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

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• Director of Psychiatric and Psychological Services, Stanford Adult CF Program
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

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

Quittner AL et al, Thorax 2016; 71(1): 26-34
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
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
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/triakta-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/triakta-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


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

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

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

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talk to your treatment team and ask to collaborate with a mental health professional</td>
<td>When did you your symptoms start, what is their frequency and severity?</td>
</tr>
<tr>
<td>What is the timing of your mental health symptoms in relation to taking Trikafta® or to other life stressors?</td>
<td>Changes in other meds (CF-related, psych meds, OTC meds)?</td>
</tr>
<tr>
<td>Are the symptoms getting better, worse, or same</td>
<td>Have you had these mental health symptoms in the past?</td>
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