Center for Regulatory Effectiveness (CRE) assessment of the following research report:

“Relationship between menthol cigarettes and smoking cessation among African American light smokers”

by:


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Center for Regulatory Effectiveness

References:


Background

On June 22, 2009, President Obama signed into law the Family Smoking Prevention and Tobacco Control Act, which gives the Food and Drug Administration the power to further regulate the tobacco industry. One element of the law imposes new warnings and labels on tobacco packaging, with the goal of discouraging minors and young adults from smoking. The bill bans flavored cigarettes, including cloves, cinnamon, candy, and fruit flavors, with a special exception for menthol cigarettes. There is a need to investigate possible health hazards of smoking menthol cigarettes as well as cessation ( quitting) efforts.

The Tobacco Products Scientific Advisory Committee (TPSAC) provisioned under the bill is to submit a recommendation on menthol cigarettes to the United States Secretary of Health and Human Services no later than March 23, 2012. The intent of this CRE assessment is to consider the merits and shortfalls of the study as well as present the reader with topics for further discussion and investigation.

The report at reference (a) was identified for review and public discussion due to its focus on the efficacy of medication on menthol smokers among African Americans. The researchers presented the following primary results:

- Compared to non-menthol smokers, menthol smokers were younger and less confident to quit smoking;
- At the 26-week [follow-up point], the 7-day verified abstinence rate was significantly lower for menthol smokers.

The researchers concluded “[a]mong African American light smokers, use of menthol cigarettes is associated with lower smoking cessation rates.” [p. 1979]

The reader should be aware that “…this study was a secondary analysis that used data from a clinical trial (reference (b)) that was not designed for testing differences in smoking cessation by menthol status.” [p. 1984] The parent (previous) trial was a double-blind, placebo-controlled, randomized trial of 755 African American light smokers. So, both the patient and the administrator of medications did not have knowledge of the type of treatment they were receiving/administering (the placebo (fake gum) vs. nicotine gum). All smokers had the following characteristics: at least 18 years of age, smoked no more than 10 cigarettes a day and
were interested in quitting within the next 14 days. The following timeline generally illustrates the 8-week clinical trial plan:

Table 1.

The 755 smokers were placed into 4 Treatment Study Groups (see Table 2). The following information, which was gathered from the primary trial report, illustrates classical issues that are sometimes overlooked when researchers use data from a previous trial in which the study objectives are not complementary:

- Firstly, notice the disproportionate amount of menthol smokers-to-total smokers. Each treatment group comprised approximately 80% of menthol smokers. This will cause results to be biased/misleading.
- Secondly, a careful review of the primary trial report (reference (b)) revealed a significant attrition rate (i.e. failure of participants to show-up for their follow-up assessments and cotinine verifications). Neither report provided information as to how the menthol vs. non-menthol groups were affected by the attrition rates. The attrition rates could cause results to be biased/misleading (an example is provided in the Summary section of this assessment).

Table 2.

<table>
<thead>
<tr>
<th>Smoker categories</th>
<th>Weeks 1-4</th>
<th>Weeks 5-6</th>
<th>Weeks 7-8</th>
<th>Weeks 8, 16, 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 Cigarettes</td>
<td>6 Pieces of Gum</td>
<td>4 Pieces of Gum</td>
<td>2 Pieces of Gum</td>
<td>Follow up assessment and cotinine verification</td>
</tr>
<tr>
<td>5-7 Cigarettes</td>
<td>8 Pieces of Gum</td>
<td>6 Pieces of Gum</td>
<td>4 Pieces of Gum</td>
<td></td>
</tr>
<tr>
<td>8-10 Cigarettes</td>
<td>10 Pieces of Gum</td>
<td>8 Pieces of Gum</td>
<td>6 Pieces of Gum</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>The 4 Treatment Study Groups:</th>
<th>Distribution of All Smokers at Start</th>
<th>Distribution of Menthol Cigarette Smokers (%) at Start</th>
<th>All Remaining Smokers at Week 8</th>
<th>All Remaining Smokers at Week 16</th>
<th>All Remaining Smokers at Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Gum and Motivational Interviewing</td>
<td>189</td>
<td>153 (81.4%)</td>
<td>145</td>
<td>145</td>
<td>157</td>
</tr>
<tr>
<td>Nicotine Gum and Health Education</td>
<td>189</td>
<td>156 (83%)</td>
<td>171</td>
<td>142</td>
<td>168</td>
</tr>
<tr>
<td>Placebo Gum and Motivational Interviewing</td>
<td>189</td>
<td>158 (83.6%)</td>
<td>134</td>
<td>137</td>
<td>150</td>
</tr>
</tbody>
</table>
The CRE conducted a limited assessment which comprised a review of the report, the primary clinical study, and internet research of the nicotine drug.

Under the Data [Information] Quality Act, the FDA is prohibited from using any information from a third-party, such as TPSAC, unless it meets the requirements of the DQA. CRE has reviewed the study by Okuyemi et al., and has identified the following shortcomings, which if valid after outside peer review, would deem it non-compliant with the DQA. CRE is requesting public comment for the material set forth herein.

**Summary of Findings and Issues**

Class sizes within the sample should be the same in order to avoid biased results.

The authors of this secondary study acknowledged the inherent limitation in that the primary clinical study sample was predominantly menthol smokers. In fact, the 755 subjects comprised of 615 menthol smokers and only 140 non-menthol smokers. The primary objective of the secondary study was to test (prove) the hypothesis that menthol smokers are less likely to quit. While it is reasonable to expect that several menthol smokers will be unable to quit smoking, the roughly 4.5-to-1 ratio of menthol smokers to non-menthol smokers likely resulted in an inflated/lop-sided comparison.

The following is just one example of how the secondary report statistics do not match the data provided in the primary clinical report (reference (b):

The authors of this secondary study reported that “…at week 26, non-menthol smokers who received nicotine gum (n = 67) had significantly higher abstinence (quit) rates than menthol smokers who received nicotine gum (n = 309).” [p. 1981] The figure directly below illustrates the results and was included in their report. [p.1982]

![Figure 1. Seven-day abstinence rate at week 26](image)

However, when the reader compares this graph against the data in Table 2, which came from the original report, it can be seen that, by week 26, there were a total of only 325 (as opposed to the
stated 376 in Figure 1) smokers-using-nicotine gum who returned for assessments and verification \((157 + 168 = 325)\). This means there were a total of 53 smokers (in the two nicotine gum-use study groups) who failed to return for the final check-up at week 26. Moreover, neither study provides the reader with information as to final size of the menthol vs. non-menthol classes. So, it is very likely that the final (week 26) size of the non-menthol group was smaller than 67 and consisted primarily of abstaining traits.

Future studies of this nature should select a sample size that has equal, or near equal, classes (e.g. menthol smokers, non-menthol smokers).

*Is age a factor in cessation rates?*

The TPSAC is studying the effects of smoking on young adults. This study included two age categories: younger than 50 years, and 50 years or older. Researchers used a logistic regression model and included the variables: smoker type along with age to conclude that “[i]n the < 50 age group, non-menthol smokers had marginally significant higher cessation rates than menthol smokers [by a 2-to-1 ratio].”

This study result may have been different if the smoking class sizes were the same.

*Are the data and statistical models transparent?*

Unlike previous studies that the CRE has assessed, the data for this study was not publically available for independent verification of results. The CRE has submitted a request for data in separate correspondence. The CRE reviewed the primary clinical study (reference b) and discovered interesting facts such as the attrition rate of participants: of the original 755 smokers who initially agreed to participate in the study, 637 (84.4%) participated at week 26. The attrition rate for this primary study was not as high as a previous study assessed by CRE, but the menthol-vs-non-menthol smoker ratio was more lop-sided in this study. This attrition parameter underscores the human factors challenge in such studies.

The researchers used a logistic regression model to conclude the relationship between menthol smoking and abstinence rates. Logistic regression models are becoming increasingly useful for researchers to use since they allow a comparison between variables that include discrete data (i.e. abstinence rates would be considered as discrete data since it is a counted measure). Future studies should include transparency and completeness of such models (i.e. the error component alone can be used by modelers to compensate for unexplained behavior/factors).