

Other studies provide support for our hypothesis that asthma attacks increased. In the *Morbidity and Mortality Weekly Report*, a telephone survey 5 to 9 weeks after 9/11 determined that 13% of respondents had asthma. Twenty-seven percent of these persons had increased severe asthma after 9/11. Although seasonal increases in asthma attacks were expected, the increased severity was also associated with self-reported (1) psychologic stress and (2) cough and dyspnea temporally associated with exposure to dust fumes.³

"Comparing the *P* values for the increases in visits differed significantly between the groups. A repeated-measures analysis would almost certainly show that they did not."¹ We did conduct a repeated-measures ANOVA by using the Statistical Package for the Social Sciences (SPSS), and this analysis indicated that the rates of increases in visits differed significantly between the groups. Although the effect of location (region) was not significant, there was a significant interaction of location over time ($P < .05$), suggesting differential rates of changes in asthma visits over time in the 2 regions.

"A repeated-measures analysis would likely show no significant difference between region 1 and region 2 children in the change in mean peak flow from before to after 9/11."¹ We did conduct a repeated-measures ANOVA with SPSS to analyze data collected for the third and fourth quarters of 2001. This analysis confirmed that the post-9/11 decrease in the percentage peak flow rate for region 1 was close to that of region 2 ($P = .06$).

"Region 2 children had nearly twice the number (of) rescue inhaler doses at baseline, suggesting significant differences between the groups in pre-9/11 management, severity, or both."¹ Data regarding rescue inhaler doses were limited and therefore highly positively skewed; therefore no meaningful conclusions can be inferred from these results.

"Oral steroid use, presumably a marker of severe asthma exacerbations, was similar and decreased by a slight but similar amount in both groups."¹ We agree that oral steroid use data were limited, and therefore no meaningful conclusions can be inferred from these results.

"For virtually every analysis, the authors present neither data on the number of children contributing data on a given measure in a given time period nor a comparison with children with missing data. This precludes assessment of potential selection bias." The selection bias caused by missing data is a legitimate concern for any study. More than 80% to 95% of children had their height and weight measured. About 75% to 82% of the sample contributed to the quarterly data of the predicted peak expiratory flow rate values. About 88% to 94% of participants contributed to all clinical parameters (see Table II and III of the original article), except for the "rescue inhaler doses," which was measured only in 65% of the participants. We also examined the demographic characteristics of those patients included in the study and those patients who had missing data on a few key measures and found that those with missing data were quite comparable with the final sample included in the reported analysis. (*P* values ranging from .48 to .62).

We appreciate the opportunity to provide answers and clarifications.

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Significance of the eudismic ratio and enantiomeric purity of the albuterol distomer

To the Editor:

I found the results about the opposite pharmacological effects of albuterol enantiomers on the contractility of the human bronchial smooth muscle obtained by Agrawal et al¹ very interesting, but I think that the controversy surrounding this issue is headed in the wrong direction.

Going back to the basics, the interaction between the enantiomers of a chiral drug and the β_2 -receptor takes place according to the 3-point contact model. This means that, although the eutomer has an effective pharmacological action because it can connect to the receptor at 3 active sites simultaneously, the distomer still is able to connect to an active site, and it may have weak or very weak pharmacological activity.

The affinity ratio between the eutomer and the distomer, as described by Lehmann et al,² is known as the eudismic

ratio, and, as stated by Agrawal et al,¹ it was found to have a variable value between 500 and 1000 for the albuterol enantiomers in a variety of cell systems and human cloned receptors. This is a very high value, and its variability might be ascribed, at least partially, to traces of eutomer in the distomer. If the distomer is contaminated with the eutomer, the effects shown by the authors may be a result of the minimal amount of eutomer, or they may be the result of an interaction between the enantiomers at a fixed ratio different from the racemate rather than the effect of the distomer, per se. Also, the higher the eudismic ratio, the more uncertain is its true value, because minute traces of the eutomer in the distomer are difficult to detect by current analytical methods.

When the degree of enantiomeric purity is not known, the results of the pharmacological characterization of chiral compounds are in doubt, and the conclusions regarding chiral aspects of structure-activity relationships should be regarded with caution. Because even small amounts of eutomer contaminating the distomer can make a great difference in results, the authors should have made known from the beginning the purity of the distomer and the method used to determine it.

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Reply

To the Editor:

I would like to thank Dr Jalba¹ for his comment and concern on the potential contamination of eutomer in the distomer of albuterol. It was an oversight on our part not to mention the purity of enantiomers in our article.²

In our study, we used albuterol enantiomers from a single lot with the purity of the enantiomers as follows. (S)-albuterol hydrochloride was 99.93% pure, with 0.02% of the minor isomer. (R)-albuterol hydrochloride was 99.88% pure, with 0.11% of the minor isomer. Racemic albuterol sulfate was 99.31% pure. The structures of these enantiomers are provided (Figs 1-3).

We agree with Dr Jalba's comments that contamination of the distomer with the eutomer may result in some of the findings shown in our article. However, in view of the high purity of the distomer, it is highly unlikely that 0.02% contamination of (S)-albuterol with minor isomer will elicit such a profound effect on the expression and activity

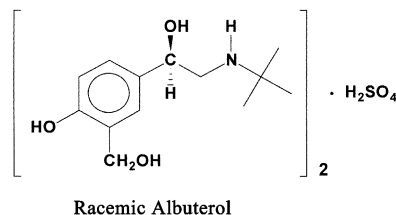


FIG 1. Racemic albuterol.

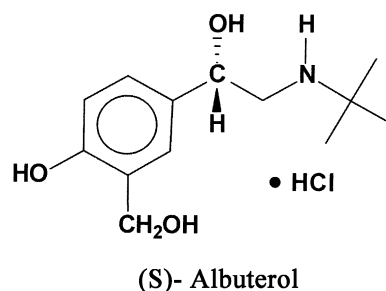


FIG 2. (S)-albuterol.

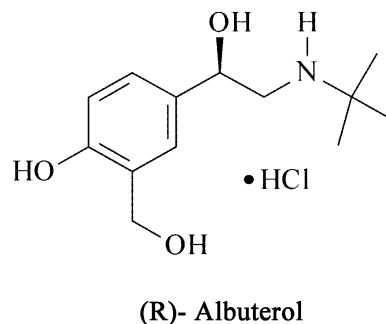


FIG 3. (R)-albuterol.

of G-proteins and nuclear factor κ B in human airway smooth muscle cells. On the basis of the findings reported in our article as well as the follow-up study on the potential binding sites of (S)-albuterol,³ we believe that (S)-albuterol binds to a site independent of (R)-albuterol to activate inflammatory pathways. Furthermore, (S)-albuterol binding sites are primarily present intracellularly in human airway smooth muscle cells.

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