73607 | 0.05132 |
| **7** | 62 | 3 | 14 | 56.3402 | 1.67231 | 0.05101 |
| **8** | 69 | 5 | 30 | 61.4202 | 2.23533 | 0.04200 |
| **9** | 62 | 8 | 31 | 66.9684 | -1.46321 | 0.03995 |
| **10** | 52 | 4 | 27 | 59.3306 | -2.15773 | 0.03920 |
| **11** | 58 | 7 | 8 | 63.0773 | -1.49041 | 0.03572 |
| **12** | 62 | 8 | 30 | 66.8784 | -1.43294 | 0.03535 |
| **13** | 66 | 4 | 20 | 58.7001 | 2.14479 | 0.03418 |
| **14** | 72 | 9 | 16 | 67.4367 | 1.34060 | 0.03302 |
| **15** | 67 | 7 | 7 | 62.9872 | 1.17533 | 0.02490 |
| **16** | 60 | 3 | 13 | 56.2501 | 1.10011 | 0.02409 |
| **17** | 62 | 3 | 27 | 57.5112 | 1.30976 | 0.02402 |
| **18** | 68 | 8 | 6 | 64.7165 | 0.96695 | 0.02223 |
| **19** | 68 | 10 | 30 | 70.5171 | -0.75449 | 0.02184 |
| **20** | 56 | 6 | 14 | 61.7984 | -1.68552 | 0.01988 |
| **21** | 70 | 6 | 20 | 62.3388 | 2.24371 | 0.01895 |

Please submit an analysis report based on your analyses. Include a description of the population, a description of the measures and covariates and how they are used in analyses as well as a description of your statistical analysis methods. Present your results in words and a discussion as defined in Exercise 1.

Write-up example—yours could look very different and still be fine:

We were interested in the therapeutic effects of a new preventative medication for migraine. In addition, we wanted to examine the possibility of a synergistic effect between the new medication and an established preventative medication: topiramate.

**Methods**

Ninety individuals with either ICHD-defined chronic or intermittent migraine were randomized to receive the new medication plus or minus topiramate or no medication. Individuals were required to have a two-year history of headache and to be free of serious illness or other causes of headache. Demographic variables collected at baseline included gender, race, and age. Also collected was baseline headache frequency and severity and baseline values for the Headache Impact test (HIT-6), a validated migraine-specific quality of life measure. The cut-off for a clinically significant difference in the HIT-6 was defined as 3.6 (give reference).

*Statistical analysis*

Univariate distributions and patterns of missing data were examined for all variables. Distributions across topiramate and the new medication were also examined. Associations between baseline variables and outcomes (headache frequency, HIT-6) were examined with t-tests and analysis of covariance, controlling for baseline values. In addition, two-way analysis of variance was used to assess synergy between the drugs. (Note: ordinarily, here you would also state that you completed an “as treated” and an “intention-to-treat analysis”. In an “as treated” analysis, you do not replace the missing data and complete the analysis excluding missing values. This can lead to bias if the reason for missingness is related to the exposure. You would also want to state your imputation method for your intention-to-treat analysis. As noted above, the most commonly used methods are “last-value-carried forward” or multiple imputation.)

**Results (highlights)**

Six people were missing data for headache severity at the end of the trial and four were missing data for headache frequency with a total of 8 of the 90 randomized subjects with missing data. Subjects with missing data were somewhat older (mean 38 vs. 36) and have a higher baseline HIT-6 (63.7 vs. 61.7). In addition, they were less likely to be in the new drug group (3 vs. 5) and more likely to be in the topiramate group (5 vs. 3). Subjects randomized to topiramate or no preventive medications were more likely to be non-Hispanic White, but mean values for headache frequency, headache severity, and HIT-6 were similar across treatment groups at baseline (Table 1).

In bivariable analysis, the new drug was associated with a statistically and clinically significant change in the HIT-6 with an unadjusted pre-post difference of 9.1 points and a between group difference of 6.7 (95% CI: 4.0, 9.5). Adjusting for baseline values, the difference was 6.5 (95% CI: 3.9, 9.2). Controlling for topiramate use, the main effects of the use of the new drug was a drop in the HIT-6 by 5.2 points (95% CI: -9.1, -1.4). Controlling for new drug use, topiramate users had an increase in the HIT-6 of 2.7 points (95% CI: -1.2, 6.6). There did not appear to be a significant interaction between the two drugs: they were neither synergistic nor antagonistic. Neither drug was associated with a significant change in headache frequency. (We did not look at headache severity).

**Discussion**

Potential points to cover: restate main findings. Talk about promising nature of new drug. Talk about how topiramate did not perform well in this population—not sure why. You would expect it to have a significant impact on the HIT-6 and headache frequency. You could mention the discrepancy between the results for the HIT-6 and headache frequency and your analysis showing that HIT-6 is more closely related to headache severity than headache frequency.

Limitations: small trial. Also, we really should have designed it as a three-arm trial of mew drug, topiramate, or both since topiramate is a known effective medication. We should really limit to either chronic daily headache or episodic migraine for a real trial.

Strengths: first study of new drug—designed as a pilot to use in design of larger, definitive trial (that will be properly designed).