CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-612/S025

20-066/S007

STATISTICAL REVIEW(S)

NOV 23 1998

Statistical Review and Evaluation

NDA 18-612, 20-066
Name of drug: Nicorette (nicotine polacrilex) gum
Applicant: SmithKline Beecham
Indication: smoking cessation
Documents reviewed: volumes 1, 26, 15 May 1998
Project managers: Indira Kumar, Sakineh Walther
Medical officer: Douglas Kramer, M.D.
Dates: 10-month user fee date 15 March 1999
Reviewer: Thomas Permutt

This supplement is for a new, mint flavor of Nicorette (nicotine polacrilex) chewing gum, an approved, over-the-counter drug product for smoking cessation. The two strengths of Nicorette (2 mg and 4 mg) were approved under separate NDAs, and this supplement applies to both. While normally changes in flavor are handled as manufacturing supplements, there are special considerations in this case. Nicotine being an addictive drug, there is some concern that a product intended to help addicted smokers stop smoking might in some cases attract nonsmokers, especially teenagers. The taste of Nicorette, which is unpleasant to many users, has been seen as a deterrent to such abuse. Accordingly, the proposal for a mint flavor includes information intended to show that the mint flavor is not more liable to such abuse than the original flavor.

This statistical review is concerned with a study of abuse liability conducted at the Johns Hopkins University by Maxine Stitzer and Jack Henningfield. Twenty-four subjects, twelve from 18 to 21 years old and twelve from 22 to 47, participated in a 12-treatment, 12-period, double-dummy crossover study. The order of treatments was assigned according to a Latin square in each age stratum. The allocation is nevertheless described as "random." It is not clear whether this means Latin squares were chosen at random, or patients were assigned to rows of the Latin square at random, but this is probably not important.

The twelve treatments were original Nicorette gum (placebo, 2, 4 and 8 mg); mint Nicorette gum (similarly); d-amphetamine (20 mg/70 kg) combined with each of original and mint Nicorette placebo; an ordinary, mint chewing gum; and a cigarette. There was also a practice session with an ordinary, fruit-flavored gum. The Nicorette sessions had dummy amphetamine, and the amphetamine sessions had dummy Nicorette; but the cigarette session had only the cigarette. The cigarette and the ordinary gum sessions are not analyzed in the study report, leaving 10 treatments.

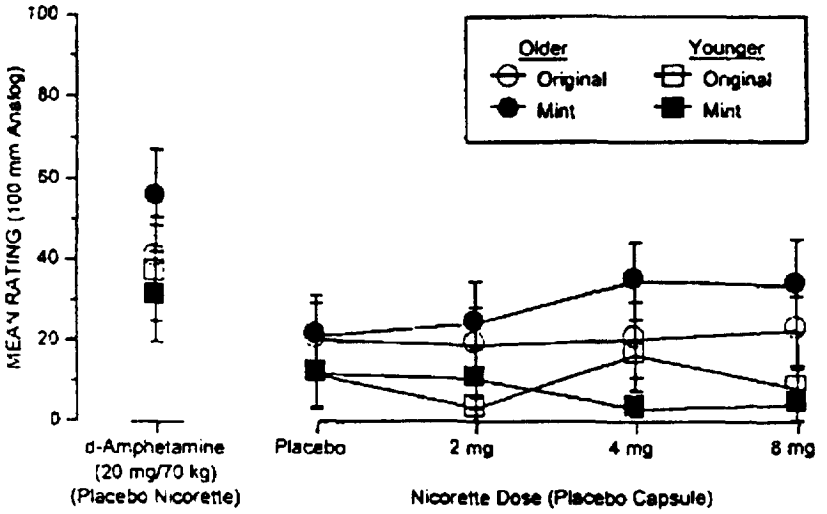
As is usual in abuse liability studies, a large number of questions were asked at a number of timepoints. The protocol specified three measures as primary indicators of abuse liability. The first was the answer (on a 100 mm visual analog scale; no information about scale anchors is given) to the question, "Do you like the drug effect?" The second was the answer to, "Does the drug have any good effects?" The third was the morphine-benzedrine scale, a standard composite of several questions relating to euphoria. The primary timepoint was 120 minutes after the dose of amphetamine (or dummy) and 15 minutes after starting the gum, 105 minutes later: it was believed that this would measure the peak effects of whichever was the active drug.

As I understand it, the purpose of this study was to compare the abuse liability of mint to original gum. Amphetamine was included to put any differences that might appear in perspective, by comparison to a drug of known liability to abuse. The statistical analysis in the study report does not address the primary question very directly. It focuses only on tests of significance. The absence of statistically significant differences, as between mint and original Nicorette, is not in itself evidence of the absence of an effect; rather, it is a lack of evidence. On the other hand, the applicant's finding of a significant difference between gum (with the mint and original flavors pooled!) and amphetamine is also beside the point. There was no expectation that Nicorette might be more abusable than amphetamine, so that rejecting the hypothesis that it is, which is what such a test allows, is of little interest. Rather, it would be important to compare the differences between mint and original Nicorette to the differences between amphetamine and placebo, to give an indication of their clinical significance.

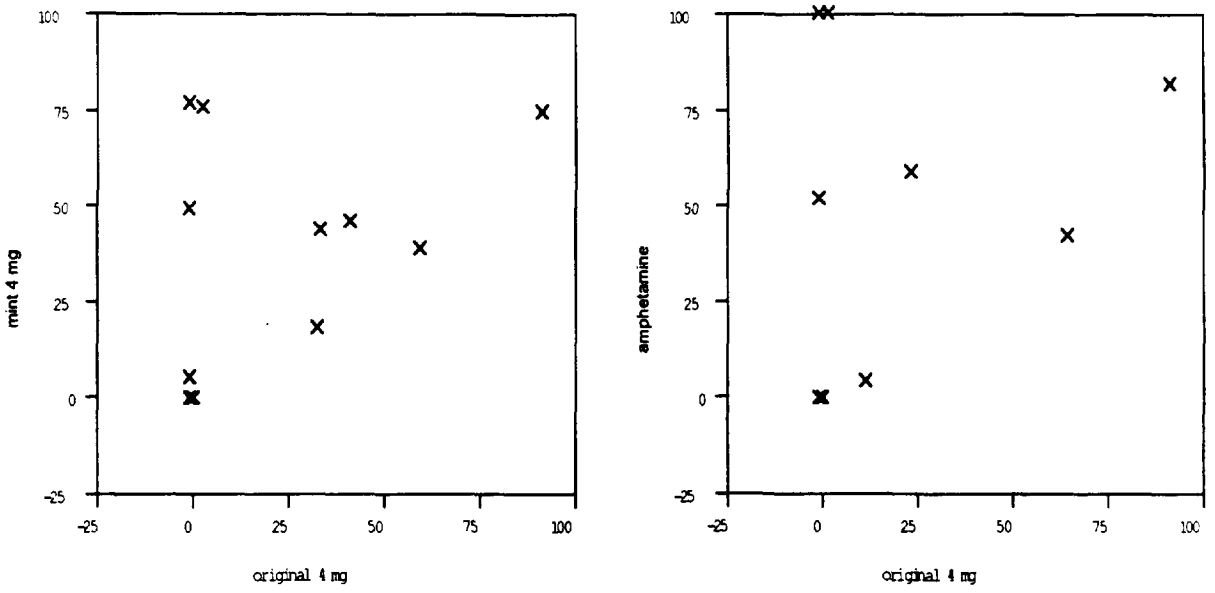
APPEARS THIS WAY
ON ORIGINAL

"Do You Like the Drug Effect?"

(Pharmacological Peak - Time 120)



The figure above (applicant's) is prominent in the report of this study and in the clinical summary. For the 4 mg gum in older subjects the means were 22 with plain gum and 36 with mint gum. The mean score for d-amphetamine with placebo plain gum was 44. In other words, mint added 14 to the average liking score for this group, and amphetamine added 22. (Amphetamine plus mint was higher still.) Neither of these differences was statistically



significant (paired t-test). Each mean difference was largely the result of a few (not the same) subjects who liked the treatment (mint or amphetamine) much better than plain nicotine gum, averaged with many subjects for whom there was not much difference (my figures, above).

To me these data suggest, if anything, that the addition of mint may affect liking almost as much as the addition of d-amphetamine, a known drug of abuse. I do not think they suggest this conclusion very strongly. In the first place, the differences were not statistically significant. This is not evidence of a lack of effect; it only indicates that the sample is too small to draw definite conclusions. Secondly, there was no reason a priori to focus on this particular comparison. While the results for the 8 mg gum in older subjects were similar, the results for younger subjects were in the opposite direction; ignoring age, mint had no effect at all on average. The stratification was mainly motivated by concern that the mint gum might be more attractive to *younger* subjects. So, I think the study gives very little positive evidence of potential for abuse of mint gum.

This is very different, however, from saying that the study demonstrates the absence of potential for abuse. The applicant describes the results as follows:

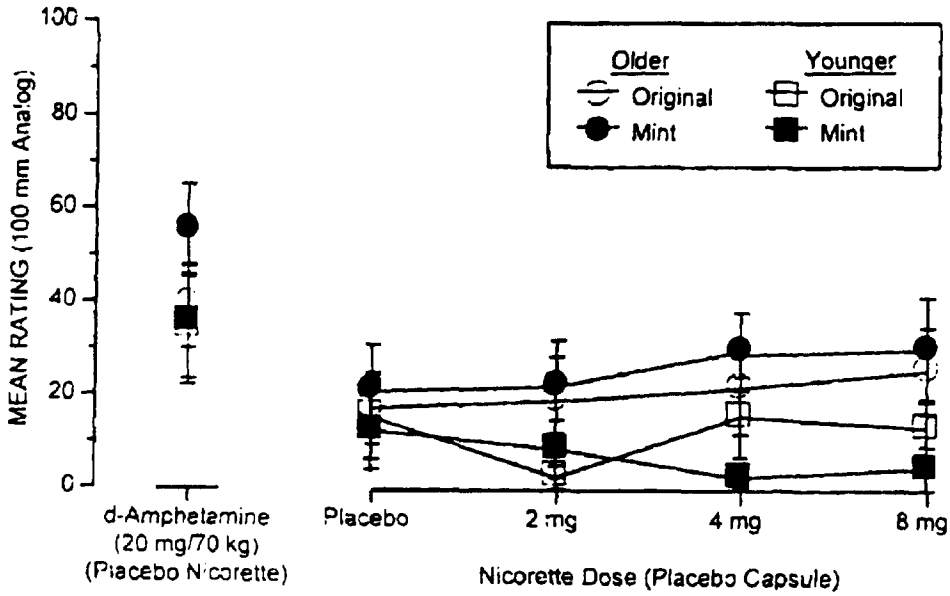
> The study's results were unambiguous: the abuse liability of mint flavor Nicorette is low, is not higher than the marketed original flavor Nicorette, and is not higher among younger than among older subjects. By every measure and by every assessment approach, the data showed Nicorette gum, both mint and original flavor, to have low abuse liability, both in younger and older adults. In no instance was there any indication that mint flavor Nicorette was associated with higher abuse liability, or that abuse liability was higher among younger subjects. In comparisons with d-amphetamine, both Nicorette flavors showed significantly lower abuse liability.

I do not think such conclusions are warranted by the data. Rather, I think there is a mild suggestion of some increased "liking," a usual measure of abuse liability, with mint flavor in some subjects over 21. On the other hand, mint was liked less than original Nicorette by those under 21, the group considered a priori to be more at risk of using Nicorette instead of illicit tobacco.

The figures below (applicant's) show the data on the other two primary measures. These are broadly consistent with those for "liking." Again, there are slight, statistically nonsignificant indications of some increased effect of mint over original Nicorette in the older subjects. Again, the applicant's conclusion (above) is based on inappropriate statistical tests and is much overstated, in my opinion.

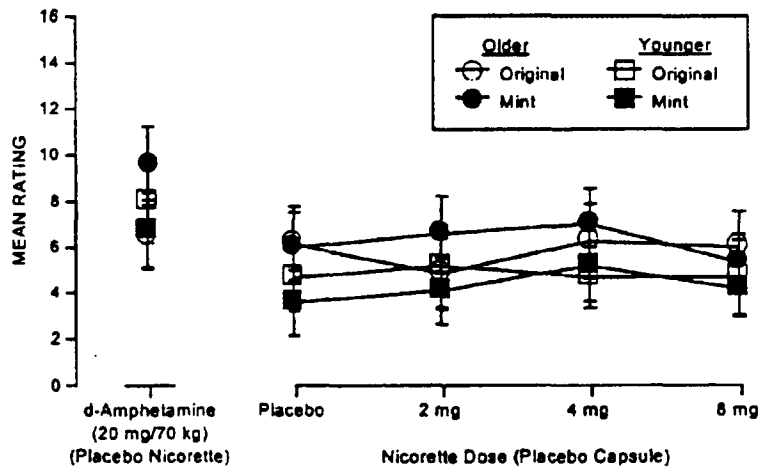
"Does the Drug have Any Good Effects?"

(Pharmacological Peak - Time 120)



ARCI - MBG SCALE

(Pharmacological Peak - Time 120)



Nevertheless, the study appears to have been designed and carried out in accordance with best current practices for abuse liability studies. Though the number of subjects was small, and the statistical uncertainty of the results accordingly large, there were more subjects than in most abuse liability studies. The data, I believe, do not justify the definitive language of the applicant's report. They do, however, serve the purpose of allaying concern about special

attractiveness of the new formulation to young adults. The supplement is approvable from the standpoint of statistics.

/S/ 11/23/98

Thomas Permutt, Ph.D.
Mathematical Statistician (Team Leader)

/S/ 11/23/98

Concur: Michael Welch, Ph.D.
Acting Deputy Director, Division of Biometrics II

archival: NDA 18-612
cc:
NDA 20-066
HFD-715/Nevius, Welch, file copy
HFD-344/Barton
HFD-560/Walther
HFD-170/Kumar, Kramer, Klein, Winchell, McCormick, Permutt
HFD-170/division file