Medicines Adverse Reactions Committee

Meeting date	4/12/2025	Agenda item	3.2.1
Title	**Cystic fibrosis transmembrane conductance regulator (CFTR) modulators and the risk of psychiatric disorders**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	
Ivacaftor	Kalydeco	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	
Ivacaftor/tezacaftor	Symdeko	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	
Elexacaftor/tezacaftor/ ivacaftor	Trikafta	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	
Ivacaftor/lumacaftor	Orkambi	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	
Deutivacaftor/ tezacaftor/vanzacaftor	Alyftrek (recently approved - no published data sheet)	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	
PHARMAC funding	Trikafta and Kalydeco are funded under Special Authority.		
Previous MARC meetings	N/a		
International action	**EMA:** PRAC recommended addition of information on risk of depression to SmPCs for Kaftrio (Trikafta), Symkevi (Symdeko), Orkambi and Kalydeco between July and October 2023. In May 2025, the PRAC recommended updating the Kaftrio SmPC with information on the risk of insomnia, anxiety and behavioural changes. Alyftrek was approved by the EMA in June 2025 and lists similar warnings. **MHRA:** Published a safety communication in May 2025 stating that the Kaftrio SPC will be updated with information on anxiety or low mood, sleep disturbance, poor concentration and forgetfulness, and behavioural changes in children.		
Prescriber Update	N/a		
Classification	Prescription medicine		
Usage data	See section 2.6.		
Advice sought	**The Committee is asked to advise:** • On the strength of the available evidence describing a possible relationship between psychiatric disorders (eg, depression, anxiety, suicidal thoughts, insomnia/sleep disturbance, poor concentration, forgetfulness, unusual changes in behaviour or behavioural changes in children) and CFTR modulators individually or as a class, including which, if any, psychiatric disorders have evidence for a possible relationship. • Whether the data sheet for any CFTR modulator should be updated to include warnings on any psychiatric disorders. • Whether any other regulatory action is needed.		

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1 PURPOSE

There has been a large number of spontaneous reports of psychiatric disorders with CFTR modulators internationally. This has triggered signal reviews by international medicines regulators, with the EMA requiring warnings on depression, including suicidal thoughts, unusual changes in behaviour, anxiety, insomnia and behavioural changes in children, in the product information for all CFTR modulators. The MHRA has also published a safety communication stating that the product information for Kaftrio (Trikafta) will be updated to include a warning on risk of psychological side effects, including anxiety or low mood, sleep disturbance, poor concentration, forgetfulness and behavioural changes in children.

This report reviews the available evidence on this potential risk.

2 BACKGROUND

2.1 Cystic fibrosis

Cystic fibrosis (CF) is a genetic condition characterised by reduced or absent function of the cystic fibrosis transmembrane regulator (CFTR) protein. CFTR is a chloride and bicarbonate ion channel located on the apical surface of epithelial cells. Loss of CFTR protein function impairs ion transport, leading to reduced secretion of chloride and bicarbonate ions and increased sodium absorption. Impaired reabsorption of chloride and sodium in sweat ducts results in elevated salt concentrations in sweat, which is a diagnostic feature of CF. [1]

Disruption of osmotic balance results in dehydration of epithelial surfaces and production of thickened mucus that adheres to epithelial linings in the respiratory tract, gastrointestinal tract, pancreas, hepatobiliary ducts, and reproductive tract. Accumulation of thickened mucus and impaired mucociliary clearance in the airways leads to recurrent respiratory infections, and persistent inflammation and infection in the lungs can lead to bronchiectasis and eventual respiratory failure. Blockage of pancreatic ducts causes pancreatic insufficiency and malabsorption of nutrients with poor growth or weight gain. Nearly all males with CF are infertile due to congenital absence of the vas deferens. Over time, complications such as CF-related diabetes, liver disease, and osteoporosis may develop. [1]

There are around 700 *CFTR* gene variants that have been recorded as causing CFTR protein dysfunction. The most common variant is F508del, a class II variant present in 85% of people with cystic fibrosis of Northern European descent. This variant results in misfolded CFTR protein with defective trafficking and destruction of the misfolded protein, meaning there is no functional CFTR channel. Some variants result in CFTR proteins that are present at the cell membrane but are defective or scarce. [1, 2]

People with cystic fibrosis (PwCF) have a variable clinical course depending on the type and degree of CFTR channel dysfunction. People with cystic fibrosis have a reduced life expectancy, but this has improved with advances in treatment. The current average life expectancy is around 50 years in the US, Canada, Germany and United Kingdom. [1]

The Port CFNZ Data Registry reports that in 2019 there were 531 people registered with Cystic Fibrosis in New Zealand. Of the 495 people in the database who had recorded genotypes, 89.7% had at least one F508del mutation. [3]

2.2 Cystic fibrosis transmembrane regulator modulators

Cystic fibrosis transmembrane regulator modulators (CFTRm) are medicines that improve the function of the CFTR protein, and they are classed as potentiators or correctors. Potentiators, such as ivacaftor, improve the function of CFTR protein present at the cell membrane by increasing the probability that the protein channel is open, so chloride or bicarbonate can flow more easily through the cell membrane. Correctors, such as tezacaftor, lumacaftor and elexacaftor, facilitate the folding of CFTR protein and trafficking to the cell surface

(Figure 1). Potentiators alone are not effective for people with *CFTR* variants resulting in absence of CFTR protein at the cell membrane, and for these people, both potentiators and correctors are needed.

CFTR modulators improve lung function, increase body mass index (BMI) and reduce the risk of pulmonary exacerbations. CFTR modulators are expected to increase life expectancy, with initiation of elexacaftor/tezacaftor/ivacaftor (ETI) therapy in adolescence projected to result in life expectancy typical of someone without chronic lung disease. [1, 2]

Figure 1: Functions of Cystic Fibrosis Transmembrane Regulator modulators [4]

Source: Welsh MJ. 2025. Rewriting the Chapter on Cystic Fibrosis: The 2025 Lasker-DeBakey Clinical Medical Research Award. JAMA 334(15): 1325-1326. DOI: 10.1001/jama.2025.14913 (accessed 3 November 2025).

The CFTR modulators approved in New Zealand are summarised in table 1.

Table 1: Cystic fibrosis transmembrane regulator (CFTR) modulators approved in New Zealand

Brand name	Active substance(s) (abbreviations)	Indications	Year first approved
Trikafta* (Kaftrio in Europe)	Elexacaftor/tezacaftor/ ivacaftor (ELX/TEZ/IVA or ETI)	Treatment of CF in patients aged 2 years and older who have at least one *F508del* mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data. [5]	2021 (funded 2023)
Kalydeco*	Ivacaftor (IVA)	Treatment of CF in patients aged 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. [6]	2013 (funded 2020)
Orkambi	Lumacaftor/ivacaftor (LUM/IVA)	Treatment of CF in patients aged 2 years and older who are homozygous for the *F508del* mutation in the CFTR gene. [7]	2023

Symdeko (Symkevi in Europe)	Tezacaftor/ivacaftor (TEZ/IVA)	Treatment of patients with CF aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive based on in vitro data and/or clinical evidence. [8]	2022
Alyftrek**	Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA)	Treatment of CF in people aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the CFTR gene.	2025

* Funded under Special Authority.
** Approved October 2025. No published data sheet.

2.3 Psychiatric disorders

Psychiatric disorders are a broad group of conditions characterised by a clinically significant disturbance in cognition, emotional regulation or behaviour, with depressive disorders and anxiety being the most common. [9]

There is thought to be a higher background prevalence of depression and anxiety amongst people with CF than in the general population, with one study reporting elevated depression scores (ie, indicating at least mild depression symptoms) in around 10% of adolescents and 20% of adults, and elevated symptoms of anxiety in 20% of adolescents and 30% of adults. [10]

The European Cystic Fibrosis Society (ECFS) standards for the care of people with CF state that variant-specific treatments, including CFTR modulators, can have indirect adverse psychological impacts on mental health. [11] People who start taking CFTR modulators may have complex and unexpected feelings, such as difficulty adjusting to a changed relationship to CF, survivor guilt, uncertainty about the future, a new perspective on past illness or body image difficulties. Some people may not experience the benefits they had hoped for, or feel worried that the benefits may not last. [12]

Reports of neuropsychiatric problems directly attributed to CFTR modulators in a small proportion of patients are also acknowledged in the ECFS standards. There is a recommendation to routinely evaluate symptoms of depression and anxiety prior to and within 3 months of starting CFTR modulator treatment. [11]

The ECFS standards include guidance on dosage adjustments and notes that case reports describe improvement of neuropsychiatric adverse events after CFTR modulator dose adjustment or interruption, and that some patients have chosen not to restart treatment. Although there is no known evidence-based approach to dose interruption, reduction and re-introduction of CFTR modulators, management strategies suggested in the ECFS guidance are shown in Table 2. [13]

Table 2: European Cystic Fibrosis Society guidance on suggested dose adjustment of CFTR modulator therapy for neuropsychiatric events.

Event	Severity	Dose adjustment	Re-introduction	Other actions
Neuropsychiatric, mood or anxiety symptoms	Moderate	Dose reduction to 1 ETI tablet in the morning and one IVA tablet in the evening, OR 1 tablet each of ETI and IVA in the morning 3 times a week.	Increase dose 12 weeks after symptoms resolve or earlier if clinically indicated. Titrate dose with clinical response ± sweat chloride.	Consider initiation or adjustment of psychopharmacologic therapy.

	Severe	Interrupt treatment.	Restart with reduced dose (1 ETI tablet in the morning and 1 IVA tablet in the evening) or alternative CFTRm. Titrate dose with clinical response ± sweat chloride.	Consider initiation or adjustment of psychopharmacologic therapy.
Insomnia or daytime fatigue		Standard dose.	Consider switching am/pm dosing times.	

Source: Southern KW, Addy C, Bell SC, et al. 2024. Standards for the care of people with cystic fibrosis; establishing and maintaining health. Journal of Cystic Fibrosis 23(1): 12-28. DOI: https://doi.org/10.1016/j.jcf.2023.12.002 (accessed 5 August 2025).

In addition to the personal psychological adjustments following treatment, there are several hypothetical explanations for a relationship between psychiatric disorders and CFTR modulator treatment discussed in the literature:

- Interaction of CFTR modulators with CFTR in the brain. The function of CFTR in the central nervous system is unknown. Elexacaftor, ivacaftor, tezacaftor and lumacaftor are lipophilic and cross the blood brain barrier. [14, 15]
- Interaction of ivacaftor with serotonin 5-HT2c receptors. [15]
- Pharmacokinetic interactions between CFTR modulators and psychotropic medicines such as SSRIs. Lumacaftor is a strong inhibitor of CYP 3A4 and may reduce exposure to citalopram and sertraline, reducing effectiveness. However, this interaction is listed for lumacaftor only. [15]
- Supratherapeutic CFTR modulator exposure (ie, overdose) due to interpatient variability. [16, 17]

The possibility of no relationship between CFTR modulators and psychiatric changes has also been discussed. Psychiatric disorders may be pre-existing, exacerbated by life stressors and part of the fluctuating course for people with these conditions. [18]

2.4 Data sheets

The New Zealand data sheets for CFTR modulators do not list neuropsychiatric adverse effects such as depression, anxiety, suicidal thoughts, insomnia or behavioural changes.

The European SmPCs for CFTR modulators include information on the risk of depression. Updates to the UK SPC for Kaftrio are planned to include warnings on psychological side effects, including anxiety or low mood, sleep disturbance, poor concentration, forgetfulness and behavioural changes in children.

The warning in the European SmPC for Kaftrio (Trikafta) is given below. Similar warnings are included in the SmPCs for Kalydeco, Symkevi (Symdeko), Orkambi and Alyftrek.

Kaftrio (elexacaftor/tezacaftor/ivacaftor)

Section 4.4

<u>Depression</u>

Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with IVA/TEZ/ELX, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders (see section 4.8). In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor

for depressed mood, suicidal thoughts, unusual changes in behaviour, anxiety, or insomnia and to seek medical advice immediately if these symptoms present.

Paediatric population

In young children (aged 2-5 years) treated with IVA/TEZ/ELX behavioural changes have been reported, which occurred usually within the first two months of treatment initiation. In some cases, symptom improvement was reported after treatment discontinuation.

Section 4.8

Psychiatric disorders: Depression, behavioural changes (frequency not known).

Comments

Data sheet updates are planned for the Kaftrio UK SPC but not yet implemented (see section 2.5 Regulatory action below).

Neuropsychiatric adverse effects are not listed in the United States prescribing information for CFTR modulators, with the exception of Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) which states that in clinical trials in patients aged 12 years and older, depression occurred more frequently in the Alyftrek treatment group (0.4%) than in the ELX/TEZ/IVA group.

Neuropsychiatric adverse effects are not listed in the Canada or Australia product information for CFTR modulators.

2.5 Regulatory action

2.5.1 European Medicines Agency

In July 2023, the European Commission approved PRAC-recommended the changes to the EU SmPC shown in section 2.4. This followed the assessment of data submitted in the 4th Trikafta/Kaftrio PSUR.

2.5.2 MHRA

On 7 May 2025, the MHRA published a safety communication, stating that psychological side effects such as anxiety, low mood, sleep disturbance, poor concentration, and forgetfulness have been infrequently reported in people with cystic fibrosis treated with Kaftrio (Trikafta). It was noted that, in some children, psychological side effects may manifest as persistent behaviour changes, such as being more disruptive or difficult to manage. The events usually occur in the first three months of treatment and may happen in people with no history of these problems.

Up to 25 February 2025, the MHRA had received 300 Yellow Card reports of suspected adverse psychological side effects in patients treated with Kaftrio (Trikafta). This is in the context of a total of 9,391 people in the UK who have taken Kaftrio (Trikafta) by 10 January 2025.

The article stated that healthcare professionals should advise patients and their caregivers that, while the risk is small, they should be alert to changes in mood and behaviour and, if they occur, to seek medical advice as soon as possible. Healthcare professionals were advised to discuss the benefit-risk balance of Kaftrio treatment with the patient or caregiver and consider treatment discontinuation if a patient develops these symptoms.

It was noted that this risk may be associated with the medication itself, but it could also be related to patients adjusting to improvements that Kaftrio has on their physical health and their quality of life.

The UK SPC will be updated to include warnings on the risk of psychological side effects, including anxiety or low mood, sleep disturbance, poor concentration, forgetfulness and behavioural changes in children and advise that patients and caregivers should be advised to monitor for these symptoms. The product information will also advise that patients or carers of patients taking Kaftrio must contact their healthcare professional as soon as possible if the patient experiences these side effects.

[redacted]

Comments

As of 17 November 2025, a signal of psychiatric disorders with CFTR modulators is listed as under evaluation by the FDA on the FDA website.

2.6 Usage

Trikafta became a funded medicine under Special Authority in April 2023. [redacted] Dispensing data for Trikafta is not available on the public pharmaceutical data web tool.

Kalydeco (ivacaftor) became funded in 2020 for people with certain responsive CFTR mutations. The available usage data for Kalydeco is shown in Table 3 below. No usage data is available for Symdeko or Orkambi as these are not funded medicines.

Table 3: Usage data for ivacaftor (2020 to 2023)

Year	Formulation	Number of dispensings	Number of people
2020	Ivacaftor - Oral granules 50 mg, sachet	<6	<6
2020	Ivacaftor - Oral granules 75 mg, sachet	<6	<6
2020	Ivacaftor - Tab 150 mg	8	7
2021	Ivacaftor - Oral granules 75 mg, sachet	<6	<6
2021	Ivacaftor - Tab 150 mg	<6	<6
2022	Ivacaftor - Oral granules 75 mg, sachet	<6	<6
2023	Ivacaftor - Oral granules 75 mg, sachet	<6	<6

Source: Pharmaceutical Data web tool version 12 September 2024 (data extracted from the Pharmaceutical Collection on 23 July 2024). URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 2 July 2025).

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Systematic reviews

3.1.1.1 Ramsey et al, 2023. Elexacaftor/tezacaftor/ivacaftor treatment and depression-related events [18]

Aim

To review available evidence on depression-related events in PwCF treated with ETI in the context of background epidemiology in PwCF.

Methods

The authors systematically reviewed and evaluated depression-related data in individuals taking ETI from clinical trials, post-marketing reports, an ongoing registry-based safety study (VX20-445-120) and available scientific literature.

The standardised MedDRA query 'depression and suicide/self-injury' was used to identify adverse events in clinical trials. Exposure-adjusted rates of depression-related events were calculated for the ETI and placebo arms of the pivotal Phase 3 Study 445–102. Rates were also calculated for the pooled population of patients aged 6 years and older who received ETI in 14 clinical trials, and compared to the pooled placebo arms of 10 clinical trials of CFTR modulators.

The Vertex Pharmaceuticals global safety database was used to identify relevant post-marketing cases up to 20 October 2022 and reporting rates were calculated.

Depression prevalence data were reviewed from the second interim analysis of the registry-based, 5-year post authorisation safety study VX20–445–120 and compared to a 5-year pretreatment period.

Results

Clinical trials: The exposure adjusted rates of depression-related events were similar between patients treated with ETI and those receiving placebo in clinical trials (Table 4). Overall, three cases of suicide attempt (0.08 events per 100 PY) and nine cases of suicidal ideation (0.23 events per 100 PY) were reported in the pooled ETI group compared with one case of suicide attempt (0.14 events per 100 PY) and two cases of suicidal ideation (0.28 events per 100 PY) in the pooled placebo group. Of the 12 cases in the ETI group, 11 resolved with continued treatment and in 1 case the patient was not taking ETI at event onset.

Table 4: Incidence of depression and depression-related adverse events in the ETI pivotal phase 3 trial (Study 445-102) and pooled clinical trial data

[redacted]

Post-marketing reports: A search of the Vertex Pharmaceuticals global safety database up to 20 October 2022 identified 899 cases reporting 1,056 depression-related adverse events out of 61,499 PwCF treated with ETI (representing over 82,053 PY). The overall reporting rate of any depression-related event was 1.3 per 100

patient-years (Table 5). Individual reports generally included limited narrative information without objective psychiatric assessment and were confounded by preexisting mental health conditions, psychosocial stressors and the heterogeneous and fluctuating nature of depression.

Table 5: Incidence of depression and depression-related adverse events in ETI post-marketing reports

[redacted]

Post-authorisation safety study: Data on depression prevalence in PwCF taking ETI were recorded by CF centre physicians during each of the 5 pretreatment years and each of the 2 years after ETI initiation in the US CF registry cohort (n = 11,651) and German CF registry cohort (n= 1,141). The annual change in depression prevalence after ELX/TEZ/IVA initiation was consistent with the annual change observed during the 5-year period before starting ELX/ TEZ/IVA in both registries. No suicide deaths were reported in the German registry, and the rate of suicide deaths in the US registry cohort was 0.01 events per 100 PY.

Literature search: The literature search identified case reports, cohort studies reporting depression-related events and studies using validated depression instruments to evaluate changes in depression symptoms before and after ETI initiation. The authors considered the case reports to be confounded by preexisting mental health conditions, psychosocial stressors and the heterogeneous and fluctuating nature of depression. The cohort studies offered limited information due to case-level information confounding factors, and lack of control population or period.

The 12 studies that measured depression symptoms using the PHQ-9 questionnaire before and after ETI initiation are summarised in Table 6. These studies showed either no change or decrease (improvement) in PHQ-9 scores on average. Piehler et al reported a trend toward a decrease in patients describing suicidal ideation. A similar study by Rieubet et al using the CES-D scale reported no significant change in CES-D score at 6 months post ETI initiation. A 6-year retrospective longitudinal study by Hjelm et al of 150 PwCF ages 12 to 22 years found that at the population level the use of more effective modulator therapies such as ETI was associated with lower PHQ-9 scores.

Table 6: Literature search results reporting changes in PHQ-9 scores after the initiation of ETI treatment

[redacted]

Definition of abbreviations: CF = cystic fibrosis; ELX/TEZ/IVA = elexacaftor/tezacaftor/ivacaftor; IQR = interquartile range; PHQ-9 = nine-item Patient Health Questionnaire.
A literature search identified published studies ($n = 3$) and congress presentations ($n = 9$) that used the PHQ-9 assessment tool to evaluate changes in depression symptoms after starting ELX/TEZ/IVA treatment.

Discussion

The authors discussed that evaluation of depression-related events in PwCF treated with ETI is challenging and needs to account for the high background rates of depression symptoms in the CF population, the heterogeneous and fluctuating nature of these events, and the impact of psychosocial stressors (including the COVID-19 pandemic) and other confounding factors. The transformative clinical benefit of ETI may change the life perspectives of PwCF, which could impact their psychological well-being. The authors concluded that the totality of the data on depression-related events in PwCF taking ETI was generally consistent with the background rate of these events in the CF population.

This study was sponsored and designed by Vertex Pharmaceuticals, the manufacturer of Trikafta, Kalydeco, Symdeko and Orkambi.

3.1.2 Observational studies reporting on changes to mental health scores

Studies reporting on changes in scores on mental health instruments, mainly Patient Health Questionnaire 9 (PHQ-9) for depression and General Anxiety Disorder 7-item scale (GAD-7) for anxiety, before and after ETI treatment are summarised in Table 9, below. Publications are summarised alphabetically by primary author, with studies in adults presented first, followed by studies in children and adolescents. Other observational studies that report on other outcomes are summarised in section 3.1.3 Other observational studies.

Comments

There were 30 publications identified that evaluated changes in mental health scores before and after treatment with CFTR modulators. Most of the studies investigated ETI and there was very limited information on other CFTR modulators. Sixteen of these publications were conference poster abstracts describing small, single-centre retrospective or prospective studies that reported on mean depression and anxiety scores and contained limited information.

None of the publications reported an overall increase in depression or anxiety scores, with the exception of Pudukoku et al, who found a small increase in overall GAD-7 score. Some studies reported on individual score trajectories, and found that while most patients had stable or improved scores, a small subset of patients had clinically significant worsening of mental health after starting ETI. In some cases, the publications noted the presence of pre-existing mental health problems or concurrent psychosocial stressors. The publications did not highlight a consistent pattern of people with low or mild mental health scores who developed severe symptoms after initiation.

Table 7: Summary observational studies reporting on changes in scores on mental health instruments (eg, GAD-7, PHQ-9 or PROMIS)

Author, year	Population	N	Methods	Results
Studies in adults				
Allgood, 2021 [19]	Adult PwCF who initiated ETI at a single US CF centre (mean age 35.6)	24	Prospective study. Patients who started ETI between Jan 2020 and July 2020 were surveyed at baseline and biweekly for 3 months. Measures included PHQ-8 and GAD-7.	No statistically significant differences between baseline and day 98 scores for depression or anxiety.
Arooj, 2022 [20]	Adult PwCF who initiated LUM/IVA	44	Prospective study. Patients evaluated 3-monthly for 1 year using PHQ-9, GAD-7 and other measures.	No change or worsening in anxiety and depression scores (GADS-7 and PHQ-9) reported.
Blackwelder, 2022 [21]	Adult PwCF who initiated ETI at a single US CF clinic.	119	Retrospective chart review. Extracted PHQ-9 and GAD-7 scores before ETI initiation (2019), scores approximately 1 year later (2021), and scores at end of 2021. Compared to patients not on ETI.	PwCF taking ETI (n=100) had an average decrease in GAD-7 score of 0.54 compared to an increase of 0.74 in those not taking ETI (n-19). PwCF taking ETI and PwCF not taking ETI both had an average decrease in PHQ-9 score of 0.58. The decrease was greater in patients with mild or moderate baseline PHQ-9 or GAD-7 scores compared to those with low scores. The difference was greatest between 2019 and 2020.
Braun 2022 [22]	Adult PwCF initiating TEZ/IVA.	42	Measured PHQ-9, GAD-7 and CFQ-R at baseline and six months.	25 patients completed the GAD-7 and PHQ-9. The scores in the GAD-7 and PHQ-9 were not significantly different between baseline and 6 months ($p = 0.55$; $p = 0.51$, respectively).
Dell, 2022 [23]	PwCF on ETI at a single US CF centre.	184	PHQ-9, GAD-7, and adult and paediatric PROMIS Depression and Anxiety Scales measured at baseline, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months.	Interim results at 6 months. Thirty-two of 184 patients received paediatric measures. Normal range score rates at baseline then 6 months were: PHQ-9, 67%/78%; GAD-7, 71%/79%; adult PROMIS Depression, 87%/91%; paediatric PROMIS Depression, 91%/85%; adult PROMIS Anxiety, 83%/87%; paediatric PROMIS Anxiety, 91%/95%. Overall trends were toward stability to slight improvement on all measures, with 5 respondents reporting shifts from 'normal' to 'severe' symptoms. No study participants required emergency or inpatient psychiatric care during this 6-month period.

Author, year	Population	N	Methods	Results
Ergenekon, 2023 [24]	PwCF at 12 Turkish centres (median age 18) taking a CFTRm for at least 3 months.	111	Measured quality of life parameters, including PHQ-9 and GAD-7 scores.	86 patients received ETI, 13 took IVA, 6 took IVA/LUM and 6 took IVA/TEZ. The authors reported statistically significant improvement in depression and anxiety at 6 months. Very limited information.
García, 2025 [25]	Adult PwCF at two Spanish CF centres	108	Prospective study measuring GAD-7 and PHQ-9, among other measures, over 12 months after initiation of ETI.	PHQ-9: At baseline, 63% had no or minimal depression symptoms, 24% had mild scores, 11% had moderate scores, and 2% had moderate-severe or severe scores. At 12 months, 93 patients completed PHQ-9. The mean change in PHQ-9 score was -0.50. There were 47 patients with scores suggesting minimal depression symptoms at baseline and 12 months, 15 patients with a reduction in depression symptoms, 12 patients with an increase in symptoms and 19 patients with elevated symptoms at both timepoints. GAD-7: AT baseline, 63% had no or minimal anxiety symptoms, 25% had mild scores, and 7% had moderate scores, and 5% had severe scores. At 12 months, 91 patients completed GAD-7. The mean change in GAD-7 score was -1.00. There were 43 patients with scores suggesting minimal anxiety symptoms at both baseline and 12 months, 12 patients with a reduction in anxiety symptoms, 14 patients with an increase in symptoms and 22 patients with elevated symptoms at both timepoints. The authors concluded that there were no significant changes in anxiety or depression scores.
George, 2020 [26]	PwCF (not further defined) initiating ETI at a single US centre.	14	Prospective study. Measured PHQ-9, GAD-7, Trait Hope Scale (THS) and CFQ-R at baseline and 1, 3 and 6 months.	Baseline median score for PHQ-9 was 5, GAD-7 was 2.5, THS-Agency was 26, and THS-Pathway was 28. There was a statistically significant decrease in PHQ-9 and increase in CFQ-R. There were no differences in GAD-7 or THS scores
Goralski, 2022 (preprint) [27]	Adult PwCF at a single US centre taking ETI.	86	Retrospective chart review. Extracted PHQ-9 and GAD-7 scores, CFTRm prescription data and mental health history. Closest mental health scores prior to and following ETI initiation were used.	The median time between baseline screening and ETI initiation was 403 days. The median time between starting ETI and next screening was 163 days. At baseline, 36% had elevated GAD-7 score and 40% has elevated PHQ-9 score. Overall, there was no change in mean GAD-7 score or PHQ-9 score. 18% had clinically meaningful worsening of GAD-7 and 15% had clinically meaningful

Author, year	Population	N	Methods	Results
				improvement after starting ETI. 15% had worsening of PHQ-9 and 14% had improvement. In 35 patients with a prior anxiety diagnosis, 29% had improved and 17% had worsened GAD-7 score post-ETI. In 32 patients with prior depression diagnosis, 19% had improved and 25% had worsened PHQ-9 scores. People with prior depression diagnosis had greater likelihood of worsened PHQ-9 score post-ETI (OR 3.58; p=0.054). The data did not highlight significant worsening of scores during the COVID-19 pandemic.
Graziano, 2024 [28]	PwCF starting ETI at a single Italian centre.	92	Prospective study. Measured PHQ-9, GAD-7, SMDT, GI Symptom Tracker and CFQ-R at initiation (T0), 1, 3 and 6 months. Also used an *ad hoc* questionnaire on neuropsychiatric effects.	92 PwCF (72 adults, 20 paediatric) were recruited between July and September 2021, prior to starting ETI (>90% of eligible patients). At T0, the mean ± SD score on the PHQ-9 was 3.7 ± 3.5, with 28% scoring in the elevated range (n = 26) and 4.3% (n = 4) endorsing suicidal ideation; 19.6% (n = 18) were mild depression, 6.5% (n = 6) were moderate, and 2.2% (n = 2) were severe. Statistically significant improvements in PHQ-9 score were seen at 1, 3 and 6 months compared to baseline. The mean score on the GAD-7 at T0 was 3.6 ± 3.4, with 37% in the elevated range (n = 34); 29% (n = 28) were mild anxiety, 7.6% (n = 7) moderate, and 1.2% (n = 1) severe. There were no statistically significant improvements in GAD-7 scores over time. Mean SMDT score improved from T0 to subsequent assessments. At 6 months, normative data indicated adolescents scored in the average range, but adults remained one-half SD below the mean. In the questionnaire of neuropsychiatric effects, 10-30% of people reported insomnia, headache, memory problems, brain fog or concentration problems during CFTRm treatment. There was a statistically significant increase in the proportion of people experiencing insomnia from 1 month (12%) to 3 months (16%). The proportion of people reporting headache, brain fog, memory problems, concentration problems remained stable over time. Female participants reported more of these symptoms than male participants. There was no baseline data. Significant increases in the CFQ-R were found across most domains.

Author, year	Population	N	Methods	Results
Hjelm, 2023 [29]	PwCF aged 12+ years at a single US centre	150	Retrospective chart review. PHQ-9 and GAD-7 scores between 2015 and 2021 were extracted.	Mean PHQ-9 and GAD-7 scores decreased over the six-year period, starting in the mild range and decreasing into the minimal range (not statistically significant). Physical health measures improved which correlated with increasing usage of CFTRm. GAD-7 and PHQ-9 scores were not significantly different pre-Covid-19 to during Covid-19. Higher FEV1pp was associated with lower PHQ-9 and GAD-7 scores. CFTRm use was associated with lower PHQ-9 score. Increased mental health visits and CF-related diabetes were associated with higher PHQ-9 and GAD-7 scores. The number of people screened increased over time which could bias the results.
Lathbridge, 2023 [30]	PwCF at a single US centre	108	Retrospective review. PHQ-9 and GAD-7 scores were retrieved for 102 of 284 patients at the centre: 66 initiating ETI and 36 controls.	There was improvement of PHQ-9 score (defined as change in category) in 38% of the ETI group vs 28% of the control group. There was worsening of PHQ-9 score in 14% of the ETI group and 36% of the control group. There was improvement of GAD-7 score in 26% of the ETI group vs 19% of the control group. There was worsening of GAD-7 score in 21% of the ETI group and 28% of the control group. The authors concluded that ETI was associated with a positive impact on mental health as evidenced by greater improvement in scores in patients who initiated ETI than in controls.
Nguyen, 2025 [31]	Adult PwCF taking ETI at a single Canadian centre.	100	Retrospective review of routinely collected GAD-7 and PHQ-9 scores (baseline, 6 months, 12 months) from July 2021 to September 2023. Severity of symptoms were defined as normal (0–4), mild (5-9), moderate (10-14), severe (15+). clinically significant change was defined as ±4 points.	100 of 117 patients (85%) taking ETI had scores at baseline and 6 months, and 90 patients had scores at 12 months. Patients with missing scores were more likely to be male, younger with milder CF, and have a baseline psychiatric diagnosis. Overall, GAD-7 scores decreased by a median of 1 point (IQR -3 to 1; p= 0.03) at 6 months and decreased by 1 point (IQR -2 to 1; p=0.03) at 12 months. There was no significant change in the distribution of individuals across the anxiety symptom severity groups from baseline to 6 months; however, there was a significant reduction in the proportion of individuals with at least mild symptoms by 12 months (see figure below). 20% of individuals had clinical improvement of their anxiety symptom scores and 10 % had clinical worsening at 6 months, which remained stable at 12 months.

Author, year	Population	N	Methods	Results
				 PHQ-9 scores decreased by 1 point (IQR -4 to 0; p < 0.001) 6 months post-ETI and decreased by 1 point (IQR -4 to 1; p < 0.001) 12 months post-ETI. 

Author, year	Population	N	Methods	Results
Ospina, 2023 [32]	PwCF at a single US centre.	157	Retrospective review. PHQ-8 was measured annually in all CF patients. Scores compared before and after starting CFTRm.	No significant differences between mean scores before and after starting CFTRm. No differences between patients who started CFTRm and those who didn't.
Piehler, 2023 [33]	Adult PwCF (median age 28) at a single German centre starting ETI.	70	Prospective study. PHQ-9, GAD-7, CFQ-R and BDI-FS assessed at baseline and at 8-16 weeks.	At baseline, 81.7% reported minimal or mild and 18.3% reported moderate or severe symptoms of depression. After initiation of ETI, PHQ-9 scores decreased by 1.0 (IQR -3.0 to 0.3; p <0.05). There was a decrease in mild (−11.3%) and moderate (−5.7%) scores, and an increase in the minimal scores (+16.9%). At baseline, 4 patients (5.6%) reported suicidal ideation whereas after initiation of ETI only one patient (1.4%) still reported suicidal ideation. At baseline, 84.3% of the patients reported minimal or mild and 15.7% reported moderate or severe symptoms of anxiety. After initiation of ETI, GAD-7 scores did not change compared to baseline (median difference 0.0; IQR -2.0 – 0.0). Figures indicate that most patients had similar or improved PHQ-9 and GAD-7 scores, with a small subset having worsened scores after ETI initiation. Two patients changed from moderate to severe PHQ-9 scores but reported life stressors. Three patients changed from mild to moderate GAD-7 scores.
Pudukodu, 2021 [34]	Adult PwCF at a single US centre taking ETI.	39	Retrospective review of PHQ-9 and GAD-7 scores in patients taking ETI prior to 11 March 2020 (COVID-19 pandemic).	In this cohort, total GAD-7 score was significantly higher after initiation of ETI (mean score change 1.77, 95% CI, 0.22–3.32). The difference was largely driven by increases in questions 5-7 (restlessness, irritability, feeling afraid). Total PHQ-9 scores were unchanged but there were increases in questions 7 (trouble concentrating) and 8 (moving/speaking slowly or restlessness).
Reilly, 2014 [35]	PwCF initiating ivacaftor	12	Prospective study. HADS score measured at baseline, 3 months and 14 months, among other clinical parameters.	The mean HADS score ± SD was 8.9 ± 4.3 at baseline, 5.13 ± 3.5 at 3 months and 2.75 ± 4.1 at 14 months.
Rieubet, 2023 [36]	Adults PwCF starting ETI at a French centre.	84	Prospective study. Measured CES-D and HADS at baseline and 6 months.	Before ETI, 39% of patients had depression symptoms compared with 27% at 6 months (p=0.24). Women were in a significantly higher depression category than

Author, year	Population	N	Methods	Results
				men (OR=5.59; 95% CI: 1.26–24.70), but were more likely to be improved at 6 months (OR=0.25; 95% CI: 0.06–0.98). Before ETI, 45% had anxiety symptoms compared with 36% at 6 months (p=0.01). Women had significantly a higher anxiety category than men (OR=4.96; 95% CI: 1.21–20.30).
Sakon, 2023 [37]	PwCF (mean age 28) at a single US centre	82	A survey on the perceived effects of the COVID-19 pandemic and ETI on mental health was distributed to 82 PwCF in early 2022.	78 of 82 respondents were taking ETI. 33 PwCF (40%) felt that COVID-19 contributed to worsening of anxiety, depression or both. 7 (9%) PwCF felt that ETI contributed to worsening of anxiety, depression or both. 18 (23%) felt ETI improved their mental health. PHQ-9 scores were available for before starting ETI and 3-6 months after starting ETI in 56 PwCF. The median change was -1.11 with a range of -22 to +14.
Sandler, 2025 [38]	Adults (16 years) PwCF at a single UK CF centre prescribed CFTRm.	190	PHQ-9 and GAD-7 scores from July 2023 to August 2024 were extracted from medical records.	Mean PHQ-9 and GAD-7 scores were 5.9 (95% CI: 5.1 to 6.7) and 4.8 (95% CI: 4.0 to 5.5) respectively. Symptoms of depression were seen in 34 (18%), and anxiety in 38 (20%). Symptoms of either depression or anxiety were seen in 48 (25%), with half of these (24) experiencing both.
Vincken, 2025 [39]	PwCF ≥ 18 years eligible for ETI (mean age 28 years)	79	Prospective study of clinical outcomes in people starting ETI, including GAD-7 and PHQ-9 scores at baseline, 3 months and 6 months.	53% had prior CFTRm use (mainly TEZ/IVA). GAD-7 and PHQ-9 scores were not significantly different at 3 or 6 months. The mean GAD-7 score (n=50) was 3 (1;6) at baseline, 2 (0;8) at 3 months and 3 (0;8) at 6 months. The mean PHQ-9 score (n=49) was 4 (1;7) at baseline, 3 (1;6) at 3 months and 3 (1;6) at 6 months. Psychiatric adverse events recorded during the study were subjective personality changes (n=4), insomnia (n=3) and severe psychotic decompensation (n=1). One person stopped ETI due to subjective personality changes and lack of respiratory improvement from baseline.
Zhang, 2022 [40]	PwCF (mean age 35) at a single US centre taking ETI.	100	Retrospective chart review of patients receiving care between Jan 2015 and Feb 2022, including annual PHQ-9 and GAD-7 scores.	57 patients had a mental health diagnosis at baseline. 5 patients received new mental health diagnoses while on ETI and two had diagnoses revoked. After initiating ETI, 22 patients initiated, switched or increased the dosage of a psychotropic medicine. 23 reported new sleep issues and 30 had pre-existing sleep

Author, year	Population	N	Methods	Results
				issues that continued. Two patients with elevated pre-ETI scores discontinued ETI permanently due to significant insomnia, anxiety, and depression symptoms. There was no change in mean PHQ-9 or GAD-7 scores after starting ETI. No association with the COVID-19 pandemic was seen.
Studies in children and adolescents				
Borawska-Kowalczyk, 2024 [41]	Adolescent PwCF on ETI aged 12-18 years at a single Polish CF centre.	99	Prospective study. Measured PHQ-9 and GAD-7 scores at baseline and every 3 months. Categorised as normal, mild or moderate/severe. PWBS and CFQ-R also measured.	The majority of patients had the same or lower PHQ-9 or GAD-7 category at 3 months. 8.22% and 9.59% of patients had a higher PHQ-9 or GAD-7 category, respectively, at 12 months. No significant changes in PWBS scales and CFQ-R scores increased.
Douglas, 2025 [42]	Paediatric PwCF aged 6-11 years starting ETI at a single Australian centre	108	Caregivers completed the Paediatric Symptom Checklist (PSC-17) and Sleep Disturbance Scale for Children (SDSC) at baseline and one month after starting ETI.	108 out of 149 (72%) eligible children enrolled in the study with 101 baseline surveys and 75 1-month surveys completed. There were no significant differences in the characteristics of ETI responders and non-responders. More than 70% of participants had normal scores at baseline and one month, while a minority of children had scores that improved, deteriorated or remained clinically significant (see figures below). New-onset symptoms were reported in 9 (12%) of children and were mild-moderate in all but one child with a developmental disorder and anxiety who stopped ETI. Follow-up consultations confirmed temporal association between ETI and new or worsened symptoms within 1-2 weeks of initiation, including aggression, irritability, difficulty initiating/maintaining sleep, increased sleep arousal and emotional lability. Limitations noted were short follow up and lack of efficacy data. Changes in scores may reflect normal perturbations in mood and behaviour in growing children. Possible selection bias and personal feeling bias were also noted.

Author, year	Population	N	Methods	Results
				[redacted]

Author, year	Population	N	Methods	Results
				[redacted]
Gravelle, 2025 [43]	Children aged 2-5 years starting ETI at a Canadian centre.	21	Prospective study. Parents reported on child mental health behaviours and completed PedsQL, CFQ-R and PSC measures at baseline, 1, 6 and 12 months.	Data was available at 1 month for 21/21 participants and at 6 months for 15/21 participants. By one month on ETI, 8/21 (38%) parents reported new mental health concerns including sleep disruption, nightmares, aggression, emotional dysregulation, hyperactivity, and eye tics. Of these, 2/8 self-resolved by six weeks and the rest reported improvement with flipped dosing. There were varying degrees of corresponding deterioration in survey scores but worsening scores were also observed in the context of no reported mental health changes.
Muther, 2023 [44]	Adolescent PwCF taking ETI at a single US centre (average age 15.3).	91	Retrospective review of available PHQ-9 and GAD-7 scores within 12 months prior to and 12 months following ETI initiation.	No statistically significant differences in total sample means from before (GAD-7, 3.18; PHQ-9, 3.34) and after ETI (GAD-7, 3.42; PHQ-9, 3.30). There was a notable increase in frequency of high scores after ETI (33 (36.3%) with high GAD-7 scores; 27 (29.7%) with high PHQ-9 scores. For GAD-7, 31 participants (34.1%) had decreased anxiety-related symptoms after ETI initiation, and 37 (40.7%) had an increase. For the PHQ-9, 33 participants (36.3%) had a decrease in depressive symptoms after ETI initiation, and 29 (30.8%) had an increase.
Pasley, 2025 [45]	Paediatric PwCF aged <18 years, starting ETI.	81	This publication presents the paediatric results of the same study as described in Dell et al (2022) above.	Depression: At baseline, the majority of paediatric patients did not endorse depressive symptoms on the PHQ-8 (72%) and the PROMIS-D (79%). A small subset of patients had elevated baseline scores on the PROMIS-D and PHQ-8; 8.8% and 13%, respectively.

Author, year	Population	N	Methods	Results
			Age-appropriate measures (PHQ-8, GAD-7 and PROMIS-Anxiety and Depression) were administered at baseline and 1, 3, 6, 9, 12 and 18 months. Patients without baseline data were excluded.	After 18 months on ETI, more patients reported scores within normal limits (WNL) on the PHQ-8 (85%) and on PROMIS-D (92%) compared to baseline. Median (IQR) scores fell in the normal range. PHQ-8 mean scores decreased by 1.28 (95% CI = −2.92, 0.36; p = 0.13) at 18 months. PROMIS-D scores decreased by 2.67 (95% CI = −4.54, −0.79; p = 0.01) at 1 month, by 2.26 (95% CI = −4.37, −0.14; p = 0.04) at 6 months, by 3.36 (95% CI= −5.57, −1.14; p<0.01) at 12 months. The percentage of patients with elevated scores fell from 13% to 3% on the PHQ-8 and from 8.8% to 2.6% on the PROMIS-D. Anxiety: At baseline, the majority of patients reported anxiety symptoms WNL on the GAD-7 (69%) and PROMIS-A (83%). Median (IQR) scores fell in the normal range. Elevated baseline scores were observed in 8.9% and 12.3% of patients on the GAD-7 and PROMIS-A, respectively. After initiating ETI, GAD-7 scores did not decrease significantly compared to baseline until 12 months (−1.37, 95% CI = −2.46, −0.28; p = 0.01) and 18 months (−1.18, 95% CI = −2.30, −0.06; p = 0.04). PROMIS-A mean scores decreased significantly at every time point compared to baseline. On both measures, the percentage of patients with scores in the "elevated" range fell to 0% by 18 months. Overall, the percentage of patients with depression or anxiety symptoms decreased over the first 18 months of ETI treatment.
Pettit, 2025 [46]	Paediatric PwCF aged 6-11 years who started ETI at a single US centre.	110	Retrospective review. Extracted records of mental health changes and other AEs for patients started on ETI between 1 June 2021 and 1 October 2022.	17 of 110 patients (15.5%) experienced an AE, including 4 patients with behavioural/mental health changes 1 to 7 months after starting ETI. One patient had a prior mental health diagnosis that worsened after starting ETI, with some improvement after changing to TEZ/IVA. Two patients decreased the ETI dose with resolution of symptoms. Two patients started an SSRI.
Pham, 2024 [47]	Children and adolescents aged 10-18 years.	31	Prospective study. PHQ-9, GAD-7, PDSS, SDSC and FEV_1 assessed before and after starting ETI.	20 participants had pre- and post-ETI anxiety and depression scores, of whom 10 remained with in normal range. Eight patients had elevated scores at baseline, of whom 3 worsened and 3 improved post-ETI. Two patients developed new-onset mood concerns post ETI. The mean PHQ-9 score was 6.36 pre-ETI and 6.60 post-ETI (p=0.83). The mean GAD-7 score was 5.33 pre-ETI and 5.85 post ETI (p=0.66).

Author, year	Population	N	Methods	Results
				21 participants had pre- and post-ETI sleep scores, of whom 6 maintained normal scores. 13 had persistent sleep disturbance and 2 developed new-onset sleep concerns post ETI. The mean SDSC score was 42.95 pre-ETI and 42.86 post-ETI (p=0.96). The mean PDSS score was 11.45 pre-ETI and 11.65 post-ETI (p=0.85).
Vance, 2021 [48]	Paediatric patients aged 12 to 20 who initiated ETI at a single US centre.	62	Prospective study of PHQ-9 and GAD-7 scores at baseline (2019) and at 3, 6, 9 and 12 months.	85% of patients had normal scores at all assessments. 8% had high scores and 7% fluctuated between normal and elevated scores throughout the timeframe.

Mental health instrument abbreviations:

- *PHQ-9 = Patient Health Questionnaire-9 (depression severity)*
- *GAD-7 = General Anxiety Disorder-7*
- *PWBS = Psychological Wellbeing Scale*
- *CFR-R = Cystic Fibrosis Questionnaire-Revised*
- *PROMIS = Patient-Reported Outcomes Measurement Information System*
- *PSC-17 = Paediatric Symptom Checklist-17*
- *SDSC = Sleep Disturbance Scale for Children*
- *THS = Trait Hope Scale*
- *Peds-QL = Paediatric Quality of Life Inventory*
- *SMDT = Symbol Digit Modalities Test*
- *PDSS = Panic Disorder Severity Scale*
- *BDI-FS = Beck Depression Inventory-Fast Screen*
- *HADS = Hospital Anxiety and Depression Scale*
- *CES-D = Center for Epidemiologic Studies Depression Scale*

3.1.3 Other observational studies

Other observational studies describing possible psychiatric effects of CFTRm, but not reporting on changes in mental health scores before and after CFTRm treatment are summarised in table 10. Articles are presented alphabetically by primary author.

Table 8: Results of observational studies other than those reporting on changes in mental health instruments

Author, year	Population	N	Methods	Results
Studies in adults				
Baromeo, 2025 [16]	Adult PwCF at a single centre	10	Single-centre retrospective case series. Examined ETI exposure before and after dose reduction due to AEs. PwCF with data on ETI levels and sweat chloride concentration (SCC) before or after a dose reduction were included. ETI exposure was characterised by Cmin and SCC was a marker for efficacy. Dose reduction strategies were reducing morning ETI dose to one tablet and/or removing the night IVA dose.	Ten people with AEs were included in the review, of whom 7 experienced psychiatric or nervous system disorders (depression/low mood, dizziness, concentration problems, epileptic seizure, lethargy, reduced appetite, worsened anxiety, irritability, memory loss, insomnia, mood swings). After dose reduction, 2 patients had resolution of psychiatric/nervous system disorders, 4 patients improved and 1 patient had minimal improvement. At the full ETI dose, the mean Cmin levels for elexacaftor, tezacaftor, and ivacaftor were higher than the Cmin values observed in published registration study data. Following dose reduction, the mean Cmin levels decreased. After dose reduction, SCC decreased in 3 patients but increased in 4 others. 1 subject maintained normal SCC levels (<30 mmol/L) and 7 patients remained within the intermediate range (30–60 mmol/L). Post dose reduction SCC was not available for two patients. The authors concluded that reducing ETI dose can mitigate AEs. The use of different dose reduction strategies limits the comparison of Cmin between patients. Other limitations include incomplete data for SCC and Cmin, the limitations of sweat chloride as a marker of efficacy and lack of data on metabolites.
Baroud, 2023 [49]	Adult PwCF taking ETI	31	Retrospective chart review was used to categorise symptom trajectories of all adults at a single CF centre who initiated ETI before March 2022 and subsequently had ≥1 outpatient visit with the consulting CF psychiatrist.	The chart review included 31 patients aged 18 to 69 years of the 148 individuals at the centre treated with ETI. At the time of starting ETI, all patients had at least 1 lifetime psychiatric diagnosis, most commonly depression, anxiety and ADHD. Four had at least 1 prior psychiatric hospitalisation, and 27 (87%) were taking at least 1 psychiatric medicine. All individuals reported improvement in overall physical health after starting ETI, with 5–43 months (mean 22.90 ± 7.13) of post-ETI follow-up. Patients were classified

Author, year	Population	N	Methods	Results
			Successful management strategies described.	according to neuropsychiatric symptom trajectory: improved, unchanged, worsening (possibly related to ETI) or new/worsening (probably related to ETI). Of the 16 patients with new or worsening neuropsychiatric symptoms classified as probably related to ETI: • 10 had neurocognitive changes (eg, word-finding difficulty, brain fog, memory impairment, concentration problems). • 6 had new/increased anxiety, including 2 with new panic symptoms. • 6 had new/worsening depression, including 3 with new suicidal ideation. • 3 had new hypomanic symptoms. • 3 had new/worsening sleep disturbances. • 3 had new fatigue. There were 6 patients noted as having other psychosocial stressors, including weight gain, survivor guilt and distress about life changes related to improved health. The authors concluded that although many individuals initiating ETI experience improvements in physical and mental health, a subset report adverse changes in neurocognition, mood, and anxiety. Of the 148 adults at the centre treated with ETI, 31 (21%) were referred to the CF psychiatrist and included in the chart review, and 16 (11%) had new or worsening neuropsychiatric symptoms classified as probably related to ETI. Strategies that resulted in improvement of symptoms included psychotropic medicines (stimulants, SSRIs, bupropion, benzodiazepines, sleep medicines), psychotherapy, and changes to ETI therapy (decreased dose, flipping AM/PM doses, discontinuation and changing modulator).
Bessonova, 2018 [50]	PwCF in US and UK CF registries	9,936	Annual analyses using US and UK CF registries compared ivacaftor-treated and untreated matched comparator patients for clinical outcomes and prevalence of CF complications, including depression.	Analyses included 1,256 ivacaftor-treated and 6,200 comparator patients from the US and 411 ivacaftor-treated and 2,069 comparator patients from the UK. Risks of adverse clinical outcomes and prevalence of CF complications were lower in ivacaftor-treated patients. The 2014 prevalence of depression was significantly lower in ivacaftor-treated patients (14%) compared to untreated comparators (17%) in the US registry and similar (4% vs 6%) in the UK registry. Because of differences in screening and data capture between countries, the prevalence of depression cannot be directly compared between the US and UK.

Author, year	Population	N	Methods	Results
Georgiopolis, 2023* [51]	PwCF aged ≥5 years currently taking ETI	554	Data from Well-ME survey in June-July 2022 was used to identify differences in PROMIS Global 10 mental health (adults) and Global 7+2 parent proxy global score (children) between sexes in PwCF taking ETI. The proportion reporting much or somewhat worse symptoms was compared with the proportion reporting no change or somewhat or much better symptoms.	Of 1,125 surveys received, 554 were from PwCF aged ≥5 years currently taking ETI. 420 (76%) aged ≥18, 134 (24%) aged 5–17, 528 (95%) white, 336 (61%) female. There were no significant sex differences in PROMIS mental health components (women 48.9±9.6, men 49.2 ±9.2) or global well-being (girls 46.7±10.2, boys 49.2±7.8). Women and girls were significantly more likely than men and boys to experience perceived somewhat or much worse anxiety, depression, and feelings of stress or guilt since starting ETI. Women were significantly more likely than men to report worse overall mental health, agitation, irritability, body image, thinking clearly, sleep, and unhealthy eating. Girls were significantly more likely than boys to experience suicidality and act out. Men were significantly more likely to report use of alcohol or drugs. Women with CF report worse mental well-being than men after starting ETI which aligns with general population data.
Lucca, 2025 [52]	PwCF at a single Italian centre	414	This study reported potentially medicine-related AEs and resulting changes to treatment. The study followed PwCF who attended Verona Cystic Fibrosis Center and initiated ETI treatment for a period of 5 years. AEs were monitored by physicians during visits and via chart and record reviews. Patients with mental health problems were referred to the CF psychologist.	There were 414 patients included in the study. The mean participant age was 28 years and 54% of participants were female. Median duration of ETI treatment was 35.60 months [IQR 26.46–39.26]. There were 85 patients (20.5%) who reported 142 AEs. The authors observed no differences in age, sex, baseline ppFEV1, or genotype between patients with and without AEs. In children, psychiatric disorders were the most frequently reported AEs, while in adults musculoskeletal and respiratory disorders predominated. There were 24 patients who presented the following psychiatric disorders: depression (n=4), low mood (4), brain fog (3), insomnia (3), behaviour changes (3), attention problem (2), anxiety (3), mood swing (1), agitation (1). There was no change to treatment in nine patients, 11 had permanent dose modification, 2 had temporary dose modification and 2 had permanent discontinuation.
Spoletini, 2022 [53]	Adult PwCF at a single UK centre	262	This chart review described the experience of a CF clinic in using sweat chloride and markers of clinical stability to titrate ETI dose reduction to minimise AEs.	Between October 2019 and October 2020, 262 adults (modulator-naïve or switched from TEZ/IVA or IVA) started ETI and were included in the chart review. 33 PwCF (12.6%) experienced one or more adverse events on ETI. 19 PwCF (7.3%) reported deterioration in mental health with anxiety, low mood, insomnia and brain fog, of whom 12 had a history of anxiety/low mood.

Author, year	Population	N	Methods	Results
				13 PwCF, of whom nine had a history of mental health issues, underwent dose reduction of ETI with monitoring of sweat test and lung function. Four people stopped treatment, and two continued the full dose with psychological support. In all cases, dose adjustment resulted in normal or borderline sweat chloride levels and lung function and respiratory symptoms remained better than pre-ETI. Resolution or improvement of AEs occurred in 10 cases. The remaining 3 cases improved after stopping treatment or switching to IVA. The authors concluded that a strategy combining dose reduction and psychological support potentially avoids discontinuation of treatment, whilst reducing side effects. It was hypothesised that these AEs are a result of a combination of predisposition to anxiety and/or depression, the presence of a pre-morbid mental health condition, individual variation in elexacaftor metabolism and increased systemic CFTR expression.
Studies in children and adolescents				
Alagedi, 2025 [54]	Children aged 2-5 years starting ETI	28	Retrospective chart review at Kings College Hospital, London to assess records of neuropsychiatric symptoms (mood disturbance, sleep and behavioural changes) following ETI treatment.	There were 28 children (median age 3 years; 21 male) included in the review, of whom 19 (68%) had been treated with LUM/IVA prior to ETI. A total of 7/28 (25%) exhibited sleep or behavioural problems. Of the 4 (14%) patients who experienced sleep disturbances; one developed vivid dreams, 2 developed night terrors, and 1 developed insomnia. Two patients required modification of ETI dosing and one switched back to ivacaftor monotherapy.
Kimber et al, 2025* [55]	Paediatric PwCF aged <6 years who were prescribed ETI in the East of England CF Network	33	Retrospective cohort study of reported sleep disturbance or behaviour change following initiation of ETI.	Adverse events were reported for 16/33 patients (48%). Of those, 8 (25%) reported isolated sleep disturbance, 2 (6.25%) had isolated behavioural change and 6 (18.75%) had changes in both sleep and behaviour. Of those reporting side effects, half had previously taken LUM/IVA. 5/16 persisted with ETI, leading to resolution of side effects in 4/5. 11/16 swapped morning and evening doses with resolution in 6/11. 4/16 chose to stop taking IVA, leading to resolution of side effects in 2/4; the remaining 2 then chose to also stop ETI. The authors propose the following pathway for managing these adverse events: 1. Persevere for ≥14 days. Address other potential causes (sleep hygiene, adjustments to nursery/school). 2. Switch medicine timings: give IVA in the morning and ETI in the evening for 14 days.

Author, year	Population	N	Methods	Results
				3. Stop IVA. 4. Stop ETI then reintroduce after a period of behavioural stability. Measure sweat chloride before and after to determine dose efficacy
Lee et al, 2023* [56]	Paediatric PwCF aged 6-11 years	83	In a large regional network (UK), 83 or 86 eligible children commenced ETI. Safety was monitored as part of routine clinical care.	Seven children (8.4%) had documented behavioural adverse events (hyperactivity, emotional outbursts, tearful, angry) from 19 days to 5 months after commencement, 6 having no previous behaviour/mood concerns. • One child was managed successfully by reducing morning ETI dose. • Two children, (1 with a prior diagnosis of Autistic Spectrum Disorder, another with associated deliberate self-harm since starting ETI), showed no benefit from dose reduction and switched to LUM/IVA, with subsequent rapid improvement. • One was successfully managed without dose reduction, the behavioural/mood issues resolving 8 months after ETI initiation. • Two were instructed to omit evening ivacaftor dose, this resolved the issues for 1 child. • One continued on full dose ETI and parents were coping with the behavioural issues.
Sermet-Gaudelus et al, 2024 [57]	Paediatric PwCF aged 2-5 years	197	Prospective observational study (MODUL-CF). Enrolled children who were starting ETI at 34 CF clinics in France. Adverse behavioural events and sleep difficulties were evaluated at baseline, 1 month and 3 months by parent/guardian standardised questionnaire.	At 1 month, 93 (47%) of 197 children were reported to have sudden abnormal changes in behaviour that were suspected to be related to ETI. 14 (15%) of 93 children had worsening of pre-existing issues and 79 (85%) had no previously documented issues. The behavioural issues were ADHD (33%), irritability (17%), and mood disorders such as abnormal sadness (11%) and suicidal ideation (1%). Sleep difficulties were observed in 46 (49%) of 93 children, including difficulty falling asleep (48%), frequent night awakening (35%), and abnormal nightmares (20%). Sleep and behavioural issues started in the first week of treatment and persisted at 3 months for 58 (62%) of 93 children. There was immediate recovery in four children who had a dose reduction and two children who stopped treatment. Children with and without behavioural/sleep issues at month 1 were similar with regard to age, bodyweight, sweat chloride concentration and ETI plasma concentration (measured in 48 children - see table below). The authors hypothesised that the observed sudden behavioural and sleep difficulties may be driven by ETI modulation of CFTR-dependent chloride transport within the brain.

Author, year	Population	N	Methods	Results
				This change might affect the developing brain in young children more than in older children and adults. Additionally, binding of ivacaftor and its metabolites to δ-opioid receptor and serotonin receptors has been identified *in vitro*. It was also noted that difficulty adjusting to health changes, lack of recognition of behavioural issues in the context of symptomatic CF and nocebo effect may be contributing factors. 

3.1.4 Literature case reports

A literature search identified 12 publications describing case reports and case series of psychiatric disorders after treatment with a CFTR modulator. The case reports are described in Table 11.

Table 9: Literature case reports and case series of neuropsychiatric adverse events with CFTR modulator treatment

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
McKinzie et al, 2017 [58]	Worsening anxiety and depression after initiation of lumacaftor/ivacaftor combination therapy in adolescent females with cystic fibrosis	15 F	LUM/IVA	Suicidal ideation Anxiety	Psychotherapy Psychotropic medicine Discontinued LUM/IVA	This case series describes 5 cases in female adolescents with worsening anxiety or depression, including suicidal ideation or suicide attempt, that may be associated with LUM/IVA. Case 1 describes a 15yo female with 5-year history of anxiety. She experienced suicidal ideation within 2 weeks of starting LUM/IVA and subsequent increasing anxiety attacks. Four months later she decided to discontinue LUM/IVA due to anxiety and menstrual irregularities with improvement in mood within 10 days.
		17 F	LUM/IVA	Depression Suicidal ideation	Psychotropic medicine	Case 2 describes a 17yo female with history of depression and anxiety on a stable dose of fluoxetine for 4 months. Within two months of starting LUM/IVA, she experienced worsening depression, including suicidal ideation. Her fluoxetine dose was increased. She discontinued LUM/IVA at a later time due to GI side effects.
		14 F	LUM/IVA	Depression Suicidal ideation	Psychotherapy Psychotropic medicine Discontinued LUM/IVA	Case 3 describes a 14yo female with no prior mental health concerns. Nine months after starting LUM/IVA she reported depression and passive suicidal ideation. She attempted suicide 2 months later and reported stressors in her life. Fluoxetine was started. The patient and family decided to discontinue LUM/IVA and her mood improved.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
		12 F	LUM/IVA	Mood disorder Suicidal ideation	Psychotropic medicine Psychotherapy Discontinued LUM/IVA	Case 4 describes a 12yo female with no prior mental health concerns. Two months after starting LUM/IVA, she had worsening mood and suicidal ideation and subsequent suicide attempt. LUM/IVA was discontinued and sertraline was started with improvement of mood within 3 weeks.
		17 F	LUM/IVA	Depression Attempted suicide	Psychotropic medicine Discontinued LUM/IVA	Case 5 describes a 17yo female with a history of depression and anxiety with worsening mood 7 months after starting LUM/IVA. LUM/IVA was discontinued and escitalopram was started. Her depression continued to worsen and other psychotropic medicines were trialled. She subsequently attempted suicide. LUM/IVA was later re-trialled with unknown outcome.
Talwalkar et al, 2017 [15]	Cystic Fibrosis Transmembrane Regulator modulators: implications for the management of depression and anxiety in cystic fibrosis	44 F	LUM/IVA	Depression Anxiety	Psychotropic medicine Discontinued LUM/IVA	This case series describes 3 patients with long-standing depressive and/or anxiety symptoms on stable psychotropic medication regimens with deterioration after starting LUM/IVA. Case 1 describes a 44yo female with a history of depression, panic disorder, and chronic pain. Her depression had been stable for years on citalopram and lorazepam. Within 1 month of starting LUM/IVA, she reported increased anxiety and depression. This affected her adherence to CF treatment with subsequent deterioration of respiratory health. She discontinued LUM/IVA after 4 months of treatment. Her mental health and respiratory symptoms returned to baseline after changes to psychotropic medicines.
		26 M	LUM/IVA	Depression	Psychotropic medicine	Case 2 describes a 26yo male with bipolar disorder and stable mood. His depression, pulmonary health, and

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						adherence had worsened after a bereavement but recovered over several months at which time he commenced LUM/IVA. He then experienced significant drops in FEV1 and BMI and disclosed at three months of treatment that he was profoundly depressed. His psychotropic medicines were changed and he improved and remained on LUM/IVA.
		36 M	LUM/IVA	Depression Anxiety Substance use disorder	Psychotropic medicine	Case 3 describes a 36yo male with depression, generalised anxiety disorder and opioid use disorder. After starting LUM/IVA, he experienced multiple acute pulmonary exacerbations, increased substance use, depression and anxiety, which worsened further after learning he was not accepted for lung transplantation. His adherence to treatment was noted as poor prior to formal discontinuation of LUM/IVA and commencement of palliative care.
Tindell et al, 2020 [59]	Trikafta and psychopathology in cystic fibrosis: A case report	19, F	ETI	Depression Anxiety Sleep paralysis	Psychotropic medicines ETI interruption and gradual up-titration	This report describes a 19-year-old female with a history depressive and anxiety disorders, ADHD, three prior episodes of sleep paralysis and a family history of schizophrenia. She was initiated on ETI with concomitant quetiapine for insomnia. Within two weeks she developed worsening mood with suicidal ideation. Subsequently had episodes of sleep paralysis with vivid hypnopompic hallucinations. She discontinued ETI with cessation of sleep paralysis and persistence of depression which was treated with sertraline. One month later, ETI was restarted and gradually titrated to a full dose. She continued to experience fluctuating depression, anxiety and sleep paralysis episodes. The authors note that psychosocial

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						stressors may have contributed to the events but considered that symptoms correlated with ETI treatment.
Heo et al, 2022 [60]	Mental status changes during elexacaftor/tezacaftor/ivacaftor therapy	31 M	ETI	Fogginess Slurred speech Cognitive impairment Vertigo	Discontinued ETI	Patient 1 had improvement in symptoms of short-term memory loss, ability to perform simple mathematical calculations, and reading comprehension within 7 days of stopping ELX/TZA/IVA. Symptoms of fogginess and vertigo improved but had not returned to baseline nine months later. Neurocognitive testing was normal 8 months after stopping medicine. Previously taking TEZ/IVA.
		45 M	ETI	Fogginess Word-finding difficulty Memory issues	Modified ETI dosage regimen	Patient 2 reported progression of symptoms (fogginess, word-finding difficulty, memory issues) over time. Modest improvement in symptoms with dose reduction. Considered some symptoms may be related to insomnia and restless sleep. Resumed full dose but swapped morning and evening doses with full resolution of symptoms.
		34 M	ETI	Fogginess Word-finding difficulty	None	Patient 3 reported fogginess and word-finding difficulty 1 month after starting ETI. He improved over 1 month to near normal while continuing full dose.
		26 F	ETI	Fogginess	None	Patient 4 reported mental fogginess and mild insomnia within one month of starting ELX/TZA/IVA. Maintained on full dose.
		31 M	ETI	Word-finding difficulty Fogginess	None	Patient 5 reported symptoms at 8 months of treatment but onset time unknown. Switched morning and evening doses with no improvement. Continued standard dosing. Previously taking TEZ/IVA.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
		14 F	ETI	Word-finding difficulty Memory issues Fogginess	Discontinued ETI	Patient 6 reported symptoms of fogginess and memory issues in the first 1-2 months of treatment. Also reported nightmares and dark/paranoid thoughts. Dose reduction was followed by discontinuation of the medicine.
Andreu et al, 2023 [61]	Neuropsychiatric symptoms in a patient under cystic fibrosis transmembrane conductance regulator modulators treatment: a case report	23 F	VX-659/ TEZ/IVA	Psychosis	CFTRm discontinued Psychotropic therapies	This case report describes a 23yo female with no previous psychiatric history who was admitted to a psychiatric inpatient unit after presenting behavioural alterations over 2 years, the beginning of which coincided with having received VX-659/TZA/IVA in a clinical trial for 3 weeks. Her symptoms included abnormal orolingual movements, bizarre poses or anomalous limb movements and persecutory delusional ideation. She had previously received a diagnosis of unspecified psychosis after two prior admissions. During her third admission, disorganised behaviour, incoherent speech, delusional ideas, dissociative symptoms and aggression were observed. She was treated with antipsychotics and electroconvulsive therapy.
Arslan et al, 2023 [62]	Suicide attempts in adolescents with cystic fibrosis on elexacaftor/tezacaftor/ivacaftor therapy	15 F	ETI	Depression Suicidal ideation	Psychotropic medicine Psychotherapy Discontinued ETI	This case series describes two cases of attempted suicide shortly after starting ETI. Case 1 describes a 15yo female without personal or family history of mental illness, and stable social and family environment. Shortly after starting ETI, she experienced sleep disturbances that improved after interchanging morning and evening doses but also experienced abdominal pain and vomiting. Three months later she reported dysphoric mood, depression and suicidal ideation and was started on fluoxetine and psychotherapy with some improvement noted over the

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						following months. However, approximately 6 months later she attempted suicide. ETI was discontinued with improvement in mood. ET was later restarted but was discontinued by the patient due to rapid recurrence of depression.
		15 M	ETI	Depression Insomnia Attempted suicide	Psychotropic medicine Psychotherapy ETI dose reduction	Case 2 describes a 15yo male with concurrent marijuana use and vaping habit, and family history of depression. Strict isolation during Covid-19 pandemic, declining grades and absence from clinic appointments were noted. At his first clinic appointment 1.5 years after starting ETI, he reported stress and mood concerns, insomnia and a suicide attempt 6 months prior. His family noted the Covid-19 pandemic and a new peer group as possible contributing factors. He was referred to outpatient psychiatry but was lost to follow-up and made a suicide attempt 3 months later. The ETI dose was reduced with rapidly improved mood.
Blaisonneau et al, 2025 [63]	Adverse effects of the tezacaftor/ivacaftor/elexacaftor combination that may lead to treatment discontinuation: a series of 10 cases (preprint)	28 F	ETI	Depressed mood Anxiety	ETI interruption and dose reduction	This case series describes 10 cases of ETI discontinuation reported by a cystic fibrosis clinic to a French pharmacovigilance centre, including 6 cases of neuropsychiatric disorders. Case 1 describes a 28yo female with past episodes of anxiety and depression who experienced depressed mood and anxiety within the first months of taking ETI, as well as metrorrhagia, blocked nose and abnormal LFTs. Switching morning and evening doses and dose reduction were tried without improvement. ETI was interrupted for one month and resumed at a reduced dose of one ETI tablet in the morning.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
		48 F	ETI	Hyperexcitability Insomnia Depression Suicidal ideation	ETI interruption and dose reduction	Case 2 describes a 48yo female who presented with hyperexcitability, insomnia and tinnitus at the beginning of ETI. No psychiatric history reported. As the symptoms persisted, ETI was stopped after 1 year with improvement. Four months later, ETI was restarted with twice weekly dosing and mood disturbances and suicidal ideation occurred two months later. The dose was reduced to once weekly with slight improvement in symptoms.
		46 F	ETI	Hyperexcitability Insomnia Mood changes Anxiety	Dose reduction	Case 3 describes a 46yo female who experienced hyperexcitability, insomnia, mood changes and anxiety, as well as menorrhagia and hypertension. No psychiatric history reported. The dose was gradually reduced over the following two years with resolution of symptoms at one dose of ETI weekly.
		43 M	ETI	Agitation Mood disorder Insomnia	ETI discontinued	Case 4 describes a 43yo male with rapid onset of agitation, insomnia and mood disorders, as well as abdominal pain, diarrhoea and rhinorrhoea. No psychiatric history reported. Switching of morning and evening doses was tried without improvement. ETI discontinued after 10 months.
		19 F	ETI	Insomnia Mood disorder Anxiety	ETI discontinued	Case 5 describes a 19yo female who stopped ETI twice, after 21 months and a further 2 months of treatment, due to insomnia, mood disorders and anxiety. No psychiatric history reported.
		34 M	ETI	Insomnia Mood disorders Hyperexcitability	ETI discontinued	Case 6 describes a 34yo male who stopped ETI after 17 months due to insomnia, mood disorders and hyperexcitability. No psychiatric history reported. Testicular pain and abnormal LFTs also reported. Dose reduction not helpful. Lost to follow up.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
Duehlmeyer et al, 2024 [64]	New tic disorder in a child with Cystic Fibrosis Treated with elexacaftor/tezacaftor/ivacaftor	7 F	ETI	Tic	ETI discontinued	Onset of eye rolling tic shortly after starting ETI which increased in frequency over 2 months with associated eye pain. ETI stopped with resolution within 2 weeks. Restarted at reduced dose one month later with return of tic within 2 days. ETI stopped with resolution of symptoms.
Godier et al, 2024 [65]	A case of elexacaftor/tezacaftor/ivacaftor-induced depressive symptoms and suicidal thoughts	38 M	ETI	Anxiety Irritability Agitation Depression	Dose reduction	Within 2 weeks of changing from LUM/IVA to ETI, a 38yo male experienced moderate anxiety, irritability, and agitation that persisted for 6 months followed by onset of depression and suicidal thoughts. Symptoms resolved within one month of dose reduction.
Peters and Brown, 2024 [66]	Separation anxiety or a Kaftrio side effect? Implementation of cognitive behavioural therapy strategies with a young child with cystic fibrosis (CF): A clinical case study	7 F	ETI	Separation anxiety Behavioural challenges Non-concordance with treatment	Psychotherapy	A 7-year-old experienced increased separation anxiety, behavioural challenges, and non-concordance with treatment. Parents were concerned this was a side-effect of ETI and stopped treatment but this was followed by an increase in anxiety symptoms. Cognitive behavioural strategies and parent training sessions resulted in improvement of symptoms that was maintained at one-year follow up. The child was due to restart ETI.
Hughes and Brown, 2023 [67]	Worsening anxiety with elexacaftor-tezacaftor-ivacaftor: navigating the mental health and pulmonary implications in an adolescent patient with cystic fibrosis	13 F	ETI	Anxiety	Dose reduction	A 13-year-old female experienced attention issues within a few months of starting ETI with worsening anxiety, insomnia, and cognitive difficulties over a period of one year. ETI was discontinued with improvement over the following months. After an exacerbation, she started escitalopram and resumed ETI at a reduced dose. Five months later she had tolerated ETI and had improved clinically.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
Cabrera et al, 2025 [68]	CFTR modulator therapy and the brain: a case of paediatric neuropsychiatric effects (preprint)	9 F	ETI	Mood lability Suicidal ideation	ETI interruption and dose reduction	This case report describes a 9yo female who was switched from IVA to ETI at 6 years of age. Three months after starting ETI she experienced headaches and unusual mood lability which were initially considered developmentally normal. Over the following two years she experienced random tearfulness, increased appetite, oppositional behaviour, and self-injurious and suicidal thoughts. The report noted history of anxiety related to needle phobia, sadness associated with bullying and recurrent abdominal pain without organic cause. ETI was discontinued with disappearance of self-injurious thoughts after 2 weeks. ETI was restarted 2 months later at a reduced dose without recurrence. Increased appetite persisted with upward trending BMI and residual behavioural symptoms. This resolved upon further dose reduction.
Lan et al, 2024 [69]	Mood swings and irritability in a patient with cystic fibrosis on elexacaftor-tezacaftor-ivacaftor therapy: a case report	29 M	ETI	Mood swings Irritability	Psychotropic medicine ETI discontinued	A 29-year-old with a history of major depressive disorder experienced mood swings and irritability that was reported six months after starting ETI. His symptoms resolved after discontinuing ETI, were stable when restarted at a low dose, but recurred at the full dose. ETI was discontinued with improvement in symptoms.
Nidegger et al, 2025 [70]	Suicidal behaviour and CFTR modulators: A case series and WHO database disproportionality analysis	39 F	ETI	Anxiety Insomnia Suicide attempt	Psychotropic medicines Dose reduction	Within one month of changing from LUM/IVA to ELX/TZA/IVA, a 39yo female with comorbid bipolar disorder and history of suicide attempt experienced worsened anxiety and insomnia. After interpersonal conflict she attempted suicide, 13 months after starting ELX/TZA/IVA. She was treated with sertraline and buspirone and the dose of ETI was decreased. Three

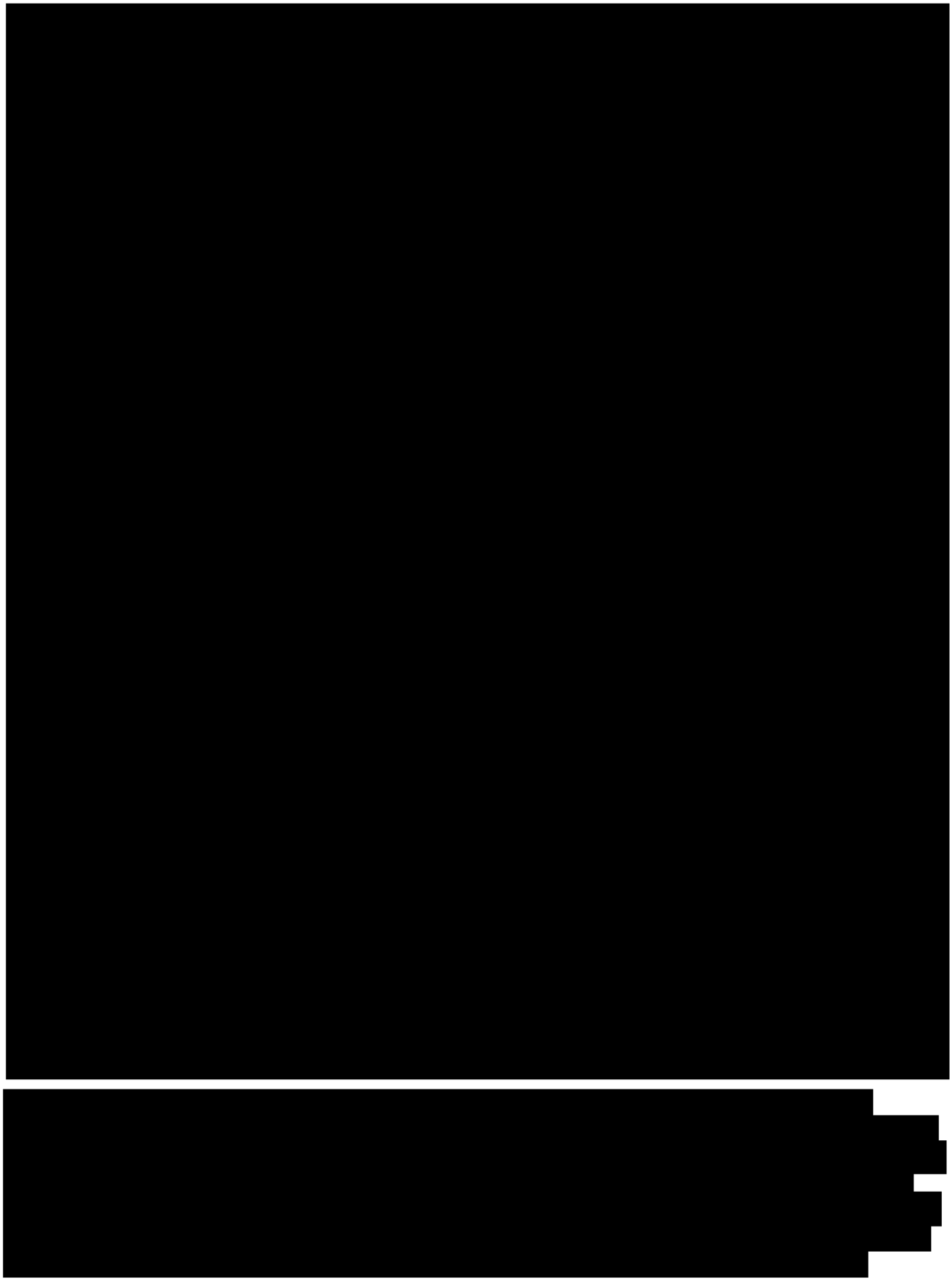
Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						months later her mood and insomnia had improved but were still unstable.
		39 F	ETI	Insomnia Suicidal ideation Depression Self-harm	Psychotropic medicines	One month after changing from LUM/IVA to ETI the patient experienced insomnia which resolved with alprazolam treatment, and suicidal ideation. She subsequently experienced recurrence of insomnia, depression and self-harm. At five months her mental health had improved without any changes to ETI treatment.
		28 F	ETI	Insomnia Anxiety Mood changes	Psychotherapy	This report describes a 28-year-old female with comorbid alcohol and illicit drug use and history of depression exacerbated by isotretinoin. One month after starting ETI, she experienced insomnia, anxiety, and sadness, alternating with periods of euphoria. Three months after starting ETI she attempted suicide. Psychotherapy was initiated and ETI was continued.
		21 M	ETI	Suicide attempt	Psychotherapy	A 21-year-old male without psychiatric comorbidities attempted suicide 4.5 months after starting ETI. ETI was continued and psychotherapy was initiated without further events.
Ibrahim et al, 2023 [71]	Individualized approach to elexacaftor/tezacaftor/ivacaftor dosing in cystic fibrosis, in response to self-reported anxiety and neurocognitive adverse events: a case series.	Adults	ETI	Anxiety Irritability Sleep disturbance Metal slowness	Short-term anxiolytics Dose adjustment	A case series describing dose adjustment strategies in 10 patients who self-reported anxiety, irritability, sleep disturbance and/or mental slowness within four weeks of starting ETI. Four patients were referred for psychological support and were treated with anxiolytics for <2 weeks. Patients with severe symptoms discontinued ETI and restarted at a reduced dose after resolution of symptoms, with subsequent dose escalation over 3 months guided by patient response. Patients with mild symptoms had

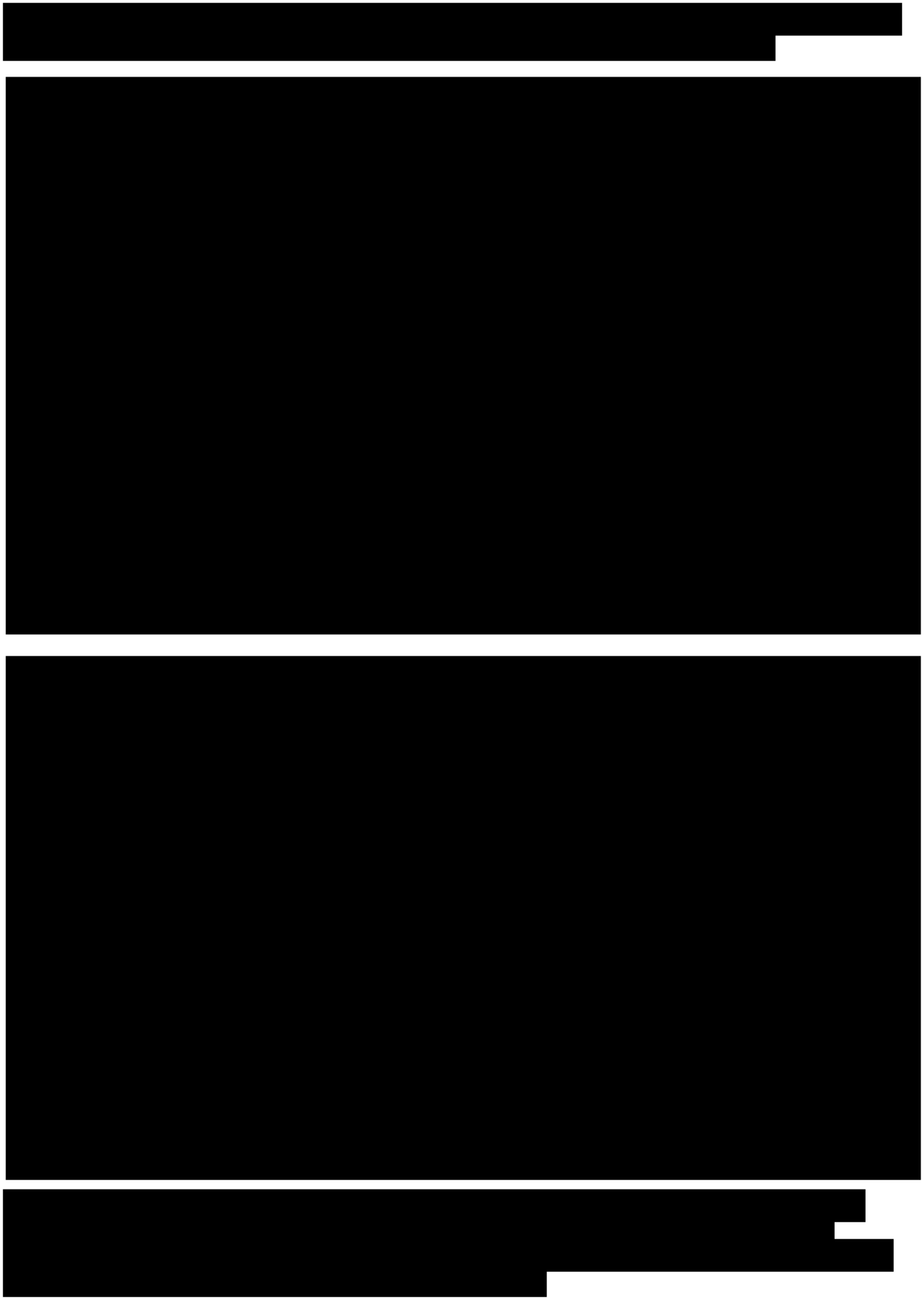
Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						their dose reduced and considered returning to a full dose after ~3 months. Nine patients that commenced the dose reduction strategy and one patient changed from ETI to IVA. Five of the nine patients had complete resolution of symptoms and 3 had partial resolution of symptoms. At 12 weeks, 6 patients remained on a reduced dose and 3 patients recommenced the full dose. There were no significant changes in clinical response.
McKinzie et al, 2024 [72]	Severe mental health changes in patients with cystic fibrosis on elexacaftor/tezacaftor/ ivacaftor therapy.	48 F	ETI	Insomnia Paranoid delusions Suicidal ideation	ETI treatment interrupted Psychotropic medicines	Case 1: A 48-year-old with a history of depression, anxiety and obsessive-compulsive disorder started ETI. She was previously taking IVA more than 5 years with reported worsening mental health. She reported passive suicidal ideation and anxiety before starting ETI with GAD-7 and PHQ-9 scores of 19 and was maintained on bupropion, clonazepam, and zolpidem. One month after starting ETI she experienced insomnia and self-initiated cannabidiol oil, 5-hydroxytryptophan, and gamma-aminobutyric acid supplements. After 3 months she was admitted with new-onset paranoid delusions and active suicidal ideation. ETI was withheld for 3 days. Psychosis improved and ETI was restarted at reduced dose. She passed away the day after discharge following a seizure.
		14 M	ETI	Depression Mania Suicidal ideation Self-harm	Psychotropic medicine	Case 2: A 14-year-old with a history of anxiety and ADHD started on ETI. Prior to this he was taking TEZ/IVA and escitalopram and had social stressors and a family history of mental health disorders. Fourteen months after starting ETI he had depression and mania symptoms and was hospitalised due to active suicidal ideation and self-harm. He endorsed increasing depressive symptoms and

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
						passive suicidal ideation starting 6 months after ETI initiation. ETI was continued and escitalopram was changed to bupropion.
		16 F	ETI	Thoughts of self-harm	ETI treatment interrupted	Case 3: A 16-year-old with a history of adjustment disorder and anxiety disorder, and lung transplantation 3 years prior, was initiated on ETI. She had previously been prescribed LUM/IVA without mental health changes. One year after ETI initiation, she reported new thoughts of self-harm, and ETI was discontinued. PHQ-9 and GAD-7 scores before this were both 3. ETI was resumed at full dosing several months later with close monitoring.
		6 M	ETI	Thoughts of self-harm Passive suicidal ideation	ETI treatment interruption	Case 4: A 6-year-old with a history of specified disruptive behaviour disorder was initiated on ETI. He was CFTRm-naïve and had no pertinent social history. Two years after initiation, he reported new onset thoughts of self-harm and passive suicidal ideation. ETI was discontinued, and caregivers saw a noticeable difference in behaviours. However, this improvement was inconsistent, and after 2 weeks, ETI was restarted at full dosing.
		14 F	ETI	Suicidal ideation Self-harm	Psychotherapy Psychotropic medicines	Case 5: A 14-year-old with a history of adjustment disorder, depression, and anxiety was initiated on ETI. She was maintained on sertraline and was CFTRm-naïve. At 1 and 2 years after ETI initiation, she required hospitalisations for acute suicidal ideation and self-harm. PHQ-9 and GAD-7 scores were 7 and 12, respectively, before the first event. ETI was continued with increased psychology and psychiatry follow-up and psychotropic medicines.

Author, year	Title	Age, sex	Suspect medicine	Symptoms	Management	Description
		18 F	ETI	Suicide attempt	Psychotherapy Psychotropic medicines	An 18-year-old with history of depression and substance use was initiated on ETI. She had previously been on TEZ/IVA and was maintained on sertraline and prazosin. Two years after ETI initiation, she was hospitalised following a suicide attempt. Her PHQ-9 and GAD-7 before this were 6 and 5, respectively. ETI was continued, and she was diagnosed with borderline personality disorder.
Corona et al, 2023 [73]	A trifecta for anxiety: a case report of elexacaftor/tezacaftor/ivacaftor associated anxiety	37 M	ETI	Anxiety	ETI stopped	A 37-year-old man experienced significant anxiety symptoms 6 months after starting ETI. He had no history of psychiatric diagnoses or anxiety symptoms. The patient reported his anxiety began on initiation of ETI and rapidly escalated over a span of 3 months with no other stressors reported. His anxiety was accompanied by sweating and tremor and progressed to the point where he stopped attending his bible group, took ten sick days in one month and avoided leaving the house. ETI was stopped with improvement after a week and near resolution in 2.5 months.

[redacted]





3.3 CARM data

There have been 12 reports received for Kalydeco (ivacaftor) or Trikafta since 2020. Three of these reports are relevant to the signal of neuropsychiatric adverse effects, of which two were for Trikafta and one was for Kalydeco. The reports are summarised in Table 12.

Table 10: New Zealand reports of neuropsychiatric disorders with CFTR modulators.

Report ID	Report date	Age, sex	Reporter	Suspect medicine	Reactions	Outcome	Narrative
137448	1/06/2020	37 M	[redacted]	Trikafta	Panic reaction	[redacted]	[redacted]
137591	1/07/2020	2 M	[redacted]	Ivacaftor	Abnormal behaviour	[redacted]	[redacted]
159726	20/11/2024	16 F	[redacted]	Trikafta	Sleep difficult Anxiety Irritable Anger Mood change Thought process disorder Indecisiveness	[redacted]	[redacted]
NZ-Medsafe-164419	15/10/2025	9 F	[redacted]	Trikafta	Emotional distress Anger Depressed mood	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

There have been spontaneous reports of psychiatric disorders with CFTR modulators. This has triggered reviews by international medicines regulators, with the EMA requiring a warning on depression in the product information for all CFTR modulators.

The EMA warning states that depression, including suicidal ideation and suicide attempt, has been reported in patients treated with CFTR modulators, usually occurring within three months of initiation and in patients with a history of psychiatric disorders. In some cases, symptoms improved after dose reduction or treatment discontinuation. It is advised to monitor for depressed mood, suicidal thoughts, unusual changes in behaviour, anxiety, or insomnia and to seek medical advice immediately if these symptoms present. There is also a warning stating that behaviour changes have been reported in young children.

The MHRA has published a safety communication stating that the product information for Kaftrio (Trikafta) will be updated to include a warning on risk of side effects on mood, sleep, concentration and behaviour. The communication states that there was insufficient evidence to indicate an increased risk of psychiatric adverse

effects with other CFTR modulators. The UK product information had not yet been updated at the time of writing of this report.

Several possible explanations for the reports of psychiatric adverse effects have been discussed in the literature, including an indirect effect of CFTR modulator treatment. People starting CFTR modulators may have complex and unexpected feelings, such as difficulty adjusting to a changed relationship to CF, survivor guilt, uncertainty about the future, a new perspective on past illness or body image difficulties. Some people may not experience the benefits they had hoped for or feel worried that the benefits may not last. It is also thought that people with CF have a higher background prevalence of depression and anxiety, and that changes in mental health may be part of the fluctuating course of these conditions and unrelated to CFTR modulators.

There was no evidence identified that describes a direct pharmacological effect of CFTR modulators that could lead to adverse psychiatric effects. However, hypothetical explanations have been discussed in the literature, including:

- Interaction CFTR modulators with CFTR in the brain.
- Interaction of ivacaftor with serotonin 5-HT2c receptors.
- Pharmacokinetic interactions between CFTR modulators and psychotropic medicines such as SSRIs.
- Supratherapeutic CFTR modulator exposure due to interpatient variability.

The published literature describing a possible association between CFTR modulators and psychiatric adverse effects is limited to case reports. Small observational studies have not found an overall increase in depression or anxiety symptoms.

A company-sponsored systematic review found similar exposure-adjusted rates of depression-related events between ETI and placebo in a pooled analysis of clinical trials. The post-marketing reporting rate was 1.3 events per 100 patient-years for any depression-related event, 0.12 events/100 PY for suicide attempt, 0.05 events/100 PY for suicidal ideation and 0.02 events/100 PY for completed suicide. The authors stated that individual reports generally included limited narrative information without objective psychiatric assessment and were confounded by pre-existing mental health conditions, psychosocial stressors and the heterogeneous and fluctuating nature of depression. The review also identified 12 observational studies that measured depression symptoms using the PHQ-9 questionnaire before and after ETI initiation which showed either no change or decrease (improvement) in PHQ-9 scores overall.

A literature search retrieved a large number of publications describing observational studies, mainly consisting of prospective or retrospective comparisons of depression and anxiety scores before and after starting ETI. The studies found no overall worsening of depression or anxiety scores. Some studies reported on individual score trajectories, and found that while most patients had stable or improved scores, a small proportion of patients had clinically significant worsening of mental health after starting ETI. It is not possible to conclude from these studies whether worsening symptoms in this small subset was related to ETI and there was limited or no information on pre-existing mental health diagnoses or concurrent psychosocial stressors. Other observational studies reported improvement of symptoms in some patients with dose modification strategies.

There were 12 publications describing case reports of psychiatric adverse events after starting treatment with CFTR modulators. The majority of cases describing depression and suicidal ideation/suicide attempt report pre-existing mental health conditions and/or concurrent psychosocial stressors. Several cases reported mental fogginess, irritability or sleep disturbances. Some of the cases report improvement of symptoms with dose adjustment or discontinuation.

[redacted]

[redacted]

There have been four relevant adverse reaction reports in New Zealand, describing panic attacks in an adult taking ETI, mood changes in an adolescent taking ETI, depression and anger in a child taking ETI, and behavioural changes in a child taking IVA.

The Committee is asked to provide advice on whether regulatory action is needed in relation to this signal.

5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the available evidence describing a possible relationship between psychiatric disorders (eg, depression, anxiety, suicidal thoughts, insomnia/sleep disturbance, poor concentration, forgetfulness, unusual changes in behaviour or behavioural changes in children) and CFTR modulators individually or as a class, including which, if any, psychiatric disorders have evidence for a possible relationship.
- Whether the data sheet for any CFTR modulator should be updated to include warnings on any psychiatric disorders.
- Whether any other regulatory action is needed.

6 ANNEXES

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7 REFERENCES

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