

Mental Health and Concerns in the Era of Highly Effective Modulator Therapies

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Depression and Anxiety in CF

- **TIDES:** The International Depression Epidemiological Study of 154 CF centers in 9 countries (US/Europe)
 - 6,088 patients with CF and 4,102 parents
 - ↑ depression in 10% of adolescents, 19% of adults, 37% of mothers, 31% of fathers
 - ↑ anxiety in 22% of adolescents, 32% of adults, 48% of mothers, 36% of fathers
 - Elevations 2–3 times ↑ those of community samples
 - Psychological distress in CF is associated with:
 - ↓ pulmonary function
 - ↑ hospitalizations
 - ↑ healthcare costs
 - ↓ health-related quality of life
 - ↑ 5-year mortality
1. *Quittner AL et al, Thorax 2014; 69: 1090–1097*
 2. *Comparison of survival probabilities among individuals screened for depression in the TIDES study (Schechter et al., NACFC 2017)*

Treatment of Depression

- CF Foundation Guidelines:
 - Psychotherapy: e.g., cognitive behavioral therapy (CBT) [also, interpersonal therapy, acceptance commitment therapy (ACT)]
 - First-line meds: selective serotonin reuptake inhibitors (SSRIs) (i.e., fluoxetine, sertraline, citalopram, escitalopram)
- In addition, the following meds are considered:
 - Mirtazapine: appetite, weight, nausea, less risk of serotonergic toxicity, fewer sexual side effects
 - Bupropion: motivation, energy, fewer sexual side effects
 - Serotonin norepinephrine reuptake inhibitors (SNRIs) (i.e., duloxetine): comorbid neuropathic pain, SSRI not effective
 - Augmentation with other meds

Attention Deficit Hyperactivity Disorder

- A childhood-onset neurodevelopmental disorder
- Prevalence 1.4-7.2% in children, decreases with age in general population
- Male to female ratio= 3-4 : 1
- Characterized by
 - inattention (e.g., makes careless mistakes, difficulty sustaining attention on tasks, trouble organizing activities, easily distracted, forgetful)
 - and/or hyperactivity (e.g., fidgets, difficulty waiting for a turn)
- Onset before age 12
- Across several settings (e.g., home, school, work)

Thapar & Cooper, Lancet 2016; 387: 1240-1250

Thomas R et al, Pediatrics 2015; 135(4): e994-1001

Attention Deficit Hyperactivity Disorder in CF

- Rates of ADHD increased in patients with CF
- 4-site multi-site study (Israel, Spain):
 - 175 patients (99 males) → 18% presented with ADHD symptoms
 - 16% in the younger group (< 18 years), and 18.9% in the adult group
 - The male to female ratio was 3:1 in children and 1:1 in adults
- US center study: 53 adult pts → 15%
- Turkish study: 32 children → 21.8%
- Does not seem to correlate with FEV1 or BMI, but small samples
- Decreases some aspects of health-related quality of life
- Can negatively affect adherence
- Genetic predisposition; CFTR expressed in neurons; life stressors; chronic inflammation

Georgiopolous A et al, Journal of Cystic Fibrosis 2018; 17: 276-280

Cohen-Cymerkoh M et al, Journal of Cystic Fibrosis 2018; 17(2): 281-285

Gundogdu U et al, Pediatr Pulmonol 2019; 54(12): 1927-1935

Do HEMTs Affect Mental Health?

We are still learning

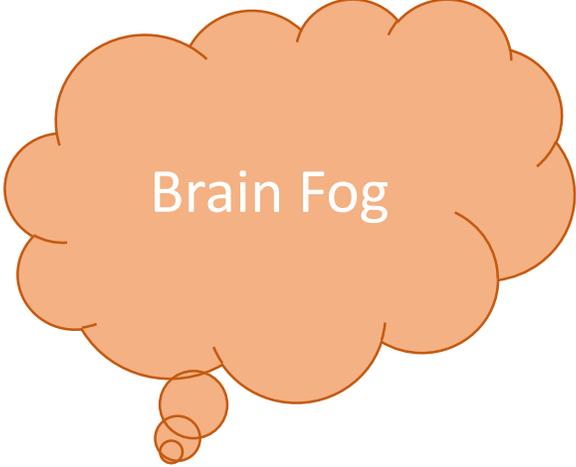
Multiple confounders

We are hearing from people with CF and community

Reports are coming out and studies ongoing

But if/when there are mental health side effects, we are mostly likely can treat and help!

Do HEMTs Affect Mental Health?



Brain Fog



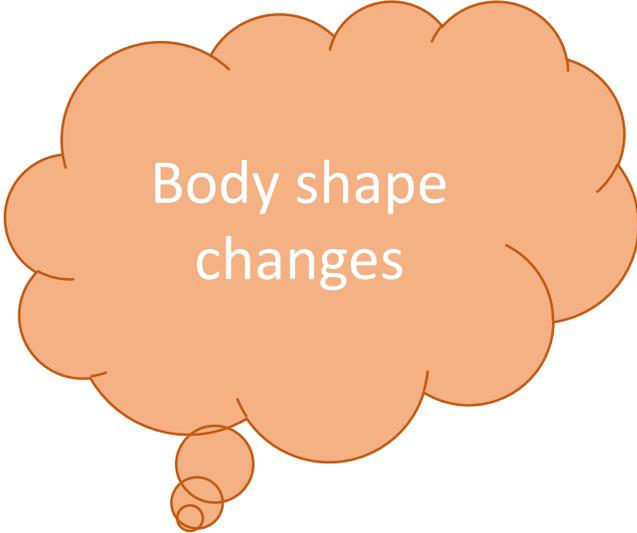
Anxiety/
Restlessness



Fatigue



Depression



Body shape
changes

Do HEMTs Affect Mental Health?

“I’ve never experienced brain fog like it, I was doing daft things all the time, forgetting words and I forgot my DOB at a hospital appt”

<https://cystic-fibrosis.com/stories/trikafta-side-effects>

“The most influential, however, has been an increase in my anxiety and depression and instability with my mental health - something that I thought I had under control”

<https://www.cff.org/community-posts/2020-05/trikafta-caused-my-anxiety-and-depression-return>

Case reports/series

- In both phase III studies of LUM/IVA (orkambi), as well as an extension study, worsening of mental health was not reported as a common side effect.
- A case series of 3 adult patients experienced worsening of depression or anxiety
- A case series 5 cases of adolescent females, 12-17 years of age, experienced worsening of depression or anxiety, two experienced suicidal ideation and 3 made suicide attempts resulting in psych hospitalizations

1. *Talwalkar JS et al, Cystic Fibrosis Transmembrane Regulator Modulators: Implications for the Management of Depression and Anxiety in Cystic Fibrosis. Psychosomatics 2017; 58(4): 343-354*
2. *McKinzie CJ et al. Worsening anxiety and depression after initiation of lumacaftor/ivacaftor combination therapy in adolescent females with cystic fibrosis. J Cyst Fibros. 2017 Jul;16(4):525-527*

Emerging Reports

- A retrospective chart review with 100 adult patients with CF included in analysis
- No significant changes in average PHQ-9 or GAD-7 scores after Trikafta initiation
- 22% of patients initiated or had a change in psychiatric medications
- Patients with changes in psychiatric meds had significantly higher PHQ-9 and GAD-7 scores vs patients not prescribed psych meds
- 23% of all patients reported sleep issues after initiating Trikafta

Zhang L, et al. Impact of elexacaftor/tezacaftor/ivacaftor on depression and anxiety in cystic fibrosis. Ther Adv Respir Dis. 2022

Emerging Reports

- Of 245 patients who started elexacaftor-tezacaftor-ivacaftor (Trikafta) in France, 101 (41%) participated.
- Median age 35; median duration of Trikafta 4.4 months
- Most contrasted treatment burden, symptom severity, depression, future marked by death or transplantation before Trikafta to renewed and unexpected physical strength, greater self-confidence, autonomy and long-term planning
- Few expressed concerns; such as changes in body representation and/or the fear of becoming dependent on the treatment

Martin C, et al. Patient perspectives following initiation of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis and advanced lung disease. Respir Med Res. 2021 Nov;80:100829

How Can Changes in Mental Health Be Explained?

- Unrelated
- Effect of CFTR modulators on the brain
- Effect of physiological changes due to CFTR modulators
- Drug-drug interactions
- Psychological/existential effects of potentially life-altering medications
- COVID-19 pandemic

Talwakar JS et al, Psychosomatics 2017; 58(4): 343-354

McKinzie CJ et al, Journal of Cystic Fibrosis 2017; 16(4): 525-527



CFTR and Brain

- Strong and widespread neuronal expression of CFTR in the human developing central nervous system.
- Patients with CF in the study did not have any cerebral abnormality
- However, there was a slight delay in CFTR expression in several brain structures & different expression and localization of CFTR depending on the brain structure and the cell maturation stage.
- CFTR is involved in circadian rhythm regulation, responsible for sleep and wakefulness-sleep regulation

1. *Marcorelles P et al, CFTR expression in the developing human brain: comparative immunohistochemical study between patients with normal and mutated CFTR. J Histochem Cytochem. 2014*
2. *Barbato E et al, Dysregulation of Circadian Rhythm Gene Expression in Cystic Fibrosis Mice. J Circadian Rhythms. 2019*



HEMTs and Other Concerns

- Body changes
- Adherence
- Fertility
- Financial planning
- Side effects
- Being left behind, not being legible

CFTR Modulators and Mental Health

- Drug-Drug Interactions
 - Lumafactor is a strong inducer of the CYP450 enzyme CYP3A4
 - Potential reduced effectiveness of the CYP3A4 substrates such as citalopram, escitalopram, sertraline, quetiapine, trazodone, clonazepam
 - Ivacaftor is a weak inhibitor of CYP3A4, and may increase the exposure to circulating substrates
 - Ivacaftor is a substance of CYP450 3A4 → potential increased exposure with bupropion
 - Elexacaftor and tezacaftor are metabolized by CYP450 enzymes 3A4/5
 - Concentration can be increased when combined with other meds metabolized by same, such as alprazolam
 - *St Johns Wort is a significant 3A4 inducer and can decrease Trikafta effectiveness*

Talwakar JS et al, *Psychosomatics* 2017; 58(4): 343-354

McKinzie CJ et al, *Journal of Cystic Fibrosis* 2017; 16(4): 525-527

Tikafta insert

If You are Concerned about Mental Health Side Effects Related to HEMTs



Talk to your treatment team and ask to collaborate with a mental health professional

When did you your symptoms start, what is their frequency and severity?

How do they affect your day-to-day life?

What is the timing of your mental health symptoms in relation to taking Trikafta® or to other life stressors?

Changes in other meds (CF-related, psych meds, OTC meds)?

How did you try to address these symptoms?

Are the symptoms getting better, worse, or same

Have you had these mental health symptoms in the past?

Family history of mental health problems?

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