Psychological wellbeing post Elexacaftor-Tezacaftor-Ivacaftor (ETI) treatment in Cystic Fibrosis

Abstract

Objectives: Cystic Fibrosis transmembrane conductance regulator (CFTR) modulator therapies have brought about significant physical health improvements however, numerous post-marketing observations have suggested a potential linkage between ETI therapy and deleterious mental health outcomes, proposing an important area of study.

Methods: Fourteen adult participants (males: 6; age range: 22 – 45 years; average FEV1: 82.71%) who had experienced a change in psychological wellbeing post-modulator therapy were recruited via social media to participate in a semi-structured interview. Following a deterioration in mental health two participants were on a reduced dose of ETI therapy and three participants had stopped ETI therapy.

Results: Alongside the manifest benefits of ETI therapy there are several new challenges a small but significant minority within the Cystic Fibrosis (CF) population are experiencing. Participants discussed a debilitating deterioration in psychological wellbeing post-ETI therapy including new and/or worsening depression, anxiety, suicidality, hallucinations, impaired memory, and hormonal changes. Changes in mental health were attributed to the challenge of acclimatising to a change in identity by some people, while others considered changes to be direct side effects of ETI-therapy.

Discussion: Being able to provide safe and effective care for physical and psychological wellbeing is critical in CF care. Alongside the physical health benefits associated with ETI therapy, there may be serious psychological implications for a minority of individuals with CF which require proactive and effective psychological support.

Key words: Cystic Fibrosis; ETI Therapy; Elexacaftor; Tezacaftor; Ivacaftor; Mental Health; Qualitative Methods

Cystic Fibrosis (CF) is the United Kingdom's (UK) most common life-limiting genetic disease (Elborn, 2016; Jackson & Pencharz, 2003) which affects approximately 10,600 individuals within the UK (The CF Trust, 2021). Historically, treatments for CF aimed to reduce severity of symptoms and slow disease progression. In 2019 modulator therapies became available in the UK via the National Health Service (NHS), targeting the underlying cause of CF by treating and correcting specific genetic mutations (Fajac & De Boeck, 2017; Keyte et al., 2017; Zemanick & Accurso, 2019). Currently, modulator therapies are available for 90% of the UK CF population (The CF Trust, 2022), with many individuals reporting a beneficial impact on physical health (Keyte et al., 2022).

Notwithstanding the excitement and hope that surrounds modulator therapies, significant challenges remain for the CF population, specifically surrounding psychological wellbeing. Keyte et al. (2022) highlighted survivors' guilt and difficulty adapting to a new self-identity following the health benefits post-modulator therapy. Research suggests the need for proactive psychological support to be embedded into CF care, encompassing acceptance (or non-judgement) of an illness identity and physiological health status to enhance quality of life and feeling content with the life that is lived in the present moment (Keyte et al., 2022). In addition to survivors' guilt and new identity challenges, people with CF have an existing higher risk of anxiety and depression (Quittner et al., 2016) with evidence suggesting that this may be elevated with CFTR modulator therapy (Dagenais et al., 2021; Jeghers et al., 2023; Talwalkar et al., 2017; Van Citters et al., 2024). It is essential for research to understand the psychiatric adverse effects associated with CFTR modulator therapy (Bathgate et al., 2025).

Original clinical trials for modulator therapies found little to no effect on depression and anxiety, however, numerous post-marketing observations indicated a potential linkage between ETI therapy and deleterious mental health outcomes (Arslan et al., 2023), with the Medicines and Healthcare products Regulatory Agency (MHRA) in May 2025 releasing an update acknowledging a small increase in the risk of psychological side effects post-ETI therapy such as anxiety, low mood, sleep disturbances, poor concentration, and forgetfulness (The CF Trust, 2025). This update follows research, case studies, and anecdotal evidence which report various mental health and neurological alterations after initiating ETI therapy. Reported changes which align with the MHRA update include anxiety, depression, cognitive impairment, memory deficits and sleep paralysis; however research, case studies and anecdotal evidence have also documented psychosis, hallucinations, suicidal thoughts, and suicide attempts (Arslan et al., 2023; Heo et al., 2022; Lyman et al., 2022; Tindell et al., 2020) which have led to an interruption or discontinuation of therapy for some individuals (Lyman et al., 2022). It is crucial for research efforts to actively comprehend the psychological challenges encountered by the entire CF community and to recommend evidence-based support mechanisms. This is vital for ensuring the sustained use of, and adherence to essential physiological treatments.

The current research provides a qualitative exploration into individuals' attitudes and beliefs surrounding what has contributed to their change in psychological wellbeing following ETI therapy. Focusing on the minority in the CF population with declining mental health is crucial, as it can significantly impact disease progression and overall quality of life. Research in this area can offer insights for healthcare providers to develop tailored interventions that enhance wellbeing for all individuals with CF.

Method

Participants

Adults aged 18 years or above with a diagnosis of CF, who had experience of being prescribed ETI therapy were eligible to participate. The research was advertised as wanting to interview individuals who had experienced a change in mental health / wellbeing post-ETI therapy (e.g., an increase in psychological wellbeing, or a decrease in psychological wellbeing). Eligible participants were recruited via social media over four months (Twitter, Facebook and Instagram), and recruitment ran until data saturation occurred.

Fourteen participants (males: 6, females: 8; age range: 22 – 45 years; mean age of participants: 31 years) were recruited with a median forced expiratory volume in 1 second (FEV_1) 82.71% predicted. Following a deterioration in mental health two participants were on a reduced dose of ETI therapy and three participants had stopped ETI therapy. Nine participants were from England, two were from Scotland, two were from the USA and one was from Wales (all participants were English speaking) (see Table 1).

INSERT TABLE 1

Semi-Structured Interview

The semi-structured interviews investigated participants' beliefs about their CF and life-impact, and then explored views and experiences with ETI therapy, focusing on any changes in psychological wellbeing. The qualitative methodology allowed for exploration of the defined areas, and elaboration by participants on other related topics (Gill et al., 2008), with question wording and order being contextual and in response to the participants' developing accounts (Braun & Clarke, 2013; Rubin & Rubin, 1995).

The semi-structured interview schedule (see appendix A) was informed by existing literature and discussions that people with CF were having via social media and was reviewed and discussed with a patient representative. All interviews were conducted online via MS Teams, with the interviews lasting a maximum of 60 minutes (mean: 49 minutes).

Ethical Approval

Ethical approval was obtained via the Business, Law and Social Sciences Faculty Research Ethics Committee at [insert University] (ref: [insert]). Written informed consent was obtained from all participants, who were given a pseudonym.

Analysis

The recordings of the interviews were transcribed verbatim. The data were analysed using reflexive thematic analysis following Braun and Clarke's (2019) model. Researchers adopted an integrative realist/constructivist approach, allowing for individual discussion and interpretation of what it is like to live with CF.

To ensure the integrity of the data, the lead researcher kept a reflective diary throughout data collection and analysis, with data triangulation being achieved in several ways. Participants were recruited internationally providing different sources of information to the study, and the research findings were presented at an international conference, an international webinar, and at a CF study day with Healthcare Professionals (HCPs) to obtain multiple perspectives on the data.

Results

Three themes were generated from the data set providing an exploration into participants' attitudes, beliefs and experiences with ETI therapy and the impact this treatment is having upon psychological wellbeing. Participants were specifically recruited if they had experienced a change in psychological wellbeing post-ETI therapy, with the findings exemplifying the impact this change in psychological wellbeing is having upon individual's lives, providing insight into what interventions may be effective in CF care when e.g., deteriorations in mental health occur alongside ETI therapy.

Note: Throughout the results section there is reference to side effects. The researchers are using the language of participants within this description and wish to acknowledge to readers that these are not proven side effects, but detailed accounts provided by individuals with CF regarding their experience with modulator therapies (in particular ETI therapy).

The fragility of a 'normal' life following ETI therapy

The more 'normal' life made possible by ETI therapy is experienced by participants as precarious with it being contingent upon the therapy continuing to work and remaining accessible. Participants described the daily struggles they experienced prior to ETI therapy as a contrast to their current health status. Complex medical regimens, frequent hospital admissions, and health deteriorations led to participants missing school, impacted on career aspirations and led to some participants deciding not to have children. Several participants explained that CF was a psychological burden impacting their self-worth as they saw themselves as a burden on others.

> *[Paisley, 31 years]: Even though you wanna date people, you feel like you don't deserve somebody. Who is gonna accept me [with CF]? I'm damaged goods […] CF messes with your sense of self-worth and how much you're really valued.

A number of participants explained how CF impacted their psychological wellbeing prior to ETI therapy; Adam explained how the impact on mental health was more difficult to cope with than the physical implications of the condition.

> *[Adam, 38 years]: I could deal with the physical [Pre-ETI therapy], whereas the mental side of things I always found much more difficult to control […] you're working really hard to try and keep yourself well, but you're ultimately failing, and mentally I was always like well you're just a mad person because you're doing the same thing every day expecting to get a different result.

Many participants did appear to have accepted CF's fatal nature, maintaining a "realistic mindset" towards their future which would often incorporate planning for one's funeral and putting provisions in place for anticipated ill-health. Nonetheless, the reality of witnessing one's health deteriorate regardless of adherence efforts remained a major challenge for many prior to ETI therapy.

The despair experienced by participants in response to their deteriorating health status explicates the hope and optimism that many held in anticipation for ETI therapy. The huge relief experienced by individuals on accessing modulator therapies was clear, with most participants explaining that ETI therapy has exceeded their hopeful expectations, coining the treatment a "miracle" and "life-changing" after experiencing increases in lung function, weight gain and energy levels.

> *[Richard, 36 years]: When you look at a chest x-ray now compared to pre-Kaftrio, they're just a normal set of lungs. There's no scarring, there's no blockages, there's no plugs […] I haven't had a chest infection since the day I started.

These health benefits have had a direct impact upon psychological wellbeing and quality of life, with some participants explaining that now their health is stabilised the "emotional burden" of CF has lifted.

However, the dramatic improvement in physical health also engendered a fear that somehow this cannot last, for some, this fear was centred around the idea that their body would "let them down". Paisley worries that her body may become allergic to ETI therapy, with Adam exemplifying how strongly the fear of losing such health gains impacted his mental wellbeing.

> *[Adam, 38 years]: I went the most anxious I probably have ever been in my life [when it was mentioned that his dose of ETI therapy may have to change]. I was so tempted not to go to the hospital to have the scan […] I said this to her [the Dr], and I meant it, that I don't know if I'd rather not live then go back to not having Kaftrio. I can't go back to how it was. I wasn't suicidal by any respect […] but I couldn't have coped without it [ETI therapy].

This is a salient reminder that the positive benefits of ETI therapy bring fresh challenges of which HCPs need to be mindful. Several participants voiced the idea that living without the health gains of ETI therapy was so unbearable that they would prefer not to live. This led

them to consider just how detrimental the mental impact must be for someone to make the choice of discontinuing ETI therapy.

> *[Adam, 38 years]: To contemplate or to actually come off the drug [ETI therapy] because of how you're feeling mentally must mean that you are in a really fucking low place, and therefore you have to acknowledge that […] I would rather not live than come off it.

All participants voiced the need for more research into the reported mental health and neurological side effects following commencement of ETI therapy.

Embodied change disrupts identity

Starting ETI therapy was momentous, described as "a day in the diary where everything stopped and started again". The new start brought drastic improvements in physical health and with this, a need for participants to interpret and incorporate this changed body and health status into their sense of self as a person with CF. Several participants discussed the conflicting emotions they have experienced since commencing ETI therapy, being happy for themselves, but sad for those who are not able to experience the benefits for different reasons. Shannon and Richard both described this as "survivors' guilt".

> *[Richard, 36 years]: I'm immensely grateful and fortunate for that [ETI therapy], especially when there is that 10% of people that don't qualify and that percentage of people that started and can't carry on […] there is a tinge of guilt. Guilt that we have it and they don't. A guilt that I've genuinely lost count of the amount of people I know that have died with CF […] Guilt for their family that this didn't come soon enough. Guilt for them.

The co-existence of survivor's guilt and gratitude made it difficult for those who were experiencing a deterioration in mental health post-ETI therapy to disclose these struggles to

others. Shannon described worsening mental health (anxiety and depression) on commencing ETI therapy but initially told no one.

> *[Shannon, 22 years]: All the people whose lives have been saved, it feels that if you've had a negative experience, kind of being open about that, you're damaging the positive ones and taking away people's hope who think that it's this like miracle and it's gonna be perfect.

This illustrates the current emotional complexity for the CF community. Some participants, such as Katie, Kirstie and Lewis explained how, following the health benefits of ETI therapy, they started to process previous CF-related trauma they had experienced.

> *[Katie, 36 years]: It's definitely opening a dam after Kaftrio because your brain, once you're well […] you have to process the trauma, but my body wouldn't allow me to before. It didn't have any energy to cope with any of that […] It's definitely got some PTSD elements to it.

Katie exemplifies the damaging impact that processing her prior trauma had upon her mental health, comparing her experience to post-traumatic stress disorder. For Katie she felt like her "brain switched off", going from a "really positive, motivated person" to someone who would do nothing all day, was not interested in social interaction, did not have energy to take care of personal hygiene, to cook or clean, and emotionally had a flat affect. Katie described experiencing thoughts about hurting herself, having no prior experience of poor mental health.

> *[Katie, 36 years]: I remember sitting in the car and thinking maybe the only way to like snap me out of this is like, what if something happened? Like, what if we had an accident?

In addition to having to process previous trauma, individuals with CF have had to adapt to a change in their identity, with participants such as Katie, Paisley, Lewis and Richard explaining that whilst the "overnight physical change" was amazing, it was overwhelming and took time to process.

> *[Lewis, 24 years]: I was dying […] I wasn't stressed. I didn't have any anxiety […] I was accepting, I knew what was gonna happen, I'd been over it over 100 million times. I was at peace waiting for the day.
>
> *[Richard, 36 years]: CF isn't likely to be the cause of death, which is all I've ever thought about. Is it gonna be, I don't know, obesity where you're putting on so much weight? Is it gonna be cancer? Is it gonna be something else? All those things that you planned for, thought about, just disappear. That takes its toll.

Participants explained how they had to acclimatise to this new era of CF care in isolation without regular clinic visits due to the COVID-19 pandemic and with no (or minimal) hospital admissions due to their improved (physical) health status. Katie illustrates how challenging it was navigating life without "a huge support system".

> *[Katie, 36 years]: I've always had such a lot of people looking after me and now it's almost me looking after myself. Looking back, I did feel lonely, and not able to cope with the big processes and changes.

The data illustrates the need for a continuation of holistic care that includes support for broader stress and quality of life issues related to increased longevity. Individuals are now planning for an unexpected future, having to arrange pensions and life insurance, with participants explaining how others do not understand the juxtaposition of this challenge. They are grateful to have this future, but emotionally it is demanding.

*[Katie, 36 years]: I've got all these different paths that I could take, you know, work wise, financially, kids, and all different things […] I didn't prepare to do anything else with my life […] I was like a retired person at 35 years old. To be given this magic drug, which is incredible and then told go out into the world and do what you wanna do is actually really scary.

Some individuals explained how today the things they "stress and worry" about are not in relation to their CF but surround daily life stresses e.g., occupational stress, financial worries. Some, like Holly, believe that ETI therapy has exacerbated their prior mental health struggles, with it being plausible that a change in identity, and a focus on life outside of CF can result in stresses and anxieties becoming intensified.

*[Holly, 29 years]: I had more control over my mental health before Kaftrio. If I get problems with CF I know how to correct it. But when it is something else in my personal life, if I got no control over it, I can't fix it, that's when the anxiety sort of kicks in.

In addition to psychological challenges around identity, many participants described gaining weight post-ETI therapy that was neither medically advised nor desired impacting identity, self-esteem and psychological wellbeing. Shannon and Jason felt that no matter how they modified their diet, or how much they exercised, they could not lose weight whilst on ETI therapy; this (alongside additional mental health deteriorations) resulted in Shannon decreasing her dose of ETI therapy and Jason stopping ETI therapy.

*[Shannon, 22 years]: What's the point of good lungs? I just hate the way I look, I hate the way I feel. I can't stop eating because of my mammoth appetite. I don't have any control over my body.

*[Jason, 30 years]: I put on three stone. That was making me feel bad about myself; the way I physically looked, I didn't like it [...] my concern was what is this doing to my body internally. When I was on Kaftrio I was exercising more, doing fasting, just

> trying to lose weight but I couldn't […] I was really worried cause my Dad passed away through heart problems. My Mom's had a heart problem. There was me putting on a lot of weight and not consuming many calories. I was like hang on what's it gonna do to me?

As evident from participants narratives the increase in weight is resulting in a decrease in body satisfaction and body esteem, and creating additional health anxieties in individuals regarding their general health (outside of CF). Bodily changes were more than a cosmetic factor, they also proposed a form of identity disruption with participants describing a loss of control over their body and negative appraisals towards their 'new' body.

This theme demonstrates the clear and pressing need for targeted psychological support to help individuals acclimatise to a change in identity and the challenges which may accompany life on ETI therapy. Several participants such as Craig, Kirstie, Shannon and Richard believed that the changes in mental health that some individuals are experiencing post-ETI therapy cannot just be explained in terms of a changing identity. Some participants strongly believed that their deterioration in mental health was a side effect of ETI therapy.

Breathing better while feeling worse: The paradox of ETI therapy health changes

This final theme provides insight into the mental health, neurological and hormonal changes some participants experienced, which they believed to be side effects of ETI therapy. These experiences left participants struggling to reconcile the immense physical health gains with considerable psychological and cognitive costs. For some individuals (e.g., Hannah, Daisy and Jason) it was apparent from their discourse that prior to ETI therapy their mental health was good, describing themselves to be "happy and resilient" individuals; whereas other participants (e.g., Holly, Katie, Craig and Shannon) had had prior experience with mental health struggles, believing ETI therapy exacerbated these. In addition to a history of mental health symptoms, there were also differences reported regarding the onset of side effects. For Hannah, Holly, Katie and Jason their side effects appeared gradually, whereas Kirstie and Shannon described a very sudden and drastic change in their psychological wellbeing (along with hormonal and neurological changes).

*[Jason, 30 years]: Roughly after one year on Kaftrio it all started [Jason began to recognise changes in psychological wellbeing]. Before then I was feeling quite low moods, not understanding them, I wasn't really sure what was bothering me.

*[Kirstie, 45 years]: This is really strange but all these things [anxiety, pain, tremors, dissociation disorder, vaginal bleeding] happened at once within two weeks of starting Kaftrio.

For participants who are experiencing a change in psychological wellbeing post-ETI therapy it is emotionally a very confusing time.

*[Kirstie, 45 years]: I have two feelings about Kaftrio, and I was like, well, how can I have two feelings? But you can feel grateful but also feel kind of resentful at the same time.

A range of mental health, neurological and hormonal symptoms were reported by participants, with many expressing that they do not feel like themselves whilst taking ETI therapy. This became even more apparent when participants missed doses of ETI therapy, with Hannah explaining how after forgetting to take her ETI therapy for four days she felt "mentally clearer". Shannon, who takes ETI therapy twice a week due to exacerbations in anxiety and depression, illustrated the drastic change in her psychological wellbeing on the days she does take ETI therapy, however, she continues with the treatment due to the beneficial physical health impact.

*[Shannon, 22 years]: I kind of dread when I do take it cause I'm like, I know it's gonna wipe me out […] it is sort of like a sick day; I know I'm not really gonna be very with it […] I'm learning to drive at the minute but on those days [when taking ETI therapy] I really feel it isn't safe driving [due to brain fog].

In addition to not feeling like oneself, Kirstie and Jason described experiencing symptoms of dissociation disorder, not feeling like they were in their body and not being sure who they were whilst taking ETI therapy, neither of whom had encountered such symptoms previously.

> *[Kirstie, 45 years]: I didn't feel like I was in my body […] I was looking at my hands like, are these my hands? I'm not really sure.
>
> *[Jason, 30 years]: I had like an out of body experience. I didn't feel myself, I didn't know who actually who I was at one point.

Alongside the sense of not feeling like oneself, many participants experienced what they described to be brain fog with this impacting their memory and cognition and therefore their daily lives. All participants reported never experiencing brain fog previously.

> *[Kirstie, 45 years]: Really unable to think straight. I was in this kind of fogginess. I couldn't remember stuff like people's names who I have known for years, like work stuff, my boss would ask what did you do this morning? But I couldn't actually remember.

For several participants, the side effects they reported were in line with symptoms of depression, with eight participants illustrating the low mood they experienced in response to ETI therapy. Such participants described an overwhelming feeling of sadness which consumed their lives, with Katie, Daisy and Jason being prescribed anti-depressants whilst taking ETI therapy despite having no history of medication for their mental health prior to ETI therapy.

> *[Hannah, 26 years]: I was numb to the world. Physically I was in the room but mentally I was elsewhere.

> *[Kirstie, 45 years]: I would just cry at nothing […] I felt really depressed. I've never had depression. It felt like somebody had sucked all the happiness out me and left like the misery and sadness. I don't think I even smiled last year.

Participants exemplified the impact a low mood had upon their lives resulting in a lack of personal hygiene, a lack of motivation to do anything or socialise, and having a detrimental impact upon work and relationships, with some participants explaining how they "neglected" loved ones whilst they "hid themselves away from the World".

> *[Jason, 30 years]: I couldn't look at anyone or talk to anyone. I just wanted to be alone, just doing nothing […] I neglected everyone around me.

For some individuals, such as Holly, Katie and Shannon, the low mood they experienced resulted in thoughts of self-harm and suicide which none had experienced previously.

> *[Holly, 29 years]: I had suicidal thoughts. I've never felt like that before; that low, to the point where I have felt like I didn't wanna wake up in the morning.

Alongside symptoms of depression, six participants reported symptoms of anxiety including experiencing panic attacks, impacting everyday life and sleep.

> *[Daisy, 23 years]: I'd kind of be falling asleep and I'd get this kind of surge. It was almost like I was falling but everyone kind of gets that from time to time. This was different. I was like whoa I'm having a stroke or something. I spoke to my doctor about it and it's a nocturnal kind of panic attack which I've never got before.

In addition to mental health side effects, a small number of participants reported what they believed to be neurological changes. Alexandra shared in detail how following

commencement with ETI therapy she collapsed and experienced paralysis on several occasions.

> *[Alexandra, 31 years]: I was talking in the kitchen [to my Husband] and suddenly my entire body. I thought I said to [Husband] I can't move, but he said I just went like, not a sentence at all, and then I just fell and I was unconscious and he caught me so I didn't hurt myself. I was only unconscious for two minutes, but when I came round my left-hand side was completely paralyzed and my left eye was blind. I thought I'd had a stroke. I was very, very scared. It came back after 15 minutes.

To treat these neurological side effects Alexandra was put on additional medications (e.g., amitriptyline) which resulted in additional side effects such as hallucinations. Alexandra was only able to stay on the full dose of ETI therapy for 15 days due to the intense neurological side effects she experienced. With HCP support she then tried various doses of ETI therapy before deciding to stop completely five weeks prior to the interview, during which time the side effects had considerably eased.

In addition to collapsing and paralysis Kirstie experienced pain and tremors, with Hannah and Alexandra experiencing constant headaches.

> *[Kirstie, 45 years]: I woke up one morning and felt really, really weird. I had a really bad headache. I felt sick. I had a burning sensation on my tongue. Tongue was swollen. I had a really rapid heartrate. I had tremors in my right hand and left leg. I was getting these waves of adrenaline, like adrenaline surges.
>
> *[Alexandra, 31 years]: Pain is something I can cope with […] but on this night I said [Husband] take me to A&E cause I think I'm having a brain haemorrhage. I thought I was going to die. I stopped Kaftrio and it cleared up within 48 hours [excruciating pain in eye and head], just gone.

As with the mental health side effects reported, these neurological changes had a devastating impact on participants ability to lead their normal everyday lives, impacting work and family relationships, as well as socialisation and personal care.

The final side effects reported were classed by participants as hormonal changes. Alexandra and Kirstie both experienced prolonged vaginal bleeding which did not stop whilst they were taking the full dose of ETI therapy.

> *[Kirstie, 45 years]: Three days after starting Kaftrio I started bleeding and it went on and on and on. I bled for 25 days. And it was like clots, like big clots […] I was getting really anaemic, so my GP put me on the progesterone only pill to stem the flow, but it didn't actually stop it, it just made it like really light but I continued bleeding.

In addition to prolonged vaginal bleeding, Kirstie explained how she believes that ETI therapy has resulted in her experiencing the menopause, within five weeks following commencement.

> *[Kirstie, 45 years]: I went onto a Facebook group which is run by medical specialists who deal with the menopause, and I looked at their checklist and I had every single symptom. All this happened within bought 5 weeks of me starting Kaftrio. There's about 38 things on that checklist […] there must be a hormone link.

Kirstie is now on a reduced dose of ETI therapy (she does not take Ivacaftor) in order to reduce these effects, with this being recommended by her HCPs.

Individuals who experienced mental health (or neurological and hormonal) side effects following ETI therapy explained how they ultimately had to choose between their physical health and their psychological wellbeing. Richard, who had experienced a continuous low mood since starting ETI therapy, explained how he favoured his physical health over his mental health, whereas other participants such as Jason felt they were left with no choice but to stop ETI therapy due to severity of their mental health crisis.

*[Richard, 36 years]: The positives far outweigh the negatives for me, but I am a million times grumpier. I definitely have a shorter fuse. My moods are lower, but for that there are benefits […] it's probably more frustrating for my wife, but she'd rather me be grumpy and alive than happy and dead.

*[Jason, 30 years]: I was in a really bad vortex of bad emotions; yes if I stop Kaftrio CF is gonna come back and I'm going to cough, but my mind every day, I remember just feeling confused, tired all the time.

Participants, such as Hannah, Katie, Alexandra, Daisy and Jason, explained how their quality of life was worse on ETI therapy than without the drug, with their mental health side effects being far more challenging to deal with than life with CF. Some participants, such as Jason, explained that because they were "well for a CFer" they found it easier to stop ETI therapy, however, Alexandra explained that even though she did really need ETI therapy due to her physical health she would prefer to die young than be on ETI therapy.

*[Alexandra, 31 years]: They're [HCPs] like well maybe we can revisit this [going back on ETI therapy] because your chest isn't doing great. No, sorry. I would rather it all catch up with me and that I die younger than live a longer life that I'm not me and I can't drive and the kids are scared of me.

Regardless of health status, stopping ETI therapy was an extremely difficult decision as understandably, no one wanted their "CF to return". The cessation of side effects reinforced their belief that this was the correct decision for themselves, with Jason explaining that on stopping ETI therapy he no longer requires anti-depressants. However, having experienced a new normal of better physical health people were highly conscious of deteriorations.

*[Hannah, 26 years]: The lung side of it all has regressed back to where it was, which is quite difficult to deal with. Because before that's just what you were used to, but now that you see that it actually shouldn't be like that and you've kind of seen that the

> grass is greener in a lung kind of way, when you get those symptoms back, it almost feels worse than it did before because you are aware of how it should be.

The need for effective, proactive psychological support to be embedded into CF care is clear. The participants who discussed the side effects they have experienced explained how awareness regarding these side effects is not widely provided (e.g., in clinical settings, within the CF community, in the media) which means that many individuals experiencing a deterioration in their psychological wellbeing are suffering in silence. All participants who experienced side effects explained how it took them time to associate such side effects with ETI therapy. Therefore, all participants (regardless of whether they themselves have experienced side effects) are passionate for research to be conducted into the impact ETI therapy can have upon mental health. The general consensus amongst participants was that raising awareness of potential changes in psychological wellbeing in CFTR use is crucial, and that any reporting of such changes should be taken seriously. Alexandra, Kirstie, Shannon and Daisy all discussed that their HCPs initially dismissed any possible connection between ETI therapy and the mental health, neurological or hormonal changes they were experiencing.

> *[Kirstie, 45 years]: I spoke to my CF team a few times [about hormonal changes]. Some of them are in complete agreement and some are quite dismissive. I feel some of them have their own agenda […] they are kind of very desperate, and rightly so, for it to work, and it does work incredibly well, but there are definitely things going on […] I felt almost they were gaslighting me; well that can't be your experience.

Kirstie's understanding of HCPs as being reluctant to acknowledge negative aspects of ETI therapy reflects the reticence shown by participants to raise any doubts or concerns which might jeopardise its availability for everyone. This fear and uncertainty illustrate a clear need for a proactive response that acknowledges and addresses the way in which both patients and HCPs may minimise or even hide negative aspects of taking ETI therapy.

*[Katie, 36 years]: We need people to come to us because when you're in crisis you can't reach out. You don't know how to find the information, you need people to come to you.

All participants emphasised the need for easy access to psychological care to be embedded within the CF team in order to prepare individuals for what life on CFTR modulator therapy will look like, the change in identity, the potential side effects; to provide support for those not eligible; for those who can no longer take ETI therapy; and for those experiencing side effects.

Discussion

The data provides insight into living with CF today through an exploration of attitudes, beliefs and experiences with modulator therapies (predominantly ETI therapy). ETI therapy has brought transformational benefits to individuals with CF, however, the experiences of participants in this study illustrate the complexity of this. The improvement in physical health has enabled many to lead a "normal" life which was previously unthinkable, however, this new normality is felt as fragile and conditional, dependent on access and tolerance to new therapies. Participants are also navigating the development of a new identity, they are no longer "just" a chronically ill person with CF. This may be further complicated by bodily changes such as weight gain with all the social and personal conflicts this may bring. Participants also described a tension between physical and psychological wellbeing and having to make difficult decisions over what aspects of health to prioritise. Overall, these findings highlight that the impact of ETI therapy is broader than biomedical, it necessitates a reshaping of identity, psychosocial wellbeing and personal meanings of health, emphasising the need for holistic care including targeted psychological support.

Whilst some participants attributed their change in psychological wellbeing to be due to their change in identity, other participants believed their reported mental health, neurological and hormonal changes were side effects of ETI therapy. It has to be noted that participants were specifically recruited if they had experienced a change in psychological wellbeing post-ETI therapy, with it being acknowledged that it is likely to be a small minority within the CF population who are experiencing a e.g., decline in mental health, however, the current study illustrated how for those who are experiencing such side effects they are having

a detrimental impact upon their everyday lives and their quality of life. For some participants the impact ETI therapy had upon their mental health and quality of life was not worth the physical health benefits, resulting in them stopping ETI therapy.

The underlying mechanisms responsible for the side effects being reported remain unknown, hence further research is much needed. Participants' narratives indicate that reducing or stopping ETI therapy improved their psychopathology, supporting previous findings of a link between ETI therapy and declining psychological wellbeing, despite possible psychosocial stressors (e.g., Tindell et al., 2020). Sergeev et al (2020) speculated that modulator therapy may cross the blood-brain barrier and have a direct action on CFTR. Other research, based on studies with non-CF mice, suggests that Ivacaftor may have a potential positive impact on behaviour. However, the decline in mental health observed in some CF individuals could be attributed to Elexacaftor and Tezacaftor, which may have serotonin-related effects that counteract the effects of Ivacaftor (Jalal, 2018; Kometer et al., 2013; Schneider et al., 2018; Tindell et al., 2020). Further research is required to assess the precise influence of CFTR modulators on the central nervous system (Bathgate et al., 2025) and to investigate the long-term consequences of the side effects experienced by individuals during the initial and progressive stages of usage (Heo et al., 2022). Simultaneously, it is crucial to acknowledge the debilitating nature of the side effects, as articulated by participants in the present study, and for care providers to actively seek information around this for the development of support mechanisms.

As discussed previously, mental health, neurological and hormonal changes resulted in some participants stopping ETI therapy or altering the dose used to reduce their side effects. It is important to note that altering the drug has not been evaluated by the manufacturer or FDA. Hence, there is a pressing demand for further investigations, as the current state of knowledge does not elucidate whether the merits of continued ETI therapy at a diminished dosage, with the aim of enhancing psychological wellbeing and preserving physical enhancements, surpass the potential hazards. This particular dosing regimen has yet to undergo empirical evaluation (Heo et al., 2022; Jeghers et al., 2023).

The experiences described by participants show the complex interplay between physical health improvements and psychosocial adjustment illustrating the importance of considering outcomes wider than merely physiological ones. The illness identity that a person holds who has lived with a life-limiting condition such as CF is not automatically changed with health improvements, instead a person must navigate towards a new sense of self. Identity is reconstructed through comparison with what is normal, and for people with CF

this version of normality is defined alongside a baseline of what is normal for CF. ETI therapy has disrupted or changed the normal, and the narrative identity theory suggests a person must integrate their past and imagine their future in order to give life unity and purpose, and to support mental wellbeing (McAdams & McLean, 2013). The paradoxical nature of physical improvements alongside changes in mental wellbeing, cognitive and hormonal symptoms illustrate the importance of a biopsychosocial model of health where the lived meaning of health for individuals is considered, emphasising the need to integrate psychological and identity focused support with physical health care.

Alongside the need for widening the evidence base in regard to psychological wellbeing and CFTR modulator therapy, it is important to reflect on what qualitative work brings to the discussion. Participants in this study strongly believed the changes in mental health experienced were due to ETI therapy. Many participants sought advice and information from their CF teams and when they did not feel validated in their experiences, they looked to a range of other sources including online information and other users' experiences which undoubtedly vary in quality and accuracy. Consequently, whilst it appears that it is a minority within the CF population who are experiencing mental health (or neurological or hormonal) side effects, being able to provide safe and effective care for both physical and psychological wellbeing is critical. The findings illustrate the support people would like integrated into their care, with many suggesting the need for proactive psychological support.

Based on the findings of the current research it is recommended that CF care incorporates validated questionnaires or screening tools to monitor individuals for new and/or worsening depression, anxiety, suicidality, hallucinations, impaired memory, and hormonal changes upon commencing modulator therapies (and in future studies of CFTR modulators). Such monitoring is particularly needed to identify individuals considering the taboo nature of mental health. Many participants illustrated that when experiencing a deterioration in mental health they found it difficult to seek help (with feelings of survivor's guilt and gratitude for the physical health benefits exacerbating this). There is certainly an ability to proactively support people with CF and to create cost-effective and proactive schemes of support (e.g., Czerwinski et al., 2020; Kauser et al., 2023; Kauser et al., 2022a, b; Keyte et al., 2020; Mantzios & Egan, 2016).

Study Limitations

This research has some limitations. The research only included individuals with CF above the age of 18 years, however, since 11th January 2022 ETI therapy has been approved by the European Commission and MHRA for eligible children aged 6-11 years via the NHS (The CF Trust, 2023), with the MHRA Drug Safety Update noting that in some children side effects may show in changes to behaviour, such as being more disruptive (The CF Trust, 2025). Consequently, research is needed to investigate attitudes, beliefs and experiences with modulator therapy within a paediatric population to further inform healthcare. Furthermore, the majority of participants discussed experiencing a change in mental health post-ETI therapy, with only three participants discussing neurological changes and two discussing hormonal changes. It must be noted that causal inferences cannot be made about the experiences discussed within this research article and ETI therapy. Whilst some individuals seemed to illustrate a clear relationship e.g., between their deteriorating mental health upon commencement of ETI therapy, other participants accounts have a more tenuous link (e.g., it cannot be concluded that for the female aged 45, who experienced symptoms associated with the menopause, that that was directly due to ETI therapy). Therefore, further research is needed to investigate more fully the neurological and hormonal changes (as well as mental health changes) some individuals are reporting following commencement with ETI therapy, and what support such individuals require, with neurological and hormonal changes currently not being acknowledged as side effects by the MHRA.

Conclusions:

Notwithstanding the excitement that surrounds modulator therapies, there may be serious psychological implications a small number of individuals with CF are experiencing which require proactive and effective psychological support. Data suggests the need for increased awareness amongst HCPs (and therefore patients) that CFTR modulators (in particular ETI therapy) may result in mental health (and neurological and hormonal) changes, with the MHRA's drug safety update (The CF Trust, 2025) being a positive step forward in beginning to recognise the many complex side effects a small number of individuals with CF are reporting. In conjunction with heightened awareness, it is imperative to implement vigilant and up-to-date mental health screening protocols to support individuals in this evolving era of CF care, with there being a critical need for treatment modification guidelines to effectively prevent and address mental health issues occurring concurrently with ETI therapy. The present research serves as a vital call to action for the enhancement of overall care and wellbeing of the CF community.

References:

Arslan, M., Chalmers, S., Rentfrow, K., Olson, J.M., Dean, V., Wylam, M.E., & Demirel, N. (2023). Suicide attempts in adolescents with cystic fibrosis on elexacaftor/tezacaftor/ivacaftor therapy. *Journal of Cystic Fibrosis, 22,* 427-430.

Bathgate, C.J., Fedele, D.A., Tillman, E.M., He, J., Everhart, R.S., Reznikov, L.R., Liu, F.F., Kirby, K., Raffensperger, K., Traver, K., Riekert, K.A., Powers, S.W., & Georgiopoulos, A.M. (2025). Elexacaftor/tezacaftor/ivacaftor and mental health: A workshop report from the cystic fibrosis foundation's priotitizing research in mental health working group. *Journal of Cystic Fibrosis, 24,* 301-309. doi: 10.1016/j.jcf.2024.11.006oi:

Braun, V., & Clarke, V. (2019). Reflecting on reflexive thematic analysis. *Qualitative Research in Sport, Exercise and Health,11, 589-597.*

Braun, V., & Clarke, V. (2013). *Successful qualitative research; a practical guide for beginners.* London, UK: SAGE.

Czerwinski, N., Egan, H., Cook, A., & Mantzios, M. (2020). Teachers and mindful colouring to tackle burnout, and increase mindfulness, resiliency and wellbeing. *Contemporary School Psychology,* 1-5.

Dagenais, R.V., Su, V.C., & Quon, B.S. (2021). Real-world safety of CFTR modulators in the treatment of cystic fibrosis: A systematic review. *Journal of Clinical Medicine, 10,* 23.

Elborn, S. (2016). Cystic fibrosis. *The Lancet, 388,* 19-25.

Fajac, I., & De Boeck, K. (2017). New horizons for cystic fibrosis treatment. *Pharmacology & Therapeutics, 170,* 205-211.

Gill, P., Stewart, K., Treasure, E., & Chadwick, B. (2008). Methods of data collection in qualitative research: interviews and focus groups. *British Dental Journal, 204,* 291-295.

Heo, S., Young, D.C., Safirstein, J., Bourque, B., Antell, M.H., Diloreto, S., & Rotolo, S.M. (2022). Mental status changes during elexacaftor/tezacaftor/ivacaftor therapy. *Journal of Cystic Fibrosis, 21,* 339-343.

Jackson, R., & Pencharz, P.B. (2003). Cystic fibrosis. *Best Practice and Research Clinical Gastroenterology, 17,* 212-235.

Jalal, B. (2018). The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. *Psychopharmacology, 235,* 3083-3091.

Jeghers, M., McBennett, K., Roesch, E., & Prunty, L. (2023). Neurological and mental health adverse events witj CFTR modulator therapies at a cystic fibrosis center. *Journal of Cystic Fibrosis, 22,* S230-S231.

Kauser, S., Keyte, R., Mantzios, M., & Egan, H. (2022a). A qualitative exploration into experiences and attitudes regarding psychosocial challenges, self-compassion, and mindfulness in a population of adults with Cystic Fibrosis. *Journal of Clinical Psychology in Medical Settings, 29.*

Kauser, S., Keyte, R., Regan, A., Nash, E.F., Fitch, G., Mantzios, M., & Egan, H. (2022b). Exploring associations between self-compassion, self-criticism, mental health, and quality of life in adults with Cystic Fibrosis: informing future interventions. *Journal of Clinical Psychology in Medical Settings, 29.*

Kauser, S., Mantzios, M., Keyte, R., & Egan, H. (2023). Understanding the experiences of how mindfulness is used by people with Cystic Fibrosis: barriers and enablers. *Mindfulness,14,* 1-13.

Keyte, R., Beswick, L., Rayner, O., Bryon, M., Carr, S.B., & Medhurst, N. (2017). Orkambi: the expectations of benefit for people in the UK with cystic fibrosis. *Journal of Cystic Fibrosis, 16,* S77.

Keyte, R., Kauser, S., Mantzios, M., & Egan, H. (2022). The psychological implications and health risks of cystic fibrosis pre- and post- CFTR modulator therapy. *Chronic Illness.*

Keyte, R., Mullis, L., Egan, H., Hussain, M., Cook, A., & Mantzios, M. (2020). Self-compassion and Instagram use is explained by the relation to anxiety, depression, and stress. *Journal of Technology in Behavioral Science, 1-6.*.

Kometer, M., Schmidt, A., Jancke, L., & Vollenweider, F.X. (2013). Activation of serotonin 2A receptors underlies the psilocybin-induced effects on alpha oscillations, N170 visual-evoked potentials, and visual hallucinations. *Journal of Neuroscience, 33,* 10544-10551

Lyman, B.C., Seay, J., Contreary, C., Savant, A.P., Dell, M.L., & Hescock, G.C. (2022). Elexacaftor-tezacaftor-ivacaftor overdose in an adolescent female with cystic fibrosis. *Pediatric pulmonology, 57,* 3174-3176.

Mantzios, M., & and Egan, H.H. (2016). Mindfulness training may enhance the psychological well-being of people with cystic fibrosis. *Mindfulness*, 1-4.

McAdams, D.P., & McLean, K.C. (2013). Narrative identity. *Current Directions in Psychological Science, 22,* 233-238. doi: 10.1177/0963721413475622

Quittner, A.L., Abbott, J., Georgiopoulos, A.M., Goldbeck, L., Smith, B., Hempstead, S.E., Marshall, B., Sabadosa, K.A., & Elborn, S. (2016). International committee on mental health in cystic fibrosis: cystic fibrosis foundation and European cystic fibrois society consensus statements for screening and treating depression and anxiety. *Thorax, 71,* 26-34.

Rubin, H.J., & Rubin, I.S. (1995). *Qualitative interviewing: the art of hearing data.* Thousand Oaks, CA: SAGE.

Schneider, E.K., McQuade, R.M., Carbone, V.C., Reyes-Ortega, F., Wilson, J.W., Button, B., Saito, A., Poole, D.P., Hoyer, D., Li, J., & Velkov, T. (2018a). Erratum: "The potentially beneficial central nervous system activity profile of ivacaftor and its metabolites". *European Respiratory Journal, 4.*

Talwalkar, J.S., Koff, J.L., Lee, H.B., Britto, C.J., Mulenos, A.M., & Georgiopoulos, A.M. (2017). Cystic fibrosis transmembrane regulator modulators: implications for the management of depression and anxiety in cystic fibrosis. *Psychosomatics, 58,* 343-354.

The CF Trust (2021). *Cystic Fibrosis FAQs.* Retrieved on 13/09/2023 from: https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs

The CF Trust (2022). *No one left behind: The Cystic Fibrosis Trust's commitment to 'the 10%'.* Retrieved on 13/09/2023 from: https://www.cysticfibrosis.org.uk/news/no-one-left-behind.

The CF Trust (2023). *Triple combination therapy Kaftrio (Trikafta in the US).* Retrieved on 13/09/2023 from: Triple combination therapy Kaftrio (Trikafta in the US) (cysticfibrosis.org.uk)

The CF Trust (2025). *MHRA issues drug safety update for Kaftrio.* Retrieved on 09/05/2025 from: MHRA issues Drug Safety Update for Kaftrio

Tindell, W., Su, A., Oros, S.M., Rayapati, A.O., & Rakesh, G. (2020). Trikafta and psychopathology in cystic fibrosis: a case report. *Psychosomatics, 61,* 735-738,

Van Citters, A.D., Aliaj, E., Alvarez, J.A., Brown, C.D., Cary, J., Cravens, R., Frederick, C.A., Georgiopoulos, A.M., Goss, C.H., Kazmerski, T.M., King, J.R., Lawrence, M., Lovell, C., Roman, C., Tillman, L., & Yu, E. (2024). Wellness in the modulator era: An observational study of the impact of CFTR modulator therapy on the well-being of people with cystic fibrosis. *Journal of Cystic Fibrosis.*

Zemanick, E.T., & Accurso, F.J. (2019). Entering the era of highly effective CFTR modulator therapy. *The Lancet, 394,* 1886-1888.

Table 1. Medical and Demographic Data collected for all participants

Pseudonym	**Sex**	**Age**	**Latest lung function result (FEV1)**	**Is the participant currently taking Kaftrio?**	**Country**	**History of mental health (self-reported)**	**Current mental health (self-reported)**	**Treatment for mental health**
Adam	Male	38	95%	Yes	UK	Nothing diagnosed (previous anxiety surrounding the lung function test)	Discourse suggested anxiety / fear surrounding "losing" access to ETI therapy	Previous counselling due to anxiety with lung function tests
Hannah	Female	26	73%	No	UK; Scotland	None prior to ETI therapy.	Post-ETI therapy experienced brain fog, impaired memory, anxiety, not feeling like herself	Due to see a psychologist due to side effects of ETI therapy
Holly	Female	29	86%	Yes	UK; Wales	Low mood / slight anxiety but nothing diagnosed (mental health struggles are not about CF but daily life stressors). Mental health was more stable prior to ETI therapy.	ETI therapy exacerbated existing mental health struggles resulting in low mood and suicidal thoughts	Previously seen a Clinical Psychologist (one or two times). Currently seeing a Clinical Psychologist due to mental health changes post-ETI therapy.
Katie	Female	36	46%	Yes	UK	None.	Katie explained that she never dealt with the trauma of CF and is now processing that post-ETI therapy.	Previously seen a Clinical Psychologist due to anxiety regarding the use of oxygen in public. Now on anti-depressants post-ETI therapy.
Alexandra	Female	31	60%	No	UK	None.	Experienced what she described to	None prior to ETI therapy.

							be neurological changes post-ETI therapy.	Had to take medication to treat neurological changes whilst on ETI therapy.
Craig	Male	25	100%	Yes	UK	Previous anxiety as a teenager when realised about the reality of CF.	Anxiety and panic attacks post-ETI therapy.	Prescribed anti-depressants and seen a Clinical Psychologist when 15 years old.
Kirstie	Female	45	97%	Yes (but stopped Kalydeco)	UK	Previous anxiety (predominantly surrounding needles).	Experienced anxiety and depression post-ETI therapy amongst other complications e.g., symptoms of the menopause, dissociation disorder, heart racing, insomnia.	Previously seen a Clinical Psychologist for her needle phobia.
Shannon	Female	22	110%	Yes (but ½ dose)	UK	Anxiety and depression.	ETI therapy exacerbated anxiety and depression as well as resulted in weight gain (which impacted Shannon's body image) and insomnia.	Anti-depressants prior to ETI therapy
Daisy	Female	23	115%	Yes	UK; Scotland	Previous depression.	ETI therapy exacerbated mental health struggles resulting in panic attacks, sleep disturbances, low mood and an inability to cope with stress.	Previous counselling when 18 years old due to life circumstances. Started taking anti-depressants six months after commencing ETI therapy.

Paisley	Female	31	50%	Yes	USA	Anxiety and depression due to CF. .	Mental health improved post-ETI therapy	Anti-depressants / anti-anxiety medication (started taking these prior to ETI therapy).
Lewis	Male	24	74%	Yes	USA	None.	Experienced brain fog and changes in motivation post-ETI therapy.	None
Stuart	Male	33	82%	Yes	UK	Anxiety around life expectancy (nothing diagnosed).	No mental health changes post-ETI therapy.	None
Jason	Male	30	105%	No	UK	None.	Diagnosed with depression whilst taking ETI therapy.	Anti-depressants and counselling whilst taking ETI therapy (not required pre-ETI therapy and stopped once ceased ETI therapy).
Richard	Male	36	65%	Yes	UK	None. .	Low mood post-ETI therapy	None