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# Cystic Fibrosis Research News

## Title:

Tobacco Smoke Exposure Limits the Therapeutic Benefit of Tezacaftor/Ivacaftor in Pediatric Patients with Cystic Fibrosis

## Authors:

Elizabeth Baker, PhD[1]; William T. Harris, MD[1]; Steven M. Rowe, MD, MSPH[1]; Sarah B. Rutland, PhD[1]; Gabriela R. Oates, PhD[1]

**Affiliations:** Elizabeth Baker, PhD[1]; William T. Harris, MD[1]; Steven M. Rowe, MD, MSPH[1]; Sarah B. Rutland, PhD[1]; Gabriela R. Oates, PhD[1]

## What was your research question?

Research in animals and in people who do not have CF shows that exposure to tobacco smoke leads to the CF gene (the cystic fibrosis transmembrane regulator, CFTR) not working correctly. Since CFTR modulators partially restore the function of the CF gene, we wanted to see if exposure to tobacco smoke reduces the treatment benefit of CFTR modulators. We focused on tezacaftor/ivacaftor (Symdeko), which was approved in February 2018 for people with CF age 12 years and older.

## Why is this important?

One-third of children and adolescents with CF in the United States are exposed to second-hand smoke, and this proportion is even higher in other countries. As CFTR modulators become a first-line treatment for CF, children and adolescents who are exposed to smoke may see less benefit from these novel treatments. Tremendous resources have been deployed to develop CFTR modulators and make them available to all people with CF. It is important to know if their effect is lessened by environmental tobacco smoke.

## What did you do?

We analysed data from the U.S. CF Foundation Patient Registry (2016-2018). We compared how lung function changed before and after treatment with tezacaftor/ivacaftor (Symdeko) in children and adolescents with CF who are exposed to tobacco smoke compared to those who are not. Exposure to tobacco smoke was determined from caregiver self-report. We accounted for the prior use of lumacaftor/ivacaftor (Orkambi) and for interruptions in tezacaftor/ivacaftor (Symdeko) use.

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## What did you find?

The sample included 6,653 individuals. Those taking tezacaftor/ivacaftor who were exposed to smoke had a lower baseline lung function and experienced a greater decline in lung function compared to those who were not exposed to smoke. Over two years, the difference in lung function between smoke-exposed and unexposed users of tezacaftor/ivacaftor increased by 1.2%, from 7.6% at baseline to 8.8% at the end of the study (Figure 1). In statistical models taking sociodemographic and clinical characteristics into account, treatment with tezacaftor/ivacaftor was linked to an improvement in lung function of approximately 1.5% among children and adolescents who were not exposed to smoke, but provided no benefit to their smoke-exposed counterparts (Figure 2).

## What does this mean and reasons for caution?

We found that exposure to tobacco smoke cancels the benefit of tezacaftor/ivacaftor (Symdeko). A major limitation is the self-reported nature of the smoke exposure information. Biochemical tests that measure actual exposure would be preferred to confirm our conclusions. We only assessed the effect of smoke exposure rather than active smoking. We also acknowledge the large variation in duration of treatment with tezacaftor/ivacaftor (from 0 to 672 days) and number of lung function tests (from 1 to 44) before and after drug initiation.

## What's next?

This finding demands programs and services to eliminate tobacco smoke exposure in children and adolescents with CF, particularly those who take CFTR modulators. Future studies will determine the effect of smoke exposure on the therapeutic benefit from ivacaftor (Kalydeko) and elexacaftor/tezacaftor/ivacaftor (Trikafta).

## Original manuscript citation in PubMed

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**Figure 1. Lung function of tezacaftor/ivacaftor users by tobacco smoke exposure (TSE)**

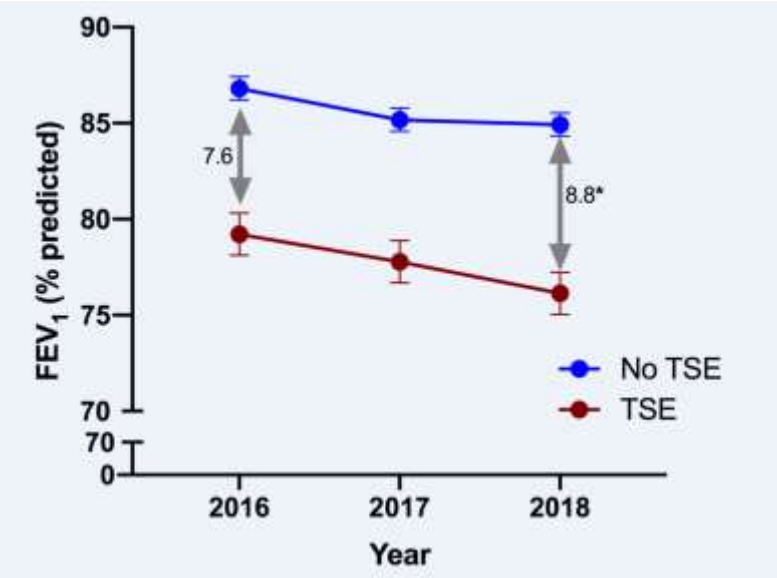


**Figure 2. Lung function by smoke exposure and tezacaftor/ivacaftor use**

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