**Sublingual Feverfew/Ginger (LipiGesic M) Reanalysis of Data**

In July of 2011, a pilot double-blind, placebo-controlled multicenter study of a homeopathic combination of sublingual feverfew and ginger (LipiGesic M) in the treatment of acute migraine was published in *Headache.*

Enrolled subjects met the International Headache Society criteria for migraine, with 2-6 attacks per month, and were randomized to treat all migraine attacks over a 1-month time period with either sublingual feverfew/ginger (LipiGesic M) or placebo 3:1. Subjects were asked to treat migraine early, and were encouraged but not required to treat when the headache was mild. Data were analyzed from 59 patients treating 221 migraine attacks. Subjects could take a rescue medication after 2 hours. The study was intended to parallel clinical practice.

The statistical methods employed for the analysis included descriptive statistics to establish mean and standard deviation for each primary and secondary end point. A 2-way analysis of variance was conducted to measure the significance of response comparing active and placebo groups. We concluded that sublingual feverfew/ginger (LipiGesic M) was statistically superior to placebo in relief of headache, and pain-free response (prespecified primary end point) and associated migraine symptoms (secondary end points). The product was well tolerated. In the article, it was suggested that this product, as an early intervention, might be a unique and valuable addition to the treatment armamentarium of many migraine patients.

Subsequent to publication, a colleague contacted us to discuss study design and statistical analyses performed in this study. He pointed out that while similarly designed studies have been used previously in migraine trials, there is concern for potential statistical errors based on the fact that multiple attacks per subject were included in the data analysis without analysis for within-subject repeated measures. This, in turn, may have artificially distorted the efficacy of the active compound. In an effort to clarify this concern, we agreed to have the study data reanalyzed using statistical modeling to account for repeated measures. Daniel Serrano, PhD, provided the reanalysis of the results. Dr. Serrano’s comments and reanalysis are as follows.

“In the multiple-attack data, attacks per subject ranged from 1 to 6. Ignoring the multiple observations per subject distorts estimates of degrees of freedom by not differentiating between number of subjects and number of observations, commonly causing liberal statistical tests and inflated rates of efficacy detection. In the context of repeated measures, many degree of freedom estimators have been developed, some giving fractional estimates (Satterthwaite, and Kenward and Roger), which, while at first odd-seeming, provide the best estimates in certain conditions. Regardless, the simplest degree of freedom estimates in repeated measures are calculated as a function of the total independent pieces of information in an analysis minus the number of estimated parameters (k). For example, with 10 subjects each having 5 repeated measures, degrees of freedom could be calculated as 50–k, ignoring the within-subject dependence of repeated measures, or as 10–k, attending to the repeated measures data.

“In the case of the LipiGesic M trial data, with N = 59 independent cases in the trial, a basic model including only the intercept and treatment effect should have 57 degrees of freedom. Were the repeated measures nature of the LipiGesic M trial data ignored, the degrees of freedom would be calculated using the total number of available data points (n = 221), resulting in 221–2 = 219 degrees of freedom for the same basic model – the issue of ignoring repeated measures within subject is, thus, rendered quite astonishing. In addition, standard errors that are denominated as a function of the independent pieces of information contributing to a given test will be excessively shrinken when the repeated measures nature of the data is ignored. This increases the odds of false positive findings for efficacy. In combination, the effects of liberal degrees of freedom and standard error estimates on statistical inference when repeated measures are ignored elucidate why it is essential to use models that can accommodate repeated measures data when seeking efficacy detection in multiple-attack trials.

“A simple procedure for doing so is to use the generalized linear mixed model (GLMM) or generalized estimating equations (GEE), which are an extension of the generalized linear model. Herein I focus on the GLMM because it tends to provide better estimates of variance, is more robust to missing data, and can accommodate a wider...
range of model complexity than GEE. A good source for notation and theory of mixed models generally, including the GLMM, is Demidenko’s treatment,5 while Agresti6 and McCullagh and Nelder4 give excellent treatments of generalized linear models. Readers with further interest are directed there for details on theory and notation. The repeated measures were accommodated in the multiple-attack design by including random effects for both subject and for repeated attacks within subject. This is equivalent to saying that there are multiple subjects with multiple attacks per subject, and that:

1. There is variability in their mean rate of symptomatology across all attacks in a random manner; and
2. The symptom behavior trajectory across multiple attacks within subject varies from subject to subject.

This model may be parameterized in SAS’ GLIMMIX procedure using the following code:

```sas
PROC GLIMMIX DATA=LIPO METHOD=QUAD(QMIN=3 QMAX=51 QFAC=3 QTOL=.05 INITPL=9) NOINITGLM INITITER=500;
CLASS SUBJECTID;
MODEL PAIN_2HR(EVENT="1")= TREATMENT EVENTS/DIST=BINARY LINK=LOGIT DDFM=BW;
RANDOM INT EVENTS/ SUBJECT=SUBJECTID TYPE=VC;
ESTIMATE “TX PAIN” TREATMENT 1/EXP CL;
RUN;
```

where the method options specify that numerical integration for the marginal likelihood will be approximated using anywhere from 3 to 51 quadrature points, increased in a factor of 3 quadrature points until optimization occurs (in this case, it took 27 quadrature points to achieve optimization), with starting values obtained from 9 iterations of pseudo-likelihood estimation. The Model statement specifies that the outcome (presence of pain at 2 hours post dose) will be modeled as a function of treatment condition and the number of attacks, and that this outcome is binary and that we will model it using a logistic function. The Random statement specifies the variables across which effects vary randomly. In this model, the subject average, or intercept, effects vary from subject to subject. In addition, the trajectory across multiple attacks, or events, varies from subject to subject. The Subject statement indicates that these effects are random ACROSS subjects, and the TYPE= option specifies that these effects are uncorrelated, where VC refers to variance component, or diagonal, parameterizations of covariance matrices. The treatment effect is tested in the Estimate statement, and the EXP and CL options request that odds ratios and corresponding confidence limits be provided as part of the output. Having reviewed the design and model employed in this reanalysis, I will next review the results of analysis.

“As reported in the study publication, LipiGesic M is highly effective, and with a more highly powered study would achieve separation on all four co-primary end points. Under the existing design, odds ratios and confidence intervals are nearly identical for both significant and nonsignificant end points – this is directly a function of power. For example, both pain and phonophobia have identical odds ratios (.21), indicating that the treatment group are 79% less likely to report these symptoms than placebo. However, whereas the upper bound for the confidence limit for pain is .88, rendering it statistically significant, the upper bound for the confidence limit of phonophobia is 1.13, rendering it nonsignificant. An identical issue was observed for photophobia and nausea, respectively. Note that efficacy was strongest for these symptoms, with treatment subjects being 87% less likely to report these symptoms than placebo at 2 hours post dose. Therefore, we can conclude that under the multiple-attack design, repeated-measures analysis accounting for the multiple attacks within subject demonstrates meaningful efficacy for sublingual feverfew/ginger (LipiGesic M). Unfortunately, the efficacy detection on some of the co-primary end points is suppressed by an underpowered pilot design. Were sufficient subjects recruited and the trial repeated, analysis would demonstrate extremely strong efficacy across all four co-primaries given the robustness and magnitude of the observed treatment effects.

“Under the single-attack design, the first attack per subject was retained, and the analysis consisted of a straightforward logistic regression predicting symptom presence at 2 hours post dose from treatment group. SAS’ GENMOD procedure was employed under the standard parameterization:

```sas
PROC GENMOD DATA=LIPO DESCENDING; WHERE EVENTS=1;
MODEL PAIN_2HR= TREATMENT/DIST=BIN LINK=LOGIT;
ESTIMATE “TX PAIN” TREATMENT 1/EXP;
RUN;
```

“As reported in the study publication, treatment significantly separated from control on all but nausea at 2
hours post dose. As with the multiple-attack findings, failure to separate for nausea was only marginal and likely due to a lack of power considering the magnitude of the odds ratios and interval limits relative to the other three co-primaries.

“In conclusion, irrespective of design-type employed, the efficacy of sublingual feverfew/ginger (LipiGesic M) appears robust, and under a more highly powered design, efficacy would most assuredly be detected on all four co-primary end points.”

The authors want to thank Dr. Serrano for his excellent analysis. We are pleased that the published conclusions and efficacy of sublingual feverfew/ginger (LipiGesic M) are supported by this reanalysis. The study authors, however, felt compelled to publish this reanalysis so that statistical modeling might be used in future study designs. These models of analysis have the advantage of making valid statistical claims from smaller sets of data. We believe that utilization of these models can ultimately enrich observations in a rather limited population size. This is critical in studies on alternative products or when sponsors have limited resources. It is hoped in the future that incorporating statistical modeling will encourage more cost-effective studies with valid statistical analysis.

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REFERENCES


Migraine Relief by Chilis and Other Alternative Medications – Caused by Platelet Inhibition?

We read with interest the Letter to the Editor by Anand and Dhikav1 in which they reported unexpected relief of migraine in a young female migraineur after intake of one-and-a-half teaspoonfuls of chili sauce, a spice long known to trigger migrainous attacks.

As an explanation for this favorable effect, the authors suppose that it might be due to the pain-killing action of capsaicin, an active component in chili and other peppers that makes them hot. Capsaicin could modulate the function of the trigeminovascular pathway by depleting substance P, the main pain transmitter in the brain.

However, capsaicin is also a strong inhibitor of platelet aggregation.2 Moreover, other spices, herbs, and nutrients used in nonmedical migraine treatment inhibit platelet activity as well (see Table). Also, a number of regular medicines can suppress platelet aggregation and relieve migraine (eg, platelet antagonists, β-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors).20

A link between migraine and platelet aggregation has been frequently reported. An attack might be caused by serotonin released from platelets that aggregate under the influence of migraine triggers, among which certain food components.20 The paradoxical finding (see first paragraph) that a spice either triggers or relieves a migraine attack could, in our opinion, be due to its ability to either stimulate

Table.—Alternative Medications That Both Relieve Migraine (First Reference) and Suppress Platelet Aggregation (Second Reference)

<table>
<thead>
<tr>
<th>Spices</th>
<th>Herbs</th>
<th>Nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chilis1,2</td>
<td>Ginkgo biloba3,4</td>
<td>Magnesium5,6</td>
</tr>
<tr>
<td>Cayenne pepper7,2</td>
<td>Feverfew5,9</td>
<td>Riboflavin3,9</td>
</tr>
<tr>
<td>Garlic and onions8,10,11</td>
<td>Butterbur5,12</td>
<td>Coenzyme Q1010,15</td>
</tr>
<tr>
<td>Ginger14,11</td>
<td>Goshuyuto15,15</td>
<td>Dark chocolate16,17</td>
</tr>
<tr>
<td>Turmeric18,19</td>
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</tbody>
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