Questions and Answers? Depression Symptoms Associated with Elexacaftor/Tezacaftor/Ivacaftor Treatment for Cystic Fibrosis

In the modulator era of cystic fibrosis (CF) care, there are some answers that are clearly established. Elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) therapy significantly increases CFTR (CF transmembrane regulator) protein function for approximately 90% of people with CF (pwCF) who have responsive CF mutations such as the common phe508del mutation (1). It has been shown to significantly improve lung function, reduce pulmonary exacerbations, and improve quality of life (1), with registry data modeling suggesting a substantial increase in life expectancy, possibly to near normal if started in childhood (2). Yet in this translational phase of the era, there are many questions that cannot yet be answered—so many, in fact, that the "state of the art" seems to be coming to terms with this and accepting that attempts to answer new questions only raise even more.

One very important question arose when ELX/TEZ/IVA was first licensed in 2019, with the emergence of case reports and small case series suggesting that some pwCF reported increased depression symptoms in association with initiation (3–8). In this issue of the *Journal*, Ramsey and colleagues (pp. 299–306) report on a valuable study systematically assessing whether there is any association between ELX/TEZ/IVA use and depression symptoms in pwCF (9). They used four main sources: pooled clinical trial data, registry information and postmarketing surveillance data, and a systematic literature review. The resulting data suggest that depression-related events observed in pwCF taking ELX/TEZ/IVA are generally consistent with the background epidemiology of these events in the CF population.

Reassuring perhaps, but is the question answered? Not quite. There may be a subgroup of pwCF who have worsening depression symptoms masked by a group of patients who experience improvement. Certainly, case reports and small series have suggested that a small proportion of individuals may have worsening depression symptoms that in some cases may improve with dose reduction or cessation of ELX/TEZ/IVA (7, 8). Ramsey and colleagues (9) discount these because of the lack of control groups and the fluctuating nature of depression symptoms, but it would seem wise to gain more data on these individuals before we dismiss these studies completely, as some patients did report subjective benefit from dose reduction or cessation. On the other hand, there are clearly individuals who have reported huge transformative gains in health and quality of life with ELX/TEZ/IVA that would be anticipated to improve mental health. Correspondingly, it might be considered strange that Ramsey and colleagues were unable to show a reduction in depression symptoms overall in pwCF after ELX/TEZ/IVA initiation. In fact, their Figure 1 suggests that the prevalence of depression, certainly in the United States CF Foundation Patient Registry, continues to increase year on year, despite the introduction of ELX/TEZ/IVA. The question of whether this is at least partly due to the additional impact of the coronavirus disease (COVID-19) pandemic and lockdown on mental health remains unanswered.

The 12 studies assessing change in Patient Health Questionnaire-9 (PHQ-9) score (the depression symptom module of a wider screening measure) cited by Ramsey and colleagues (in their Table 3) suggest generally reassuring population mean responses, but looking at each study in detail paints a more complex picture (9). Seven of the 12 studies present the ranges of individual changes in PHQ-9 score with ELX/TEZ/IVA initiation, and all seven show a subgroup of pwCF who had worsening depression symptoms associated with initiation (determined by increased PHQ-9 score). Borawska-Kowalczyk and colleagues (10) reported that although there was no overall change in PHQ-9 score, 15% of pwCF had increased scores after ELX/TEZ/IVA initiation. Piehler and colleagues (11) demonstrated clearly that although overall the group showed reduction in depression symptoms as measured by PHQ-9, there was certainly a proportion of subjects who had worse PHQ-9 scores after commencing ELX/TEZ/IVA therapy; indeed PHQ-9 score increased by 17% in the group with minimal depression symptoms at baseline (*see* Figure 1).

Similarly, Blackwelder and colleagues (12) reported that in adults with low PHQ-9 scores at baseline, scores increased by a mean of 0.53 after ELX/TEZ/IVA initiation, in contrast to a control group of pwCF not taking ELX/TEZ/IVA, who had an average decrease of 0.58, removing a pandemic-effect explanation. Zhang and colleagues (13) reported that although there was no overall significant change in PHQ-9 score, 5% of patients received new mental health diagnoses, and 22% increased, switched, or added psychotropic drugs, suggesting that a subgroup may have had worsening depression symptoms. Pudukodu and colleagues (14) focused their analysis on data that were exclusively prepandemic and reported that 21% of patients initiating ELX/TEZ/IVA therapy had significant increases in PHQ-9 score, balanced by 18% who had significant decreases. A study by Sakon and colleagues (15), although showing a reassuring mean decrease in PHQ-9 score of -1.11, saw a range of -22 to $+14$, and 9% of respondents reported that ELX/TEZ/IVA therapy had been associated with a decline in mental health. Lastly, Dell and colleagues' (16) data were collected during the pandemic, and five respondents reported shifts from "normal" to "severe" mental health symptoms associated with ELX/TEZ/IVA initiation.

As the CF community transitions to the new era, there are many things that were known that are no longer known. There are now questions that have no adequate answers. However, this does not mean that helpful responses cannot be generated. Ramsey and colleagues' (9) paper will reassure the CF community that at a population level, ELX/TEZ/IVA therapy does not appear to be associated with a worsening in depression symptoms. Yet important questions remain. Are a small proportion of individuals particularly
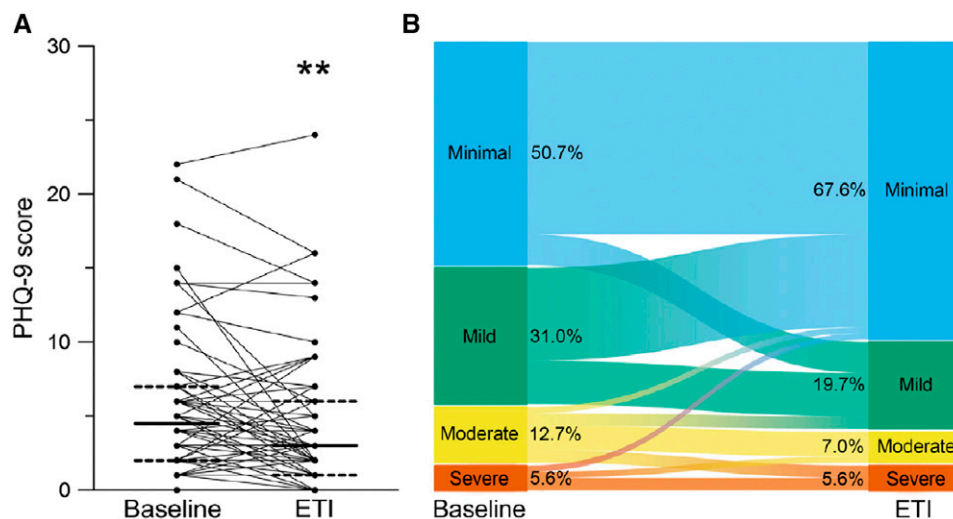
Figure 1. Effects of ELX/TEZ/IVA on symptoms of depression measured by Patient Health Questionnaire-9 (PHQ-9) score, measured at baseline and at 8–16 weeks after the initiation of ELX/TEZ/IVA in 70 adults with cystic fibrosis. (*A*) Paired individual PHQ-9 scores. Solid lines represent the group median and dashed lines represent 25th and 75th percentile. (*B*) Alluvial graphic showing the flow of individuals' PHQ-9 scores among minimal, mild, moderate, and severe depression symptom categories, demonstrating that a proportion of individuals had worse PHQ-9 scores with ELX/TEZ/IVA therapy. **Denotes $P < 0.01$ compared with baseline. Reprinted by permission from Reference 11. ELX = elexacaftor; ETI = elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; TEZ = tezacaftor.

prone to mental health issues on ELX/TEZ/IVA, and can we identify them in advance? Are the reported depressive side effects simply a "starting phenomenon" that will improve as the therapy delivering life-changing benefits is continued? Are there any effects on anxiety or behavior in younger children? Questions, questions, questions. ∎

Tim W. R. Lee, M.D.
Leeds Centre for Children's Respiratory Medicine
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

Alistair J. A. Duff, D. Clin. Psych.
Leeds Centre for Children's Respiratory Medicine
and
Department of Paediatric Psychology
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

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⚷ Adding Pieces to the Puzzle: Ultrafine Particles and Lung Cancer

Ultrafine particles (UFPs) in the air are so small that they weigh close to nothing (1). Nevertheless, they are around in bountiful amounts—if you are standing alongside a busy road, expect to inhale around 3 million of them with every breath you take (2). What makes this particularly worrying is the fact that toxicologists have claimed that these ultrafine particles may be especially unhealthy if they get into your lungs. They are so small that they can escape pulmonary clearance mechanisms, transport carcinogens such as polycyclic aromatic hydrocarbons adsorbed on their huge mass-specific surface deep into the lungs, reach the alveoli where they cause oxidative stress, and even cross biological membranes, thereby getting access to the systemic circulation and end-organs (3).

Most regulatory systems around the world are based on mass concentrations of particulate matter—an extremely useful measurement that is relatively easy and cheap to conduct and therefore ideal for widespread monitoring. In fact, effective regulation of air pollutant emissions and concentrations based on particle mass have led to substantial improvements in air quality and reductions of air pollution–related morbidity and mortality in many regions of the world (4, 5). However, these regulations based on particle mass are not able to protect against the potential adverse effects of UFP exposure, at least to the extent to which they are not correlated with fine particle mass.

So, what are these independent effects of UFP on human health? Unfortunately, we do not know yet for sure (6). Only in the last 20 years alongside the development and more widespread use of instruments that can count particle number concentrations (instead of mass concentrations) has the investigation of UFP-related health effects under real-world circumstances begun. However, measuring and modeling of UFP remains expensive and is not a routine element of air quality monitoring yet. Modeling of long-term exposure is exceptionally difficult, as models need to capture very small-scale concentration differences occurring within a city on a scale of 20 to 50 m (7). Therefore, we still lack a comparable evidence base that we now have for fine particles and their long-term effects on health. Because of this lack of sufficient evidence, the World Health Organization refrained from deriving guideline values for UFP in its most recent Air Quality Guidelines, instead only formulating a "Good Practice Statement" on measuring, classifying, and investigating UFP-related health effects (2).

The study by Jones and colleagues in this issue of the *Journal* (pp. 307–315) adds a valuable piece to the puzzle of long-term effects of exposure to UFP (8). The paper reports on a large cohort study of more than 45,000 participants and almost 1,800 lung cancer cases, investigating the association of lagged long-term UFP exposure with the incidence of total and subtype lung cancer, revealing mixed results.

Clearly the most difficult issue in this study, as in other studies on long-term UFP exposure and health, is the exposure assessment back in time. Jones and colleagues used a land use regression model to predict long-term UFP exposure at participants' addresses. This land use model was based on a measurement campaign of mobile 30-minute measurements conducted in 2016. Concentrations were also back-extrapolated to the 1980s and 1990s. Because there are no UFP data available for comparison and validation of this approach, the authors compared the model output with historical UFP measurements from exposure studies after the year 2000, displaying moderate correlations but a systematic underestimation of UFP concentrations.

The authors combined the cohort data with the information from cancer and mortality registers. To estimate lung cancer hazard rates, 2-year risk sets were defined throughout the follow-up period. For all individuals covered in each set, 5- and 10-year exposure lags were obtained. The Cox proportional hazards model was adjusted to the minimally required set of the potential confounders defined in a directed acyclic graph. A set of stratified analyses were done to show the relationships within different risk factors. Several interesting issues were addressed in this paper.

The high spatial resolution of the land use regression model with a relatively high explained variance is an important asset of the study, as it allows picking up small-scale traffic-related exposure differences in the study population. Interestingly, one of the main predictors of UFP exposure was distance to airports—a still-underappreciated potential source of UFP exposure in the general population. The backward extrapolation technique used in the paper allowed for the recreation of historical UFP concentrations. Although this technique is not novel *per se*, it has not been applied to UFP exposures before. Validation with the few available historical UFP measurements showed acceptable results, encouraging exposure scientists and epidemiologists alike to make use of historical data. Attention should be given, though, to different size cut-offs and time periods when using this kind of data, as measurement techniques have evolved and changed substantially during the past decades.