



LETTER

Regarding “Phenylpropanolamine and Hemorrhagic Stroke in the Hemorrhagic Stroke Project”

Dear Editors:

Stier and Hennekens’ “Phenylpropanolamine and Hemorrhagic Stroke in the Hemorrhagic Stroke Project: A Reappraisal in the Context of Science, the Food and Drug Administration, and the Law” (1) contains a number of material errors and omissions and a tendentious methodology. For reasons detailed in this letter, we believe the article was intended only for litigation advantage to phenylpropanolamine (PPA) manufacturers in pending court cases.

Although not disclosed in the article by Stier and Hennekens (1), the PPA manufacturers advanced some of the same critiques of the Hemorrhagic Stroke Project (HSP) to the Food and Drug Administration (FDA) in 2000, and the FDA rejected them. The article is literally a rehash of defense positions in the PPA litigation, which were advanced in detailed Daubert briefs (motions brought by the PPA manufacturers to exclude the HSP and other scientific evidence that PPA causes hemorrhagic stroke) filed with the court overseeing all federal court PPA cases (the PPA Multi-District Litigation [MDL]). These PPA manufacturers’ arguments, repeated in the article, were rejected by the PPA MDL judge in a published decision. (See in *Re PPA Litigation*, 289 F. Supp. 2d 1230, W.D. Washington 2003; “The defendants’ ex post facto dissection of the HSP fails to undermine its reliability.”)

The methodology used by Stier and Hennekens is not disclosed; thus, readers cannot tell that the article is an opinion piece, not a balanced scientific analysis. No mention is made of a large multicenter case–control study of PPA in decongestants and the risk for hemorrhagic stroke conducted in South Korea, supervised by the Korean FDA and presented at a recent international stroke meeting (2) that also found a statistically significant increased risk for hemorrhagic stroke from PPA ingestion. No mention is made that the PPA MDL Court rejected the criticisms advanced by Stier and Hennekens. The points we raise in this letter, which address the issues raised in the article by Stier and Hennekens (1), also were advanced in the litigation briefs and thus were known to Stier and Hennekens. Yet the investigators did not disclose to readers that they were presenting only the defense perspective on the study.

The HSP has led to four peer-reviewed journal articles, not just one, as reported in the article. In addition to the article in the *New England Journal of Medicine* (3), the HSP investigators also published related articles in *Neurology* (4) and *Stroke* (5, 6).

Stier and Hennekens claim that litigation uncovered information not known to the FDA when it relied on the HSP study to withdraw PPA from the market. The public record and litigation record make clear that the FDA was well aware of almost every one of the issues discussed in the article, but disagreed with the assessment advanced by Stier and Hennekens. The PPA manufacturers submitted detailed critiques of the HSP that were considered and rejected by the FDA (FDA Statistical Review of Epidemiological Report [September 26, 2000], MDL no. FDA00485; Review of Study Protocol, Final Study Report, and Raw Data Regarding the Incidence of Hemorrhagic Stroke Associated With the Use of Phenylpropanolamine [September 27, 2000] prepared by FDA epidemiologists La Grenade and Nourjah, Office of Drug Risk Assessment, MDL no. FDA00498. All citations to documents use the MDL exhibit numbers. These documents are publicly available in the MDL Court in Seattle). These same (and more) critiques then were advanced by drug company lawyers in the PPA MDL proceedings (including an expert report submitted by Dr Hennekens that essentially mirrors his manuscript). The PPA MDL Court rejected these arguments (in *Re PPA Litigation*, 289 F. Supp. 2d 1230 W.D. Washington 2003).

According to an FDA staff epidemiologist’s review of the HSP, the FDA possessed the raw data for the study and conducted its own analyses (MDL no. FDA00498). Thus, any issues of potential confounding were fully known to the FDA reviewers. These analyses assessed recall and selection bias, participation rates, confounding, the “small numbers” of exposures and sparse data issues, protocol review, control selection, sample size and statistical power, and other issues raised by the PPA manufacturers who were then, as they are now, determined to undermine their own study because the results meant uncertainty for the future of their PPA product lines.

Stier and Hennekens (1) contend that the adjustment for level of education should have been based on using three categories or based on a continuous variable instead of using the two categories that were used (less than high school and high school or above). They claim that by using a “three or more” category definition of education, for the “first use” category, the p is increased and the odds ratio is decreased from 3.13 to 2.62. They do not mention that the use of two categories for education was used across the board for all categories, not just for “first use.” Using the two-category definition had the effect of increasing the p (and losing conventional statistical significance) for the category “any PPA

use in 3 day window (all subjects),” and it increased the p for “cough/cold use in 3 day window (all subjects).” For “first use,” it resulted in a p of 0.042 compared with 0.076 for three categories and 0.16 for continuous variable (MDL no. HSP-Y-0016639). In addition, FDA epidemiologists analyzed the HSP data for education and concluded that confounding by education was sufficiently controlled in the published analysis (MDL no. FDA00498, at 7).

The article critiques the participation rates used in the HSP. The FDA was aware of the participation rates and concluded that this was not a source of bias in the study results (MDL no. FDA00485, at 14–15, “The difference in participation rates between cases and controls does not bias the study findings”). Unless eligible controls who refused to participate in the study were more likely to be exposed to PPA than controls who did participate, the control participation rate would not affect results of the study. The investigators wrote to the *New England Journal of Medicine* editors, “We know of no reason why control subjects who choose to participate would be differentially exposed to PPA compared to control subjects who choose not to participate” (MDL no. HSP-Y-0022357). Dr Ralph Horwitz, the lead investigator for the HSP, testified that “There was no evidence that there was selection bias introduced by the 36% participation rate for controls using random digit dialing” (Horwitz deposition, p. 376).

The FDA also was fully aware of the statistical power of the study and p values. These issues were discussed in the FDA reviews and are disclosed in the Final Report of the study to the FDA (MDL no. FDA00485, MDL no. FDA00498, Tables 1–5). Stier and Hennekens (1) do not mention that the power was calculated and results were analyzed by using a one-tail test of significance, but in the *New England Journal of Medicine* article, results were reported with two-sided p values (3). The study design was approved by the PPA manufacturers, the FDA, and the Scientific Advisory Group ([SAG]; Brass Dep., p. 605; Kernan Dep., p. 487; Horwitz Dep. p. 511). Stier and Hennekens point to a finding that was “based on just seven participants (six exposed cases and one exposed control),” failing to mention that the study was designed with a low exposure expectation. The authors estimated that “0.502% of control subjects would report an exposure to [PPA] within 24 hours before the focal time” (3).

Stier and Hennekens question direct referrals in the study. The HSP principally enrolled cases by monitoring hospital admission logs for patients with hemorrhagic stroke. The HSP study centers enrolled nearly all the acute-care hospitals in their geographic locations (Brass Dep. p. 578). The three exposed direct referrals would have been enrolled anyway from the admission logs when they were admitted to the hospital (Brass Dep. p. 578). In addition, the article overlooks the fact that in addition to the

27 PPA exposed cases and 33 exposed controls, there were more than 40 additional PPA exposures (cases and controls) that were not included as exposed to PPA in the analysis, pursuant to the study protocol, because they were outside the exposure window or because they ingested PPA after the identified focal time (MDL no. HSP-Y-0029089-91).

The article criticizes the loss of blinding of interviewers. However, unblinding of interviewers that could have pushed the study to overestimate the true effect was addressed by the medication verification procedures: “Only verified exposures to medication were counted in the analysis” (3). The verification procedures required subjects to pick out brand name medications from a book and produce the medication container so that the lot number could be recorded (3). In addition, the structured interview instrument provided additional assurances that interviewer bias, if any existed, would not be an issue that impacted on the results (3). The FDA was made aware that interviewers were not blinded (Horwitz Dep. P. 165), and it was disclosed in the Final Report, provided to the FDA (MDL no. FDA 00498, at 22).

Because the investigators were not able to maintain blinding because of publicity about the study, they decided to eliminate the requirement for blinded interviewers. This protocol change was approved by the SAG and study sponsors (Kernan Dep. p. 501; Brass Dep. p. 479). No one raised any concern that the loss of blinding would undermine the validity of the study. Such epidemiologists as Dr Hennekens recognize that blinding is not critical to a successful study. In their book *Epidemiology in Medicine*, Hennekens and Buring wrote that blinding should be used “insofar as possible” in recognition of the difficulty in achieving that objective (7).

The article questions the loss of blinding in Rhode Island because the consent form references PPA. Although this was an obvious error, any impact is entirely speculative:

1. There were a total of 43 hospitals from six states in the study; thus, any impact would be limited to subjects enrolled at Rhode Island Hospital (3).
2. For there to be any impact, the subject would have to know what “PPA” is. As noted in market research conducted by one of the PPA manufacturers, few consumers were aware of the ingredients in cough/cold products (MDL no. NOV00590). Subjects were not asked about ingredients; they were asked to identify medications they took by product name, e.g., Dimetapp, (Wyeth, Madison, NJ) Tavist D, (Novartis, E. Hanover, NJ) etc. The article also misleadingly cites a deposition of a plaintiff who also was a case subject in the study, claiming she was told that the study was about PPA. The investigators mischaracterized the testimony. The witness testified that she was not told what medications the study was investigating, that she did not know what

PPA was, she was not told what products contained PPA, and that she thought the study was about phenylamine, an ingredient in gum and diet soda (Littlejohn Dep. P. 165-166).

3. Assuming the reference to PPA somehow triggered more subjects to name a product that turned out to contain PPA, for there to be any effect from the PPA reference in the consent form, the reported use would have to be a false report, and the study's verification procedures, designed to weed out false recalls of PPA exposures, would have to fail.
4. Because the consent form was used for both controls and cases, any effect should operate in both groups in the same manner and thus have no impact on the results.
5. Documents from the PPA manufacturer's lobbyist (Consumer Healthcare Products Association [CHPA]) show the distribution of exposed cases and controls by region, and Rhode Island contributed a disproportionately low number of exposed cases and exposed controls (Doc no. NCH256257, at 13, Tables 1 and 2). Rhode Island enrolled 14% of all cases and controls in the HSP, but only 10% of exposed cases and 5.1% of exposed controls. This indicates that the consent form error in Rhode Island had no substantive effect on the conduct of the study.

Stier and Hennekens fail to mention any of these five points.

The article raises the issue of recall bias, but fails to mention that verification procedures in the study addressed recall bias (3). It also fails to consider the effect of nondifferential misclassification, which would tend to bias the effect measures toward the null (8).

The article also questions a change in the definition of "first use," but does not mention that this change was made with knowledge of the FDA, SAG, and the study sponsors. The change in the definition was applied consistently to all subjects. Stier and Hennekens (1) also misstate the reason for the change, which really was because "cases and controls both expressed a great deal of uncertainty regarding exposure within [the 7-day clear period] window," and "the data...allows the investigators to be more confident about exposures within a 14-day window" (MDL no. HSP00159, at 5-6). All protocol changes, including this one, were approved by the FDA (Horwitz Dep. p. 174). At the time of the change, there were only two exposed cases (MDL no. HSP00159 at 5-6), whereas at the end of the

study, there were seven (MDL no. HSP00159 at 3, Table 4). Thus, at the time the change went into effect, no one could have known what effect the change would have on cases not yet enrolled. Finally, although the length of the clear period changed midstudy, for the analysis, the same definition of "first use" was applied to all subjects.

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Richard Clapp is an epidemiologist on the Faculty of the Boston University School of Public Health. He provided expert testimony and reports regarding the HSP and its subsequent publications on behalf of the plaintiffs in the MDL. He received no remuneration for work on this letter.

Michael Williams is a plaintiffs' attorney from Portland, OR, who has represented many clients who ingested PPA-containing cough and cold products. He was an active participant on behalf of the plaintiffs in the Daubert hearings in the PPA MDL.

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