THE PSYCHOLOGICAL IMPLICATIONS AND HEALTH RISKS OF CYSTIC FIBROSIS PRE- AND POST- CFTR MODULATOR THERAPY

Abstract

Objectives: Cystic Fibrosis (CF) care is entering a period of personalised medicine with the emergence of CF transmembrane conductance regulator (CFTR) modulator therapies. Anecdotally individuals are reporting life-changing effects of modulator therapies, proposing an important area of study.

Methods: Twenty adult participants (males: 8, age range: 22 – 51 years, average FEV_1: 53.45%) were recruited via social media to participate in a semi-structured interview; 17 participants were currently taking Elexacaftor/Tezacaftor/Ivacaftor (Kaftrio).

Results: An appreciation of a “normal life” post-modulator therapy is paramount, with improvements in symptoms and quality-of-life bringing a more urgent imperative for the provision of effective support to encourage positive health and lifestyle choices.

Discussion: In this new era of CF care, there remains many challenges present for the CF community, with participants suggesting that proactive psychological support is required along with proactive awareness regarding health risk behaviours for the current and future CF generations.

Keywords: Cystic Fibrosis; CFTR Modulator Therapies; Kaftrio; Trikafta; Qualitative Methods

Cystic Fibrosis (CF) is the United Kingdom's (UK) most common life-limiting genetic disease,[1, 2] caused by defects in a recessive gene (CFTR) located on chromosome seven, which affects approximately 10,600 individuals within the UK.[3] Symptomology for CF varies, but commonly affects respiratory and digestive systems and is incurable and progressive. The CF population have already experienced an increase in life expectancy; people born during the 1990s are expected to survive to more than forty years of age.[1] The need for a changed approach in healthcare to meet this new populations needs has been acknowledged, with calls for a more individualised approach[4] focusing on quality-of-life as a more holistic measure of health than, for example, lung function.[5] The reduced life expectancy does add an emotional burden,[6, 7] with Quittner et al.[8] reporting symptoms of depression and anxiety which significantly impair quality-of-life.[9] Research highlights the importance of prioritising mental health to maintain quality-of-life.[10]

Previous treatments for CF aimed to reduce the severity of symptoms and to slow disease progression, however, recently there has been the development of new medications which are revolutionising CF care. In 2019, modulator therapies became available in the UK via the NHS, with these drugs targeting the underlying cause of CF by treating and correcting specific genetic mutations, and are genome-specific.[11-13] Currently, modulator therapies (Kalydeco, Orkambi, Symkevi and Kaftrio) are available for 90% of the UK CF population,[14] however, quality-of-life, reformulations of identity and mental health have not been explored in this new era of CF care. Anecdotally individuals with CF today are reporting the changing effects of modulator drugs on physical health and quality-of-life, with reports of dramatic increases in lung function, weight gain, and the ability to participate in previously inaccessible activities. Research is needed to investigate the psychological implications associated with life-changes pre- and post- modulator therapies to provide a greater understanding and to inform future CF care and treatment.

The health benefits reported by people with CF post-modulator therapy is likely to impact self-identity. Whether an individual has accepted (or retaliated against) their *illness identity*, all individuals' lives will have been "restricted" by CF, and this will have influenced their identity as a person. Health risk behaviours (predominantly smoking, excessive alcohol consumption and illicit drug use) are prevalent within the CF population, with a desire to be normal, acceptance of CF and awareness of risks being influential in initiation and engagement.[15-17] The probability of future CF generations being more vulnerable to initiate in such behaviours due to their improved health status and impending new 'normal' identity needs to be explored. Aligned with health risk behaviours are concerns around adherence, particularly given the evidence that when people with CF feel well, they are less likely to adhere to their medical regimens.[15, 16] Research is needed to explore whether (and how) the improved health-status that may come with modular therapies changes identity and impacts health behaviours and psychological wellbeing.

While there is much excitement and hopefulness around modulator therapies from the CF community, these therapies will not be available or suitable for everyone. It is vital for research to proactively understand the psychological implications faced by the whole CF community during this period of medical advances to provide the appropriate evidence and support. The current research provides a qualitative exploration into how modulator therapies (or the prospect of modulator therapies) have affected individuals' lives, encompassing both physical and psychological wellbeing. This research will inform healthcare on how to encourage adherence and health behaviours in support of holistic wellbeing in this new era of CF care.

Method

Participants

Adults aged 18 years or above with a diagnosis of CF were eligible to participate, irrespective of being prescribed a modulator therapy. Eligible participants were recruited via social media over seven months (Twitter, Facebook and Instagram), and recruitment ran until data saturation occurred.

Twenty participants (males: 8, age range: 22 – 51 years; mean age of participants: 35 years) were recruited with a median forced expiratory volume in 1 second (FEV_1) 53.45% predicted. 17 participants were taking Kaftrio; one was ineligible for Kaftrio, one did not have access to Kaftrio in their country of residence (Australia), and one had to stop Kaftrio due to side effects. For participants currently taking Kaftrio their mean FEV_1 before Kaftrio was 35.75% predicted, with an average 14% increase in FEV_1 upon initiation with modulator therapies. 15 participants were from England, two were from the USA, one was from Ireland, one was from Germany and one was from Australia (all participants were English speaking) (see Table 1).

INSERT TABLE 1

Semi-Structured Interview

The semi-structured interviews started by investigating participants' beliefs about their CF and the impact CF has had upon their life, exploring reasons behind their lifestyle choices. The interview schedule then discussed views towards, and any experiences with, modulator therapies. The qualitative methodology allowed for exploration of the defined areas, and elaboration by participants on other related topics,[18] with question wording and order being contextual and in response to the participants developing accounts.[19, 20]

The semi-structured interview schedule (see appendix 1) 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. Due to the COVID-19 pandemic, all interviews were conducted online via MS Teams, with the interviews lasting a maximum of 60 minutes (mean: 42 minutes).

Ethical Approval

Ethical approval was obtained via the Business, Law and Social Sciences Faculty Research Ethics Committee at [insert University] (ref: [insert surname] /#7939/sub2 /R(A) / 2020 / Nov /BLSS FAEC). Written informed consent was obtained from all individual participants included in the study, with all participants being provided a pseudonym by the researcher.

A number of measures were in place should any participant become distressed during the interview. These included the interviewer explicitly acknowledging participants distress, initiating a break or termination of the interview if desired, moving on from the distressing topic or allowing the participant to express their distress whilst containing it within the context of the interview. These steps would have been taken in collaboration with the interviewee. Although none of the participants expressed distress during the interview, they were signposted to support services and encouraged to contact their CF team for further support if needed.

Analysis

The recordings of the interviews were transcribed verbatim. The data was analysed using thematic analysis following Braun and Clarke's[21] model, as this is a flexible method. A contextualist method was used as reasons for engaging in health behaviours are context-dependent.[22-24] Researchers adopted an integrative realist/constructivist approach, acknowledging that some aspects of living with CF exist independently of participants' constructions, e.g., that CF is a genetic disease, results in physical symptoms, is life limiting and that access and availability of treatments vary by genotype and geographical location. These realities of CF are constructed and understood within participants own experiences and therefore a flexible interview methodology was employed to allow for individual discussion and interpretation of what it is like to live with CF.

Codes were initially generated by one researcher, and subsequently revised and evaluated by everyone on the research team until they reached an agreement for each code. Themes were constructed together and confirmed once agreement on their representation of data was reached. Similarly, researchers evaluated how each code fitted (or not) within the themes. These collaborations helped to ensure the reliability of the data generated.

To further ensure the validity of the data the lead researcher kept a reflective diary throughout data collection and analysis, this allowed for them to consider how their prior knowledge of CF may influence interview prompts and to be conscious not to prompt around their own areas of expertise but rather to allow the participant to direct more. Data triangulation was achieved in a number of ways. Participants were recruited internationally providing different sources of information to the study. The research findings were presented at an international conference and at two different CF research meetings to obtain multiple perspectives on the data. Research findings were emailed to participants for feedback and were made available via social media inviting individuals with CF who had not participated in the study to provide feedback. Responses demonstrated support and agreement with the research teams interpretations of the data.

Results

Four themes were constructed from the data set (see table 2) providing an exploration into participants' attitudes, beliefs and experiences with modulator therapies. These findings exemplify what it is like to live with CF today, providing insight into what interventions may be effective in CF care.

INSERT TABLE 2

“I’ve always felt really pressured time-wise; I can’t think too far ahead”

This initial theme provides insight into what it is like to live with CF and the difficulty of living with a reduced life expectancy, with the increased emotional burden being clear (predominantly pre-Kaftrio). Participants, such as Emma, explained how the impact CF has upon their psychological wellbeing is often more difficult to deal with than the physical complications associated with their condition, with some participants explaining that they have lived with anxiety and depression for most of their lives.

> [Emma, 32 years] “I sort of got this conviction that I would maybe die at eighteen or twenty, or sort of turn eighteen and decline really bad in my health […] I think my mental health has been more affected than my physical health”

Whilst participants appeared to have accepted CF’s fatal nature and the complications associated with their CF, maintaining a “realistic mind-set” towards your future whilst continuously surpassing anticipated life expectancy does have a toll on mental health, with there being a clear need for psychological support embedded within the multi-disciplinary care for individuals with CF.

Several individuals reported self-imposed restrictions in their personal and professional lives, for participants such as George, Kirstie and Amelia this meant deciding not to have children due to their deteriorating health and reduced life expectancy. It is therefore not surprising that many individuals expressed the need to find ways to escape from CF; Katie, who is not eligible for modulator therapies, explained how in the past she used alcohol for this reason which she felt enabled her to have a normal identity.

> [Katie, 22 years] “There have been a few times where I’ve drunk a lot […] the reason was for just that night I wanted to be normal, and not have my CF […] I think it is a bit of an escapism”

Not fully engaging with treatment regimens also offers an escape from the illness identity and CF, with several people discussing how occasional non-adherence is inevitable due to a lack of time and forgetfulness. There was frustration that even with complete adherence health declines will occur, with George explaining how difficult life became, with his health deteriorating despite adherence efforts (before Kaftrio).

> [George, 36 years]: “There’s nothing worse than going into hospital or going for a clinic and your lung function has slipped even though you’ve been working your arse off […] it’s the most stressful, awful feeling in the world”

The despair experienced by George and others explicates the excitement and wonder at the positive health impact of modulator therapies.

“I feel like a completely different person, CF is barely ever on my mind, I don’t cough, my mind is clear”

This second theme provides insight into the extent and the nature of the impact modulator therapies are having upon physical health and quality-of-life. Many explained how they have “lived in hope that this day would come”; the overwhelming relief on accessing Kaftrio is clearly evident in Lucy’s data. Lucy was not eligible for previous modulator therapies and she had anticipated having only 10 years of life left prior to accessing Kaftrio. She had been emotionally preparing for “end stage CF” focusing on working on her “pain tolerance”. When Lucy finally received Kaftrio the experience was extremely emotional for both her and her family - she was excited and relieved to have the prospect of a brighter future, which for Lucy meant to feel better and to outlive her parents.

> [Lucy, 30 years]: “I cried tracking the UPS driver, and then I cried when it [Kaftrio] got here […] I bawled, foetal position on the floor […] I couldn’t move, it was so emotional for me and I was so excited”

For most people interviewed, the positive impact of Kaftrio exceeded their hopeful expectations, with participants reporting increases in lung function, energy levels and weight gain. Anthony explains how, at aged 51 years, he experienced unexpected improvements in his health.

> [Anthony, 51 years]: “The tablets probably took me back five or six years in time. I never envisioned I would get this function back”

It was clear from participants accounts the difference Kaftrio has made in reducing the burden of CF on their daily lives, with many participants perceiving that Kaftrio has improved all aspects of their physical health.

> [Kirstie, 35 years]: “There’s not a part of my body that doesn’t feel different - muscles, my lungs, my legs; like everything is different”

> [Amelia, 24 years]: “I used to have one meal a day, it would be a few mouthfuls of food and I used to feel sick all the time. I just hated food. Now I look forward to eating, I look forward to going out for meals. So that’s really good. I don’t feel sick and I don’t dread eating anymore, I enjoy it.”

These health benefits have had a direct impact upon psychological wellbeing, with several participants reporting that they have not required a hospital admission in over twelve months. Participants often reported feeling like they had been “born again” and had a “second chance at life”, with many explaining that Kaftrio has removed the “emotional burden of CF”. For many, the health benefits following Kaftrio were immediate and phenomenal, and were described as lifesaving by several people. George outlined that prior to Kaftrio living with CF was still dying with CF, whereas today his health status is the best it has ever been.

> [George, 36 years]: “What if I wasn’t taking this drug [Kaftrio]? I’d still be dying […] all the drugs, everything, it was probably just keeping me above the water”

The majority of participants experienced what they called “the purge”, explaining how their thick sticky mucus thinned, enabling them to “cough up” large amounts of mucus. The realisation that this amount of mucus was present in the lungs and would have remained so without Kaftrio was starkly felt. Following the purge, came the disappearance of the “cough, sputum and crackle”, enabling participants to identify, and be identified by others, as a ‘normal’ person. For Amelia the change in her health status was extraordinary; before starting Kaftrio Amelia’s parents were told to prepare for the worst, with Kaftrio being Amelia’s “only hope”.

> [Amelia, 24 years]: “I don’t cough anymore whereas before I used to cough constantly, from the moment I woke up. I could never enjoy myself going out because I was always coughing”

Another participant, Liam, was due to be listed for a lung transplant, with Liam explaining how Kaftrio has given him hope for the future. Kaftrio is allowing people to enjoy their life without constantly being preoccupied with their reduced life expectancy. Amelia discussed that her health deterioration was such that she had completed a do not resuscitate form as she did not want to live as she was any longer.

> [Liam, 39 years]: “I can see a future now. There was a time three years ago that I was concerned for my wife and my daughter. I saw a time of not being there for them, whereas now I can’t see me not being there […] it’s given me a lot of hope”

> [Amelia, 24 years] “I do actually want to live now […] I always used to sit back and look at people and think how can you enjoy being alive, but now I get it”

Within participants’ accounts, there was a clear shift from living in the now to living for the future, with this having implications for mental health, as well as identity formation and reformation, encompassing a range of things such as career opportunities and family planning. Many participants discussed the improved fertility status that a number of females like Lucy are experiencing as a result of Kaftrio.

> [Lucy, 30 years] “In January I got pregnant, it was incredible because we’d spent a year unsuccessfully trying to get pregnant, I mean I didn’t even have implantation, I didn’t have a miscarriage, I had nothing […] and then the first month we try [post-Kaftrio], I got pregnant”

In addition to the prospect of starting a family (for females with CF), many participants also discussed the impact Kaftrio has had upon their family and friends, explaining what a relief it is for their loved ones to see their improved health status, and to experience a reduction in “caring responsibilities”, with families being able to “enjoy life more” without the individual with CF having to miss out on events.

> [Kirstie, 35 years]: “She’s [Mum] been through all of it with me, and realising really that that stress is off her shoulders, that’s when you realise how much it affects other people. I was aware of that, but you can’t dwell on that when you’re in that situation. I’ve never considered myself a burden, but in some sense you are, but without wanting to be”

In terms of career opportunities, many participants explained how their improved health status means they can work, and be more ambitious about their career prospects, as they are no longer restricted by their life expectancy.

> [Ashley, 37 years]: “Because of Kaftrio I’m back at college to retrain [as a marine engineer for the Navy] so that has made a big big difference. I can develop myself a career”

Whilst this is really positive, some participants such as Kirstie illustrated how “terrifying” it is stepping back into the world of work, this was seen to be a welcomed challenge by participants, with individuals feeling like teenagers again. This is a reminder that alongside all the positive benefits of Kaftrio there does remain a number of challenges for the CF community which Healthcare Professionals (HCPs) need to be mindful of.

“Kaftrio really has caused a divide in the CF community”: eligibility, side effects, survivors’ guilt and dealing with the trauma of my past

This theme focuses upon some of the challenges the CF community are facing today. Participants’ who did not have a CFTR genotype considered eligible for Kaftrio (or previous modulator therapies) described a mixture of intense emotions - frustration and sadness for themselves, whilst being very happy for those who are eligible. Success stories on social media often elicited complex reactions including feelings of resentment and guilt by those not eligible, or those like Charlotte who had experienced side effects.

> [Charlotte, 40 years] “It was certainly demoralising, because obviously you’re happy for other people but you just feel a bit, not exactly resentful but you just think oh put a cork in it [on social media]”

Similar beliefs are shared by individuals who are eligible for Kaftrio, but currently do not have access to the therapy in their country of residence.

> [Caroline, 38 years (Australia)]: “Highly irritating […] it does feel a bit like torture, to know that it exists, and it’s as effective as it is, it’s literally sitting on a shelf somewhere […] meanwhile people are actually dying, or getting worse, so ultimately shortening their lifespan, and we just don’t have it”

All participants (regardless of eligibility status and experience with modulator therapies) felt that medical advances have provided hope that future drugs will be on the horizon, however, there was understandable anxiety about whether these “new drugs” would be available in time, with individuals in the 10% not eligible for Kaftrio in the UK feeling like the “forgotten individuals with CF”.

> [Katie, 22 years] “I did feel quite hopeless, and thinking oh god, and this is quite blunt, but like will I be alive when something like that for me happens”

Participants currently taking Kaftrio also experienced conflicting emotions, being happy for themselves, but sad for those who are not eligible for modulator therapies, or those who have passed away prior to Kaftrio, which Emma describes as survivors’ guilt.

> [Emma, 32 years] “I had a few days where I was feeling almost like survivors’ guilt […] I was so happy and relieved and at the same time I was also feeling awful because there are so many people that are worse than I’m doing and who need this drug so badly and can’t have it”

Consequently, despite the excitement that surrounds Kaftrio, it currently is an emotionally complex time for the CF community, with the need for psychological support being clearly demonstrated. On an individual level some participants such as Kirstie and Amelia illustrated how following the health benefits of Kaftrio they started to grieve for everything that had happened in their lives prior to this point (in terms of their CF), and started to process the trauma they have experienced.

> [Kirstie, 35 years] "I was equally happy and sad at the same time, because it was almost like the stages of grief. I was grieving what had happened to me through my whole life, and you have to face it as well"
>
> [Amelia, 24 years] "It just does still affect you mentally. Even though now I'm so much better than I was, and I *should* be happy, I'm still struggling"

Another area where participants demonstrated the need for psychological support was in the presence of side effects which can result in the termination of treatment, a treatment which many see as their "only hope". Regardless of experience with modulator therapies, anxiety regarding the long-term efficacy of modular therapies is prominent in the data, with Jessica explaining how she has always found it difficult to deal with the uncertainty of future health deteriorations.

> [Jessica, 26 years]: "I still worry a lot of the time that my liver won't cope with it [Kaftrio], even though the results have been good, and I worry that the effects won't always work. It's almost like, pinching yourself, you catastrophise in your head, like oh when's it going to stop working"

Individuals with CF today are adapting to a change in their identity, as well as a change in the support available to them from fellow "CFers", with many explaining how they had to initially acclimatise to this new era of CF care in isolation without regular clinic visits due to the COVID-19 pandemic. Several participants emphasised that Kaftrio has caused a divide in the CF community, with those who are not eligible for modulator therapies, or those who have experienced side effects needing to withdraw from social media to escape the "success stories" and preserve their emotional wellbeing, with social media previously being their source of support.

> [Katie, 22 years]: "When the news originally broke [about Kaftrio being available via the NHS] I had to take a break from social media. I was seeing all these posts saying like oh I can have a family now, I can start living like a really long life. I don't have the barrier of the life expectancy anymore […] I know I'm not in a great place with my health […] if that [Kaftrio] would have been available for me, it probably would've really helped at the time […] I just had to take a break because of my mental health"

This theme therefore demonstrates the clear and pressing need for targeted psychological support for everyone, those who are eligible, those who are not eligible, and those for whom the health benefits might come too late.

"You don't appreciate the light until you've been in the dark"; what should the future of CF care look like?

This final theme provides insight into participants' views regarding CF care for current and future CF generations in light of actual and projected changed experiences of living with CF post-modular therapy. Many participants, such as Liam discuss how changes in physical symptoms such as a reduction or absence of coughing make it more difficult to recognise exacerbations.

> [Liam, 39 years]: "I had a little blip a couple of weeks ago and ended up on oral antibiotics, but the strangest thing was I felt good, but the little lung function machine was saying you've lost 500ml on your lung function […] I don't feel like I can read my body. I felt like I was so in tune with my body […] I don't know my own body anymore. It's a total retrain, and we've just got to learn as we go"

Liam described his fear that this new lack of body awareness may have a detrimental impact upon his physical health, with participants stating that today CF care is going through a "challenging" period of time where patients and HCPs are "retraining" in light of modulator therapies.

Several participants discussed weight management as a new challenge, with many experiencing increases in weight following Kaftrio necessitating a change in eating behaviours for weight regulation.

> [Anthony, 51 years]: "I actually have to watch what I eat now, which is a complete turnaround, and after you've done it for all your life, it's quite a hard thing to take on board"

Participants, such as Anthony, emphasised the difficulty of "breaking the habit of a lifetime". The CF community have traditionally been encouraged to eat high calorific foods, with many finding it a struggle to maintain their weight. The overnight shift in being expected to eat a more balanced diet and to be mindful about weight gain is a challenge, with many requiring support in changing eating behaviours.

In terms of future CF generations, there was the consensus that they will not experience CF in the same way, they will not face the same health struggles that those who lived before Kaftrio have faced, and therefore there was the worry that perhaps they will not appreciate Kaftrio's life-changing impact.

> [Lucy, 30 years]: "The young kids, they aren't gonna understand the actual benefits [of Kaftrio] […] I have had times of my life where it feels better to not breathe than breathe […] I'm so excited to take my Trikafta every day, it's such a joy […] some of these children and young pre-teens and younger are not gonna have the same feelings about it because they've never had that elephant on their chest"

Participants outlined that adherence is already an issue within the CF population, reasons include a lack of time, a desire for normalcy, feeling well and experiencing no adverse effects from non-adherence. It is plausible that Kaftrio could exacerbate this for treatments outside of modulator therapies; this is something for clinicians to be mindful of, along with the challenges of encouraging adherence in a cohort of patients who may be feeling relatively well and leading a more "normal life".

> [Caroline, 38 years] "I'm a bit less compliant now than I used to be. Orkambi helps me so I can afford to do a little bit less. If I decided to have a week's break between nebulising antibiotics then that's probably okay. The doctors might not say so, but my body says you'll be okay"

The data illustrates a feeling of increased autonomy from medical recommendations and advice; instead, there is a reliance on one's own body to indicate when something is wrong which directs adherence behaviours. This is consistent with lay perceptions of health and illness which may not be accurate, or may be influenced by mistaken beliefs.

Participants suggested that with future CF generations potentially being able to lead a more "normal life" this could be coupled with increased experimentation of normalised health risk behaviours. Health risk behaviours were perceived by many as "having some fun" which understandably is a life-aim for some, especially young people.

> [Liam, 39 years]: "Some days [post-Kaftrio] you feel like you don't have CF. So with that in mind, you're a young kid, it could be quite dangerous. It might be that generation that go absolutely mental in their teenage years […] if you're feeling as good as I am now as a teenager, then yeah they could be having some fun"

Individuals reported being unaware of the CF-specific adverse effects of smoking, excessive alcohol consumption and illicit drug use, demonstrating the need for proactive awareness to be integrated into CF care for current and future CF generations. For example, the combination of excessive alcohol consumption and Kaftrio on the liver can be catastrophic.

> [George, 36 years]: "There was a guy in America who posted a video about how he took Kaftrio, or Trikafta in America, couldn't believe it and just went out partying the

> next two months […] the next liver test he had, he failed it, and he was in tears in this video basically saying don't make the mistakes I've done"

Sexual behaviours and contraception use formed another point of discussion for participants in light of the improved fertility status reported following Kaftrio. Kirstie emphasised the imperative of such discussions with HCPs having previously undergone a medically advised termination due to her poor health status.

> [Kirstie, 35 years] "I got pregnant by accident […] I was on the pill, so I was being sensible. I have antibiotics I take if my chest is having a flare up. If I take extra antibiotics on top of what I'm normally on, that counteracts contraception […] if you ask the questions, you'll get the answers, but it should be there available to you"

The need for psychological support embedded within CF care was clearly demonstrated, with participants such as Jessica expressing the need for proactive rather than reactive psychological support.

> [Jessica, 26 years]: "I wish it was just as common to see the psychologist in your clinic appointments as it is to see your physio, the dietician […] when I've really struggled, you kind of don't ask for help even though you want it. So actually, to have it given to you without you needing to ask, would be really helpful"

The data outlined the potential benefits of embedding self-care practices within CF care. Participants shared their experiences with mindfulness and yoga and how this benefited psychological wellbeing.

> [Kirstie, 35 years] "Those kind of mindfulness things have stuck with me, so anytime that I'm super frazzled or whatever, I always go back to that, that did really help […] yoga massively helped me"

The data also illustrated the need for holistic care, including support for broader stress and quality-of-life issues related to increased longevity. Participants praised the role of the Social Worker, with the current CF generation planning for a future they did not expect to have, having to arrange pensions and life insurance.

> [Charlotte, 40 years] “It leads to all kinds of things that I hadn’t even bothered thinking about, like pensions, and I’m like oh shit, bit late to be thinking about a pension”

Overall, this theme provides insight into the support participants feel is essential to be embedded within CF care for the current and future CF generations. Despite the excitement that surrounds Kaftrio there are still several challenges present for the CF population, with the need for proactive psychological support being demonstrated within this research.

Discussion

The data provides insight into living with CF today through an exploration into attitudes, beliefs and experiences with modulator therapies (predominantly Kaftrio). Whilst most participants articulated that they felt lucky to be living through this period of medical advances, significant challenges remain, predominantly around psychological wellbeing. Most eligible participants had started Kaftrio within the previous twelve months, and the data presents a prospective understanding of attitudes, beliefs and experiences transitioning into modulator therapies.

The findings illustrate the support people would like integrated into CF care. Many suggested the need for proactive psychological support, particularly for those unable to take modular therapies, but also for those who can. Research illustrates that some people with CF are experiencing higher depression and anxiety symptoms following commencement of CFTR modulator therapy,[25, 26] with acknowledgment that ill mental health impacts quality-of-life.[9, 10]

Overall, alongside the excitement surrounding modulator therapies, there was a consensus that it is an overwhelming and divisive period for the CF population. Individuals discussed how they would previously utilise fellow “CFers” as a source of emotional support via social media; however, a break from social media (particularly when not eligible for modulator therapies) was often needed to preserve emotional wellbeing, leaving a gap in support. It is clear from the data the need for professional proactive psychological support as individuals navigate their way through this new era, with some discussing the benefits of mindful practices. There is certainly an ability to proactively support people with CF through contemplative and non-contemplative practices, and create a cost-effective and proactive scheme e.g.,[27-31].

The data also shows how HCPs need to be mindful of the impact modulator therapies could have upon individual's decisions regarding health behaviours, highlighting the need for support of adherence decisions[32] and weight management e.g.,[33-37]. Furthermore, the data provides insight into the need for proactive awareness regarding health risk behaviours (e.g., smoking, excessive alcohol consumption, illicit drug use and contraception use).

Consistent with previous work, this research illustrated that awareness regarding health risk behaviours is not currently strongly embedded within CF care. As found in previous research, it was apparent that people were not advised on the wide range of health risk behaviour engagement.[15-17] It is therefore recommended that the UK (as well as international) standards of care should provide advice and counselling on a wider range of health risk behaviours. Future CF generations may be more vulnerable to initiate health risk behaviours due to identity and health status changes potentially making them feel that they can engage in normalised behaviours alongside their peers.

There is a greater need for sexual health awareness including contraception use and birth control methods due to improved fertility. As discussed by Keyte et al[15-17] proactive awareness regarding health risk behaviours needs to be revisited on several occasions in an attempt to overcome potential self-regulatory failure when individuals are faced with health risk behaviour temptations. Interventions need to go beyond providing awareness, with screening for psychological distress and avoidance of CF as these are influential factors affecting health risk behaviour initiation.[15-17]

Study Limitations

This research has some limitations; only one participant was recruited who was currently not eligible for modulator therapies, further research is required to investigate more thoroughly the experiences of those who are ineligible to support the needs of this population who currently feel like the "forgotten individuals with CF". Another participant had to stop modulator therapies due to side effects, the devastating impact this can have upon an individual's psychological wellbeing was recorded, however future research is needed, again to fully support such individuals in terms of both their physical and psychological wellbeing. Lastly, the range of mental health and neurological side effects reported in response to Kaftrio warrants further investigation; such research would provide an exploration into what individuals feel is contributing to their decrease in wellbeing (e.g., is it that some individuals are struggling to adapt to their change in identity) and therefore inform healthcare on what interventions could be integrated into CF care.

Conclusions:

Overall, this research provides an exploration into what it is like to live with CF today. Notwithstanding the excitement the CF community is experiencing in response to modulator therapies, this research has highlighted that there are still several challenges present for the CF community, with a clear need for proactive, effective psychological support. Future research should investigate a range of experiences including people not able to start or continue with modular therapies. Research and clinical recommendations on CF care for current and future generations may need a closer inspection of acceptance (or non-judgment) 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.

Declaration of Conflicting Interests:

The authors declare that there are no conflicts of interest.

References

[1] Elborn S. Cystic fibrosis. *The Lancet* 2016; 388, 19-25.

[2] Jackson R and Pencharz PB. Cystic fibrosis. *Best Practice and Research Clinical Gastroenterology* 2003; 17, 212-235.

[3] The CF Trust. *Cystic Fibrosis FAQs,* https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/faqs (2021, accessed 4 August 2021).

[4] Owen E. Putting people with CF at the heart of everything we do. *UK CF Conference 2016; putting the person in personalised medicine.* East Midlands, UK: The Cystic Fibrosis Trust, https://www.cysticfibrosis.org.uk/get-involved/conference-and-meetings/ukcfc/video-gallery (2016, accessed 13 September 2016).

[5] Cox K. Cystic Fibrosis in the changing NHS. *The UK Cystic Fibrosis Conference; Fighting for a Life Unlimited,* https://www.youtube.com/watch?v=QVz8mCR6rtU (2015, accessed 12 January 2016).

[6] McHugh R, McFeeters D, Boyda D and O'Neill S. Coping styles in adults with cystic fibrosis: implications for emotional and social quality of life. *Psychology, Health & Medicine* 2016; 21, 102-112.

[7] Withers AL. Management issues for adolescents with cystic fibrosis. *Pulmonary Medicine* 2012; 1, 1-10.

[8] Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, Tibosch M, Brucefors AB, Yüksel H, Catastini P, Blackwell L and Burker D. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of the international depression epidemiological study across nine countries. *Thorax* 2014; 69, 1090-1097.

[9] Yohannes AM, Willgoss TG, Fatoye FA, Dip MD and Webb K. Relationship between anxiety, depression, and quality-of-life in adult patients with cystic fibrosis. *Respiratory Care* 2012; 57(4), 550-556.

[10] Cronly JA, Duff AJ, Riekert KA, Fitzgerald AP, Perry IJ, Lehane EA, ... and Savage E. Health-related quality-of-life in adolescents and adults with cystic fibrosis: physical and mental health predictors. *Respiratory Care* 2019; 64(4), 406-415.

[11] Fajac I and De Boeck K. New horizons for cystic fibrosis treatment. *Pharmacology & Therapeutics* 2017; 170, 205-211.

[12] Keyte R, Beswick L, Rayner O, Bryon M, Carr SB and Medhurst N. Orkambi: the expectations of benefit for people in the UK with cystic fibrosis. *Journal of Cystic Fibrosis* 2017; 16, S77.

[13] Zemanick ET and Accurso FJ. Entering the era of highly effective CFTR modulator therapy. *The Lancet* 2019; 394, 1886-1888.

[14] The CF Trust. No one left behind: The Cystic Fibrosis Trust's commitment to 'the 10%', https://www.cysticfibrosis.org.uk/news/no-one-left-behind (2022, accessed on 1 March 2022)

[15] Keyte R, Egan H, Nash E, Regan A, Jackson C and Mantzios M. An exploration into experiences and attitudes regarding risky health behaviours in an adult cystic fibrosis population. *Psychology, Health and Medicine* 2020; 25, 1013-1019.

[16] Keyte R, Egan H and Mantzios M. An exploration into knowledge, attitudes and beliefs towards risky health behaviours in a paediatric cystic fibrosis population. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2019; 13, 1-10.

[17] Keyte R, Egan H and Mantzios M. Cystic Fibrosis health care professionals' perceptions of risky health behaviours. *Chronic Illness* 2019; 1-12.

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

[19] Braun V and Clarke V. *Successful qualitative research; a practical guide for beginners.* London, UK: SAGE, 2013.

[20] Rubin HJ and Rubin IS. *Qualitative interviewing: the art of hearing data.* Thousand Oaks, CA: SAGE, 1995.

[21] Braun V and Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; 3, 77-101.

[22] Willig C. Beyond appearances: a critical realist approach to social constructionism. In Nightingale DJ and Cromby J. *Social constructionist psychology: a critical analysis of theory and practice.* Open University Press: UK, 1999.

[23] Brendel E and Jager C. *Contextualisms in epistemology*. The Netherlands: Springer, 2005.

[24] Burr V. *An introduction to social constructionism.* Routledge: UK, 1995.

[25] Dagenais RV, Su VC and Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: A systematic review. *Journal of Clinical Medicine* 2021; 10(1), 23.

[26] Talwalkar JS, Koff JL, Lee HB, Britto CJ, Mulenos AM and Georgiopoulos AM. Cystic fibrosis transmembrane regulator modulators: implications for the management of depression and anxiety in cystic fibrosis. *Psychosomatics* 2017; 58(4), 343-354.

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

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

[29] Mantzios M and Egan HH. Mindfulness training may enhance the psychological well-being of people with cystic fibrosis. *Mindfulness* 2016; 1-4.

[30] Mantzios M and Giannou K. When did colouring books become mindful? Exploring the effectiveness of a novel method of mindfulness-guided instructions for colouring books to increase mindfulness and decrease anxiety. *Frontiers in Psychology* 2018; 9, 56.

[31] Mantzios M and Giannou K. A real-world application of short mindfulness-based practices: a review and reflection of the literature and a practical proposition for an effortless mindful lifestyle. *American Journal of Lifestyle Medicine* 2019; 1-6.

[32] Keyte R, Egan H, Jackson C, Nash E, Regan A and Mantzios, M. A weekend / weekday comparison in adherence to daily treatment regimens for adults with cystic fibrosis. *Health Psychology Report* 2018; *1-8.*

[33] Egan H, Keyte R, Nash EF, Barrett J, Regan A and Mantzios M. Mindfulness moderates the relationship between emotional eating and body mass index in a sample of people with Cystic Fibrosis. *Eating and Weight Disorders* 2020; 1-11.

[34] Egan HH and Mantzios M. Mindfulness and mindful eating: reflections on how individuals with Cystic Fibrosis may benefit. *Eating and Weight Disorders* 2016; 1-3.

[35] Mantzios M, Egan H and Patchell C. Can existing knowledge on eating behaviours and obesity support people with cystic fibrosis who are nutritionally compromised? *Frontiers in Psychology* 2016; 7, 1477.

[36] Mantzios M, Egan H and Asif T. A randomised experiment evaluating the mindful raisin practice as a method of reducing chocolate consumption during and after a mindless activity. *Journal of Cognitive Enhancement* 2020; 1-9.

[37] Mantzios M, Skillett K and Egan H. A randomised experiment between mindful construal diaries and the mindful raisin practice on chocolate consumption. *European Journal of Health Psychology* 2020; 1-14.

Table 1. Medical and Demographic Data collected for all participants

Pseudonym	Sex	Age	Modulator therapy currently prescribed and duration since treatment commenced	Latest lung function result (FEV_1)	Lung function result (FEV_1) prior to commencing modulator therapy	Country
George	Male	36 years	Kaftrio – three months	91%	85%	England
Lucy	Female	30 years	Kaftrio – thirteen months	55%	40%	USA
Alice	Female	32 years	Kaftrio – eight months. • Previously prescribed Orkambi for 3 years, 7 months	32%	21%	England
Emma	Female	32 years	Kaftrio – started treatment two months ago but stopped following two weeks due to side effects (rash, pneumonia, infection)	49% (increased to 66% whilst taking Kaftrio)	48%	Germany
Henry	Male	33 years	Kaftrio – two months	88%	45%	England
Katie	Female	22 years	Not eligible	45%	/	England

James	Male	40 years	Kaftrio – four months	88%	65%	England
Kirstie	Female	35 years	Kaftrio – two months (stopped whilst undergoing IVF, restarted modulator therapy twice)	45%	39%	England
Mandy	Female	39 years	Kaftrio – three months. • Previously prescribed Orkambi and then Symkevi; being taking modulator therapies for 2 years 5 months prior to being prescribed Kaftrio.	30%	14%	England
Charlotte	Female	40 years	Kaftrio – seven months. • Previously prescribed Orkmabi for 4 years 2 months.	45%	25%	England

Ashley	Male	37 years	Kaftrio – four months. • Previously prescribed Symkevi for twelve months.	44%	36%	England
William	Male	46 years	Kaftrio – three months. • Previously prescribed Orkmabi for three years.	37%	22%	Ireland
Rachel	Female	37 years	Kaftrio – four months. • Previously prescribed Symkevi for ten months.	45%	30% (prior to Symkevi).	England
Anthony	Male	51 years	Kaftrio – six months. • Previously prescribed Symkevi (for six months), and Kalydeco (for six months).	20%	33%	England

Matthew	Male	25 years	Kaftrio – six months	72%	50%	England
Jessica	Female	26 years	Kaftrio – twelve months	46%	20%	England
Jayne	Female	47 years	Kaftrio – one year and three months	53%	/	USA
Liam	Male	39 years	Kaftrio – seven months. • Previously prescribed Orkambi for two years.	74%	32%	England
Amelia	Female	24 years	Kaftrio – one year and two months. • Previously Orkambi (for two years) and Symkevi (for two years)	35%	15%	England
Caroline	Female	38 years	Orkambi (5 years) – no access to Kaftrio due to country of residence	75%	60%	Australia

Table 2. The themes that emerged in the present study

Themes	Codes
“I’ve always felt really pressured time-wise; I can’t think too far ahead”	Living with a reduced life expectancy and planning for end-stage CF; CF complications; Health declines are inevitable and are difficult to cope with; You can never switch off from CF; The emotional burden of CF; Anxiety and hypochondria; Accepting CF is difficult; Adherence part of daily life; Health declines result in adherence; Age results in adherence; Non-adherence is inevitable; Non-adherence due to a lack of time; Non-adherence for a normal identity; Being well results in non-adherence; Health declines result in non-adherence; Health declines regardless of adherence efforts; Non-adherence as treatments make me feel worse; Guilt for non-adherence; Exercise is preferred over physiotherapy; Weight management is difficult; CF prevents me living life how I want to; The impact CF has on education and work; More support needed from HCPs to help individuals with CF study / work; The impact CF has on your identity; Living for today; Engagement in health risk behaviours; Engagement in health risk behaviours due to having a reduced life expectancy; Health risk behaviours allow you to escape CF and have a normal identity; No adverse effects for health risk behaviours; Adverse health effects results in termination of health risk behaviours; Replace one health behaviour with another; HCPs do not discuss health risk behaviours; HCPs need to discuss sex; CF and family planning; CF limits the number of friends you have / impacts on forming relationships; CF is socially isolating

	due to cross-infection; Support from fellow CFers is cathartic; Grateful for HCPs
“I feel like a completely different person, CF is barely ever on my mind, I don’t cough, my mind is clear”	Lived in hope that this day would come; Kaftrio came at the right time; Seeing success stories made me excited; Hopeful for the future despite eligibility; This is going to be life-changing; Excitement and happy tears; Kaftrio celebration; The health improvements have been phenomenal and immediate; The purge; The disappearing cough, sputum and crackle; No side effects / benefits outweigh side effects; My treatment burden has decreased; Adherence has improved due to modulator therapy; I now exercise for fun and not for treatment; Kaftrio and eating behaviours / weight gain; Kaftrio allows me to live in the moment; Kaftrio has removed the emotional burden of CF; This is life changing / life-saving, I have been born again; I have a life and a future that is not dominated (or as dominated) by CF – I feel like a normal person; Kaftrio allows me to have a normal identity; Kaftrio means I can work; Kaftrio and family planning; The impact Kaftrio has upon family and friends; Partners / Parents deserve this more than me; I am lucky to be living through this time and so grateful for Kaftrio; Future generations of CFers will not know what it is truly like to have CF
“Kaftrio really has caused a divide in the CF community”: eligibility, side effects, survivors’ guilt and dealing with the trauma of my past	Anxiety regarding eligibility; Not being eligible for / having access to modulator therapies – frustration and hope (or hopelessness); Happy for you, sad for me; How to cope when not eligible; Social media can be upsetting when not eligible / experiencing side effects; Divide in the CF community and the forgotten individuals; Survivors Guilt – what about those who are not

	eligible?; Pessimistic (realistic?) views towards modulator therapies; Why am I not excited?; Anxious towards Kaftrio – will this work for me? It is my only hope; HCPs not aware of the emotional impact of Kaftrio; Taking Kaftrio is overwhelming – I am now grieving for everything which has happened to me in my life; Having to adjust to the potential of losing loved one's; Starting on CFTR modulator therapies can be tough; Taking Kaftrio can be a challenge; Conscious about weight and body image; Not having a large increase in lung function can be disappointing; Side effects; Don't take Kaftrio off me – you can't take it off me; Will Kaftrio / CF specialist care always be available?
"You don't appreciate the light until you've been in the dark"; what should the future of CF care look like?	CF care is changing; Everyone is re-learning what CF is; The new challenges associated with weight management; If you haven't lived through the dark, you cannot appreciate the light – how will this impact health behaviours?; Future CF generations need to be educated as to what CF truly looks like (pre-kaftrio); Don't forget you still have CF; Adherence is already an area of concern, will Kaftrio exacerbate the issue?; Routine means (some of) the "original" CFers continue with adherence, but what about future CF generations?; Not feeling ill can result in non-adherence, so will non-adherence be more of an issue for future CF generations?; Guilty for non-adherence due to symptoms, will the future CF generations still experience this guilt without a cough etc?; Adherence needs to be a focus for future CF generations; Will future CF generations be more vulnerable to initiate / experiment with health risk behaviours?; The

	impact excessive alcohol consumption can have upon Kaftrio; HCPs never discussed health risk behaviours – this needs to be a discussion for the new generation of CF patients considering the impact Kaftrio is having upon health and identity; HCPs need to discuss fertility and safe sex; Psychological support needs to be embedded within CF care; The role of the Social Worker – I now have a future to plan for; Genetic Counselling in CF pregnancies

Appendix 1 – Sample Interview Schedule

<u>Ice Breakers Question's:</u>

- Thank you for taking part
- What were your first thoughts when you were asked to take part in this research?
- Did you have any hesitations about agreeing to take part?
- So, to begin with, can you tell me a bit about your life?
    - What do you do in your spare time?
    - Do you work / study?
    - Live with your family?

<u>Impact of Cystic Fibrosis on the individual's personal life pre-modulator therapy:</u>

- Could you tell me about some of the challenges you have faced in terms of living with CF?
    - Has it always been this, or were other aspects / things more easier or difficult to cope with when you were younger?

<u>Adherence:</u>

- How have you found sticking to your treatment regimen over the years? Have there been some aspects that are more difficult?
    - Has this changed over time / circumstances?
- What things have made it difficult to stick to the regimen?
  Areas for further elaboration may include:

    - Not enough time in the day with their job etc
    - The belief that the medical regimen was not benefitting them
    - The fear of antibiotic resistance
    - Self-prescribing according to their symptoms
    - Situations which made the individual less likely to take their medication / complete physiotherapy e.g., at college / work, at a friend's house

- What treatments have you tended to "miss out"?
- At the end of the day if you had missed a treatment how did it make you feel?
- When you woke up in a morning did you plan to do all your treatments?
- Were there some days when you would wake up and you knew you were just not going to do everything?

<u>Risky health behaviours:</u>

- Are there things that you think are "not good" for your health?
  Examples may include:
    - Smoking
    - Drugs
    - Drinking alcohol

- Do you feel that these behaviours have had an impact on your Cystic Fibrosis? (if they disclose engagement)

    - Did you think about CF when you started e.g., smoking?
    - Can you remember why you started smoking, what were the triggers, what did you think about at the time? What was happening?
    - Some people with health problems say that they have engaged in behaviours that are not good for their health because these behaviours give them a sense of being “normal. What do you think about that?

- Is there anything else in your life that you may not have done if you were being "really healthy"?

Attitudes towards new modulator therapies:

- Could you tell me how you feel in regards to the new CF treatments now available in the UK?
    - Are you eligible for the treatments? (if not focus on their attitudes, beliefs and feelings).
    - Have you started the treatment?

- What were your feelings about these treatments before you started taking them?
    - Hopes and fears

Impact of Cystic Fibrosis on the individual’s personal life post-modulator therapy?

- What has your experience been like since you commenced the treatment?
    - Is it how you expected it to be?

- What if any impact has the treatment had upon your life?
    - Work / studying
    - Family relationships

Eating behaviours

Has it impacted on your eating behaviours? In what way?
Did you have any issues with eating before?
Do you find eating more pleasurable now?
Do you spend more/less time thinking about eating? Preparing food?
Has your weight changed? Are you happy with the change?

- Since starting the treatment, what would you say some of the challenges are that you now face in terms of living with CF?
    - How do the challenges associated with CF compare to life pre-modulator therapy? Are these different from pre modulator therapy?
- How have you found sticking to your overall treatment regimen since starting the new treatment?
    - What things make it difficult to stick to the regimen?
    - What treatments do you tend to “miss out”?

  - At the end of the day if you had missed a treatment how does it make you feel?

- Thinking about your past, is there anything you would change if you had have known that you would have had access to this treatment within your lifetime?
  - Work / studying
  - Starting a family

- Thinking back to e.g., smoking, what impact do you think this will have upon CF now that individuals’ have access to these new treatments?
  - Do you think individuals’ attitudes towards such behaviours will have changed in light of these new treatments?
  - What do you hope for your future in terms of e.g., smoking? (if the individual has disclosed engagement)

Conclusion:

- What would you want to tell a young patient with Cystic Fibrosis?
- What would you tell a family who had just had a child with CF, or who have a young adult with CF?
- Honestly if you were to have this discussion with another person who has Cystic Fibrosis, outside of this research, would this conversation be the same?
- Do you have anything else to add?