

Mental Health and Modulators: Side Effects Screeners

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Modulators – new challenges in mental health

Standards of care for *CFTR* variant-specific therapy (including modulators) for pwCF¹

Standards for the care of pwCF; establishing and maintaining health²

1

Neuropsychiatric side effects have been reported for all available CFTRm therapies¹

Alterations in mood, anxiety, sleep and neurocognition, as well as suicidal ideation/attempts¹

2

Pharmacovigilance Risk Assessment Committee (PRAC) for the European Commission recently determined that there is at least a reasonable possibility of a causal relationship between ELX/TEZ/IVA and depression^{2,3}

3

'pwCF and their families should be encouraged to report both positive and adverse experiences to the CF team, regardless of presumed causality'²

4

Mental health should be monitored in accordance with CFF/ECFS guidelines, including screening for depression and anxiety before and no later than 3 months after initiating CFTRm^{2,4,5}

Systematic screening & follow-up

CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulator; ECFS, European Cystic Fibrosis Society; ELX, elexacaftor; IVA, ivacaftor; pwCF, people with cystic fibrosis; TEZ, tezacaftor.

1. Dagenais RVE, et al. J Clin Med. 2020;10:23. Erratum in: J Clin Med. 2022;11:318; 2. Southern KW, et al. J Cyst Fibros. 2024;23:12–28; 3. EMA. Committee for medicinal products for human use Minutes for the meeting on 22-25 May 2023. 4. Southern KW, et al. J Cyst Fibros. 2023;22:17–30; 5. Quittner AL, et al. Thorax. 2015;71:26–34.



Case series and reports of unique experiences – adolescents and adults

| Study | N |
|---|----|
| Tindell et al. (2020), Psychosomatics ¹ | 1 |
| Heo et al. (2022), J Cyst Fibros ² | 6 |
| Lyman et al. (2022), Pediatr Pulmonol ³ | 1 |
| Spoletini et al. (2022), J Cyst Fibros ⁴ | 19 |
| Ibrahim et al. (2023), Front Pharmacol ⁵ | 10 |
| Baroud et al. (2023), Pediatr Pulmonol ⁶ | 16 |
| Arslan et al. (2023), J Cyst Fibros ⁷ | 2 |
| McKinzie et al. (2024), Pediatr Pulmonol ⁸ | 6 |



ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor.

1. Tindell W, et al. Psychosomatics. 2020;61:735–8; 2. Heo S, et al. J Cyst Fibros. 2022;21:339–43; 3. Lyman BC, et al. Pediatr Pulmonol. 2022;57:3174–6; 4. Spoletini G, et al. J Cyst Fibros. 2022;21:1061–5; 5. Ibrahim H, et al. Front Pharmacol. 2023;14:1156621; 6. Baroud E, et al. Pediatr Pulmonol. 2023;58:1920–30; 7. Arslan M, et al. J Cyst Fibros. 2023;22:427–30; 8. McKinzie CJ, et al. Pediatr Pulmonol. 2024.

New mood and neurocognitive findings: Children

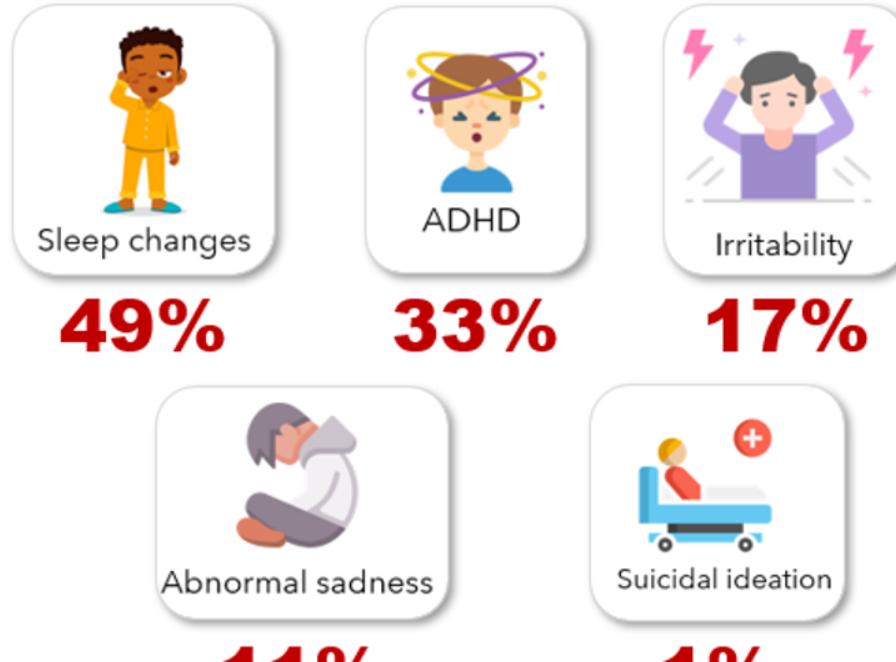
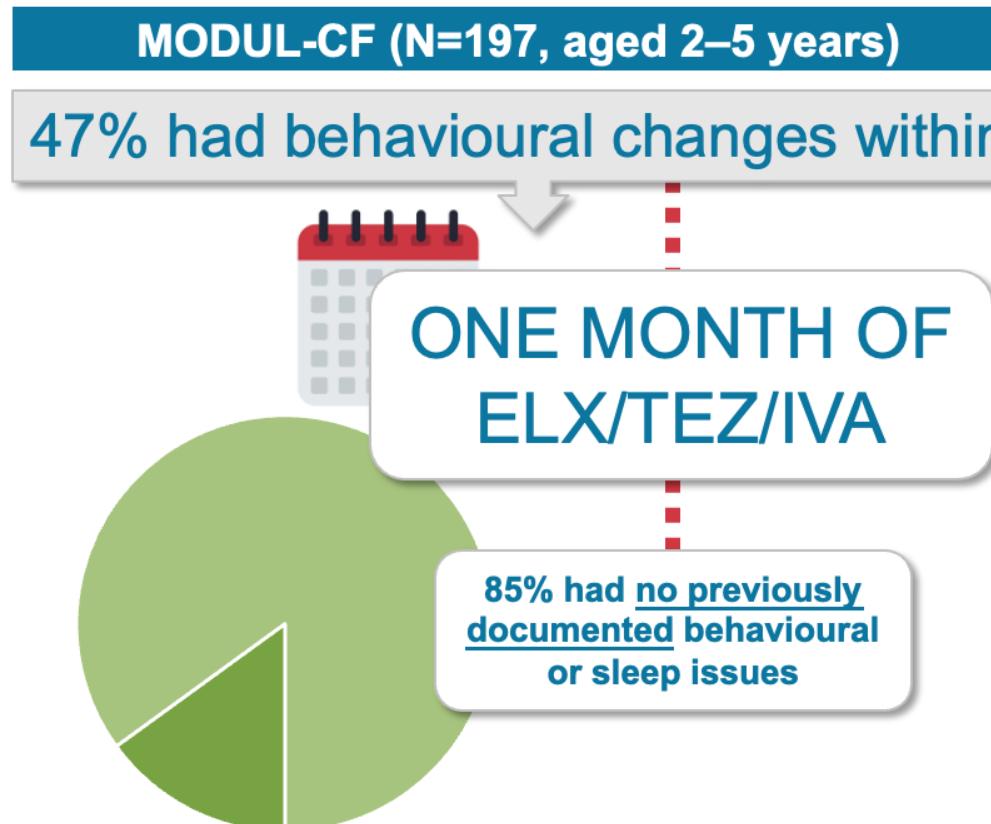


Figure created using data from Sermet-Gaudelus et al. 2024.

Images provided by the speaker.

ADHD, attention deficit hyperactivity disorder; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor. Sermet-Gaudelus I, et al. Lancet. 2024;404:117–20.

New mood and neurocognitive findings: Adolescents and children



Depression



Anxiety



Sleep changes

31 adolescents (aged 10–18 years)¹

- 10% developed anxiety/depression concerns
- 10% developed sleep concerns



SIX MONTHS
OF ELX/TEZ/IVA

108 children (aged 6–11 years)²

- No significant changes in mental health or sleep
- Neuropsychiatric symptoms in 12% of children



PSC-17
SDSC

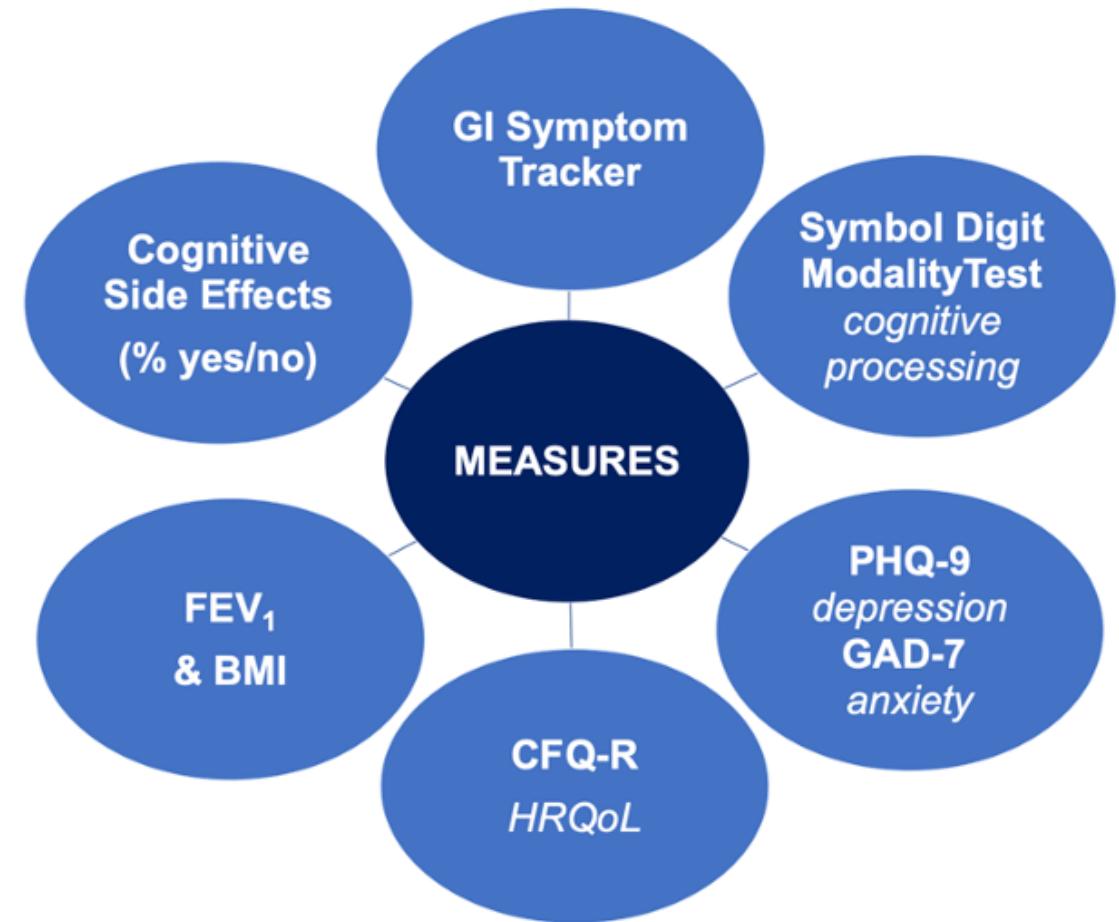
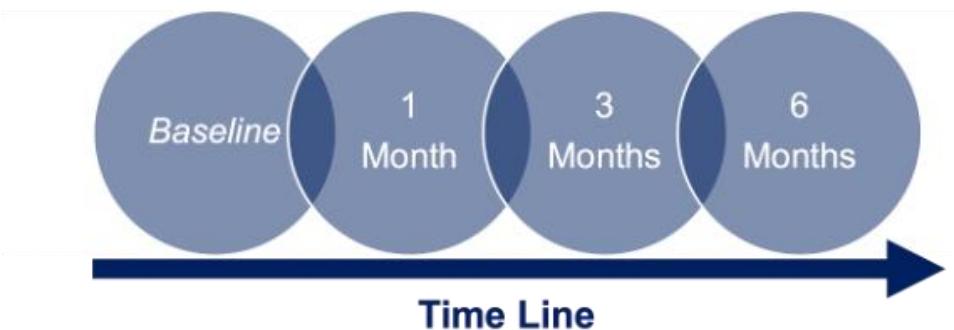
BEFORE ELX/TEZ/IVA
AND ONE MONTH AFTER

Images provided by the speaker.

Longitudinal Effects of Elexacaftor/Tezacaftor/Ivacaftor

Multidimensional Assessment of Neuropsychological Side Effects and Physical and Mental Health Outcomes in Adolescents and Adults

Check for updates



BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire Revised; FEV₁, forced expiratory volume in one second; GAD-7, Seven-Item Generalised Anxiety Disorder; GI, gastrointestinal; HRQoL, health-related quality of life; PHQ-9, Nine-Item Patient Health Questionnaire; SDMT, Symbol Digit Modalities Test; T, time after starting elexacaftor/tezacaftor/ivacaftor. Graziano S, et al. Chest. 2024;165:800–9.

Mental health side effects checklist (ages 12 years to adulthood)



| | In the 3-months after starting | | | | In the past 2-weeks | | | |
|----------------------------|--------------------------------|-----------|-------|------------|---------------------|-----------|-------|------------|
| | Never | Sometimes | Often | Very Often | Never | Sometimes | Often | Very Often |
| | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Headache | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Sleep Problems | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Concerns about weight gain | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Brain Fog | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Worsening mood | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Concentration Problems | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Increasing anxiety | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |

Figure from Graziano et al. 2024.

*This checklist is based on published literature, including case reports and case series on the side effects of ELX/TEZ/IVA.



Longitudinal Effects of Elexacaftor/Tezacaftor/Ivacaftor

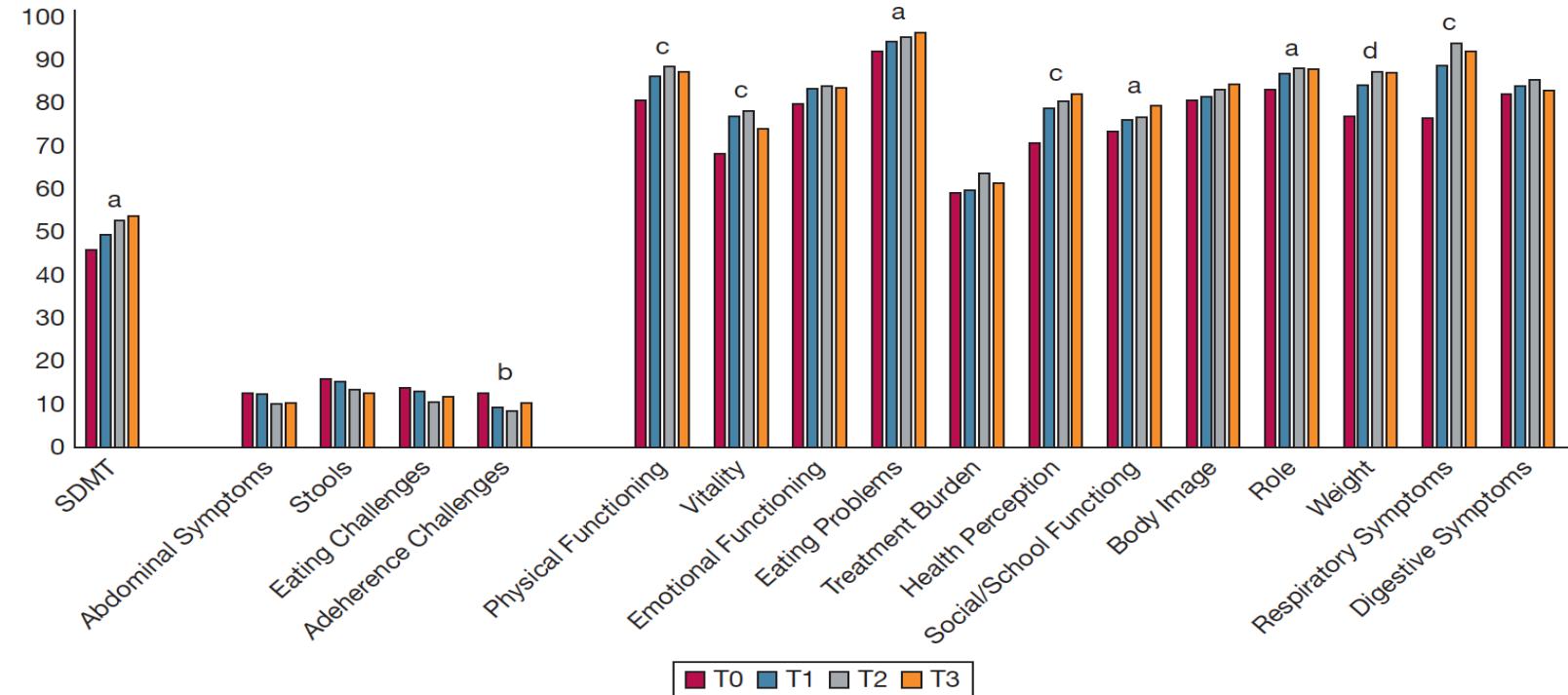
 Check for updates

Multidimensional Assessment of Neuropsychological Side Effects and Physical and Mental Health Outcomes in Adolescents and Adults

improvements

- FEV₁
- BMI
- Depression
- Cognitive processing
- Some GI symptoms
- Most HRQoL

Changes in cognitive processing, GI symptoms and HRQoL over 6 months



BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire Revised; FEV₁, forced expiratory volume in one second; GAD-7, Seven-Item Generalised Anxiety Disorder; GI, gastrointestinal; HRQoL, health-related quality of life; PHQ-9, Nine-Item Patient Health Questionnaire; SDMT, Symbol Digit Modalities Test; T, time after starting elexacaftor/tezacaftor/ivacaftor. Graziano S, et al. Chest. 2024;165:800–9.



Neuropsychological side effects occurred in 10–29%, with no improvement over time

Frequency of patients responding 'yes' to neuropsychological side effects across assessments (N=92)

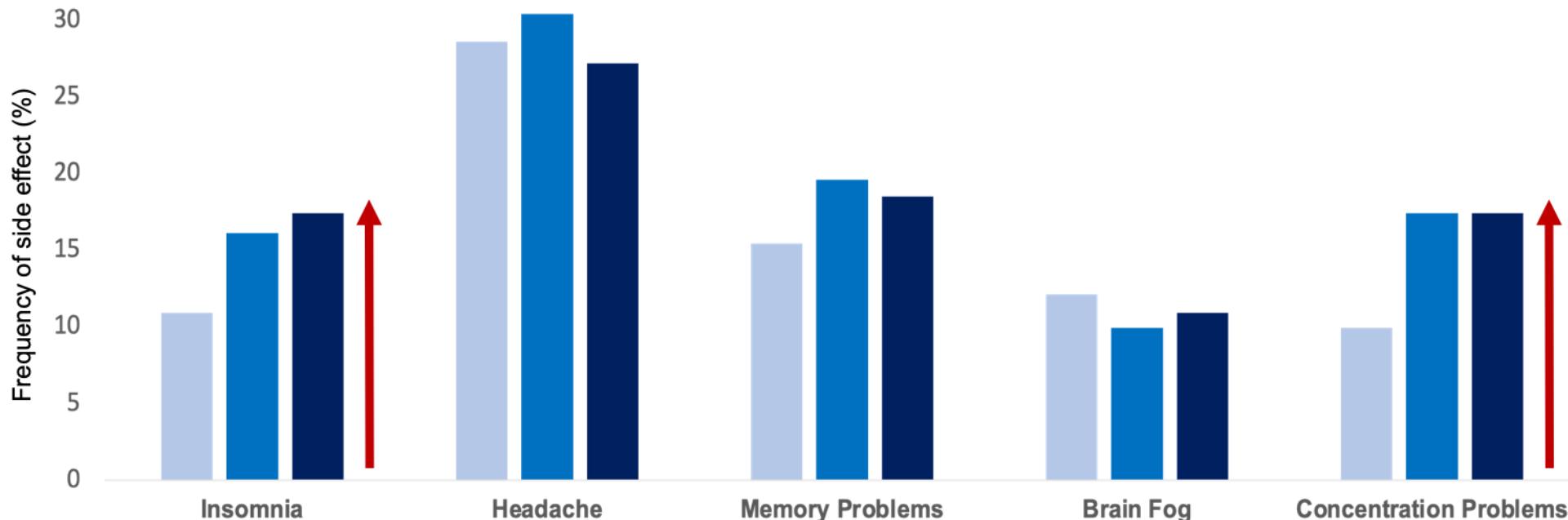


Figure from Graziano et al. 2024.



Women reported more side effects than men

Depression and anxiety among pwCF

PHQ-9 and GAD-7 scores across 4 time points

| N=92 | T0 | T1 | T2 | T3 |
|----------------------|-----------|-----------|-----------|-----------|
| PHQ-9, mean (SD) | 3.7 (3.5) | 2.8 (2.8) | 2.7 (3) | 2.7 (2.6) |
| - No symptoms N (%) | 66 (71.7) | 71 (77.2) | 70 (76.1) | 74 (80.4) |
| - Mild, N (%) | 18 (19.6) | 18 (19.6) | 18 (19.6) | 16 (17.4) |
| - Moderate, N (%) | 6 (6.5) | 2 (2.2) | 3 (3.3) | 1 (1.1) |
| - Severe, N (%) | 2 (2.2) | 1 (1.1) | 1 (1.1) | 1 (1.1) |
| - Item #9, N (%) | 4 (4.3) | 3 (3.3) | 4 (4.3) | 2 (2.2) |
| GAD-7, mean (SD) | 3.6 (3.4) | 3.1 (2.6) | 3.5 (3.9) | 3.3 (3.2) |
| - No symptoms, N (%) | 58 (63) | 67 (72.8) | 66 (71.7) | 70 (76.1) |
| - Mild, N (%) | 26 (28.3) | 21 (22.8) | 19 (20.7) | 15 (16.3) |
| - Moderate, N (%) | 7 (7.6) | 4 (4.3) | 4 (4.3) | 6 (6.5) |
| - Severe, N (%) | 1 (1.1) | 0 (0) | 3 (3.3) | 1 (1.1) |

28%

37%

Table from Graziano et al. 2024.²

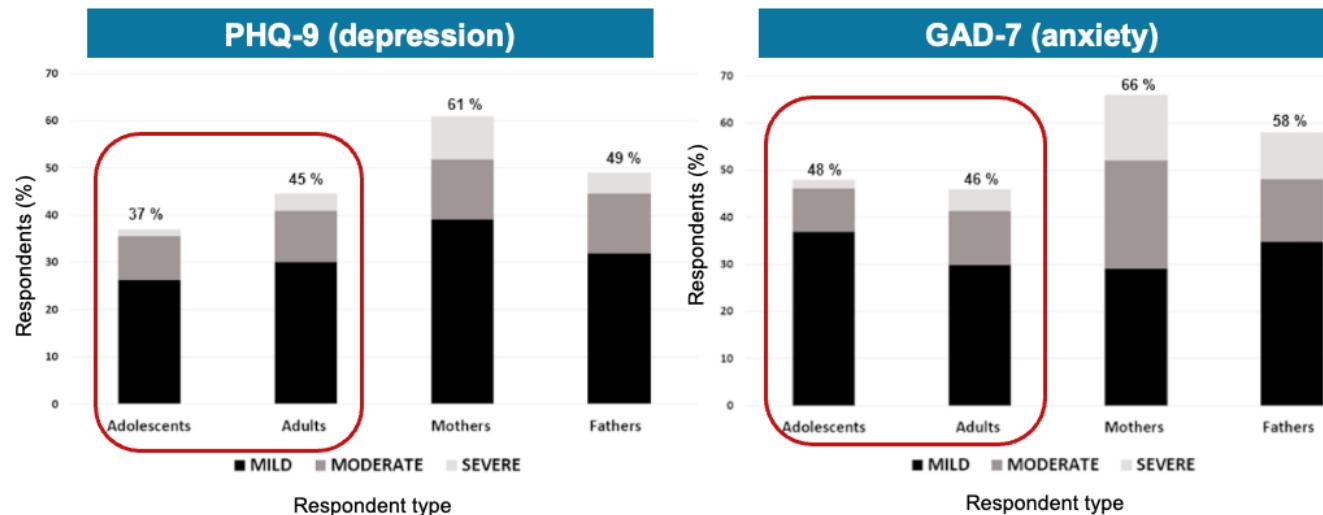


Image from Graziano et al. 2020.¹

Contents lists available at ScienceDirect

Respiratory Medicine

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Clinical Trial Paper

Rates of depression and anxiety in Italian patients with cystic fibrosis and parent caregivers: Implementation of the Mental Health Guidelines

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4 – 7 JUNE 2025
MILAN, ITALY



48th EUROPEAN CYSTIC FIBROSIS CONFERENCE



General Mental Health Screener (GEMS-CF)

Alexandra L. Quittner, PhD, Beth Smith, MD, Anna M. Georgiopoulos, MD, Jianghua “Wendy” He, PhD

Funded by the Cystic Fibrosis Foundation, Smith22A0-I

Development of the GEMS-CF & GEMS Mod-SE: *General Mental Health Screener & Modulator-Side Effects*



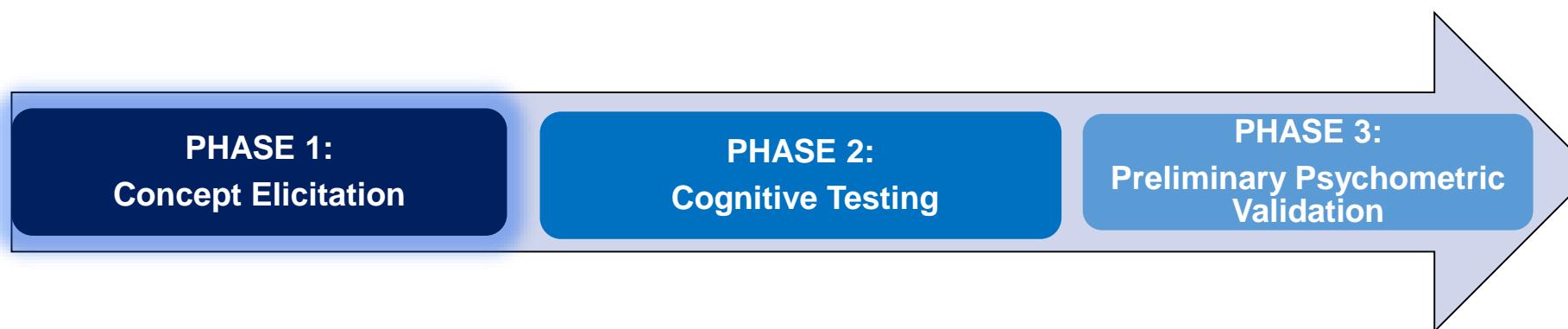
Three-phase study aimed to develop a brief screening tool to assess MH comorbidities (*GEMS-CF*) and side-effects of modulators (*GEMS Mod-SE*):

PHASE 1: Concept elicitation

- Mixed methods evaluation of mental health concerns in AWCF
 - Qualitative interviews of adults with CF (N=60)
 - Focus groups of CF healthcare providers (N=19)

PHASE 2: Cognitive testing (N=23)

PHASE 3: Preliminary validation (N=54)



GEMS-CF: Thematic Coding of Comorbidities (N=60)

| Ranking | Top MH Comorbidities Identified Other than Depression and GAD | Number (%) |
|---------|---|-----------------|
| 1 | Procedural Anxiety | 54 (90%) |
| 1 | Disrupted Sleep | 54 (90%) |
| 3 | Negative Body Image | 51 (85%) |
| 4 | Trauma/PTSD Medical Traumatic Stress N=38 Physical/Emotional/Sexual Abuse N=25 | 48 (80%) |
| 5 | Attention-Deficit Hyperactivity Symptoms | 44 (73%) |
| 6 | CFTR Modulator Side Effects | 40 (67%) |
| 7 | Lifetime Suicidal Ideation or Attempts | 23 (38%) |
| 8 | Disordered Eating | 22 (37%) |
| 8 | Substance Misuse | 22 (37%) |
| 10 | Mood Swings/Anger/Agitation | 19 (32%) |

Demographics for Current & Past ETI Users

Purposive Sampling (N=45)

Phase 1

| Age | Gender | Race & Ethnicity | Modulator Status | Socioeconomic Status | LGBTQ+ | PHQ-4 Score |
|----------------------------------|------------------------|---|--|---|-----------------|--|
| 18-29 years N=15 | 8 Women 7 Men | 7 White 4 Black 2 Hispanic 2 Other | 12 currently on ETI 1 discontinued due to side effects 2 discontinued due to other reasons | 7 low SES | 6 LGBTQ+ | |
| 30-49 years N=14 | 7 Women 7 Men | 10 White 1 Black 2 Hispanic 1 Other | 14 currently on ETI | 3 low SES | 3 LGBTQ+ | |
| ≥ 50 years N=16 | 6 Women 10 Men | 13 White 1 Black 2 Other | 12 currently on ETI 4 discontinued due to side effects | 2 low SES | 3 LGBTQ+ | |
| 19-74 years TOTAL N=45 | 21 Women 24 Men | 30 White (67%) 6 Black (13%) 4 Hispanic (9%) 5 Other (11%)* *Arab, Native American, French-Canadian Inuit, Mixed race including Black and/or Hispanic | 38 currently on ETI (84%) • 5 discontinued (11%) due to side effects • 2 discontinued (4%) due to other reasons (family disapproval; post lung/liver transplant) | 12 low SES* (27%) * Below the US Federal Poverty Level | 12 LGBTQ+ (27%) | Anxiety 29% mild 11% moderate / severe Depression 20% mild 7% moderate / severe |

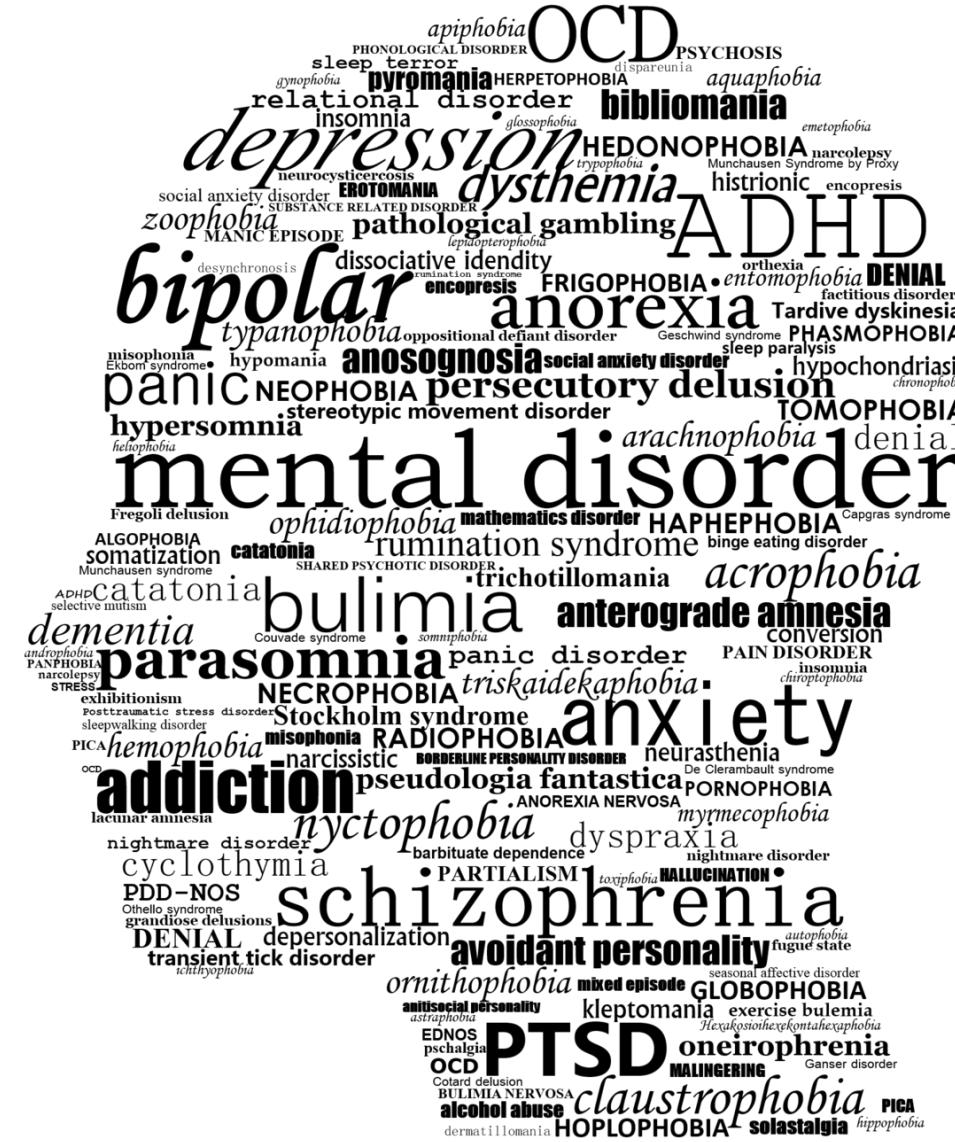
Thematic Coding of Qualitative Interviews

Top CFTR Modulator Side Effects (N=45*)

| Ranking | Currently/previous taking ETI (*5 of whom discontinued due to side effects) | Number (%) |
|---------|--|-----------------|
| 1 | Uncertainty about the Future | 19 (42%) |
| 1 | Body Image | 19 (42%) |
| 3 | Brain Fog & Cognitive Issues | 17 (38%) |
| 4 | Insomnia | 15 (33%) |
| 5 | GI Issues | 13 (29%) |
| 5 | Anxiety | 13 (29%) |
| 5 | Pain | 13 (29%) |
| 8 | Mood Swings | 9 (20%) |
| 8 | ADHD/Inattention | 9 (20%) |
| 10 | Eating Challenges | 8 (18%) |

Of note: 3 of 45 (6.7%) endorsed suicidal ideation/attempts related to ETI

“Trading my lungs for my mental health.”



Uncertainty about the Future

“I try not to think about the future because that gives me a lot of **anxiety**.”

“Definitely thinking more about the future and a little bit of **a sense of playing catch-up**”

“Trikafta changes things for the better in so many ways, but it also requires me to change along with it. So while there's benefits, it also puts **burdens and responsibilities of figuring out how to live as a person whose trajectory is all of a sudden different**. And now there's a future to think about, which is awesome. But **I wasn't prepared for it**.”

“There is a big joke, too, about **Trikafta should come with a 401(k)** because I didn't plan for retirement.”

“I think I was in like a **massive state of shock**... It was really hard to grasp this big life change...And then there's this always perpetual lingering experience of how long is this going to last?...fear of what if Trikafta doesn't work as well as I thought....And there's also this **enormous amount of grief** that you've lived for so long and all of the interwebs of pain that's there that you carry into this new life...”

Body Image

"I broke down for some time, but I was like, "It's life. I have to face it. There's nothing I can do to stop it [weight gain]."**...**The exercises I try to do... So I just felt, "Hey, I just have to just accept it, accept my fate."

"But it's sort of a double-edged sword because I've never been this big. And this is like more of like an average build now. But I guess I still **feel quite bad about my body a lot**. And my dysmorphia has never been this bad."

"The medicine ramps up my appetite. And this is a **big daily struggle**. I'd be at work, and there's some donuts on the table or something and I just can never stop myself....so I've gotten chubbier than I would have been...."

"I definitely feel like Regina George in Mean Girls because I've gained so much, and nothing fits....when you're so used to being one size for almost 10 years-- I've had to slowly revamp my closet again, and I'm not that happy about it because I don't have that extra money to do it...."

Brain Fog & Cognitive Issues

“There are times where I'm like, **I just can't remember anything.**”

“It's just **not your typical forgetfulness**”

“I can't remember things, and I **can't always find the words** that I need, and **I can't memorize** and remember things that I used to be able to, names especially.”

“I retired about a year ago. And part of the reason why I retired...there's two different aspects of that. One is the **concentration and the brain fog**, which is I literally don't remember things. Entire things I do, I do not remember. Someone will say like, "Hey, you were just using that screwdriver yesterday. Do you remember what you did with it?" And I want to look smart, so I want to be like, "Oh, yeah. It's here." But in my mind, I'm thinking, "It could be in the fridge." Literally, it could be in the fridge. I'm going to go check my sock drawer. Nothing remotely works anymore.”

Insomnia

“I find **sleeping difficult** sometimes. But it's not every time ... let's say just two nights in a week.”

“My **sleep quality** kind of reduced. I found it **difficult to fall asleep**. I also was **waking up periodically**.”

“I was **restless** and always waking up at the slightest sounds.”

“Because being on your Trikafta, there's sort of a **burst of energy** after you take it. So **you have to time it right in the evening or the day so that you're not having a burst of energy when you're trying to sleep**. And that's thrown off my sleep schedule.”

“It gave me **more insomnia**. I just felt like it was an **espresso shot in my body** at all times.”

Mood Symptoms

“I definitely noticed **more agitation and mood swings** and just more intrusive thoughts.”

“I'm **snapping more** ...I could be perfectly fine, and then it's just snap and it's like then I feel bad because I either don't know why I did it, or I did it, and then it's just I don't want it to escalate...my husband and I, we've talked about this. We could be having fun and happy and joking...he could say something, and then all of a sudden, I just snap.”

“I don't know if I can say that any more accurately, but now I find a lot of things **incredibly annoying**. I find a lot of people incredibly annoying. The things that people talk about or people are concerned themselves with, I look at it as trivial or annoying.”

ADHD-like Symptoms

“a lot of **difficulty concentrating.**”

“So just being able to focus on what I'm doing. If I've got people-- especially if I've got people talking in the room and stuff, it's **hard for me to stay focused** on exactly what I'm trying to say...if I have other people talking, it's really hard to focus on what I'm trying to tell them. And this is **way more than it used to be**. I've never really had issues like that until I got onto Trikafta.”

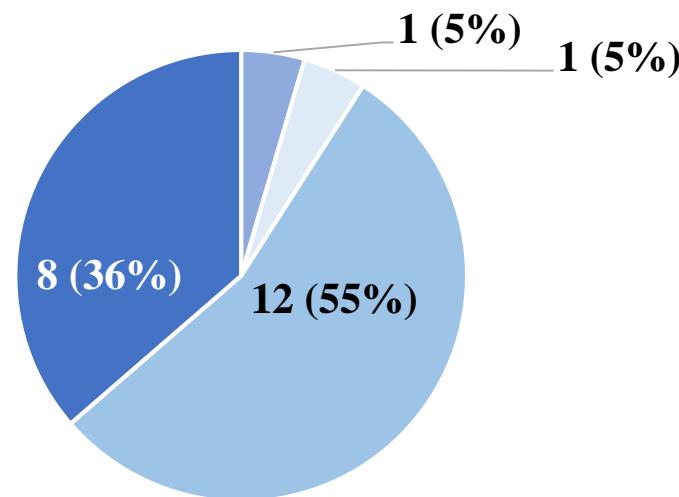
“It's a constant **struggle to keep organized.**”



GEMS Mod-SE Initial Draft

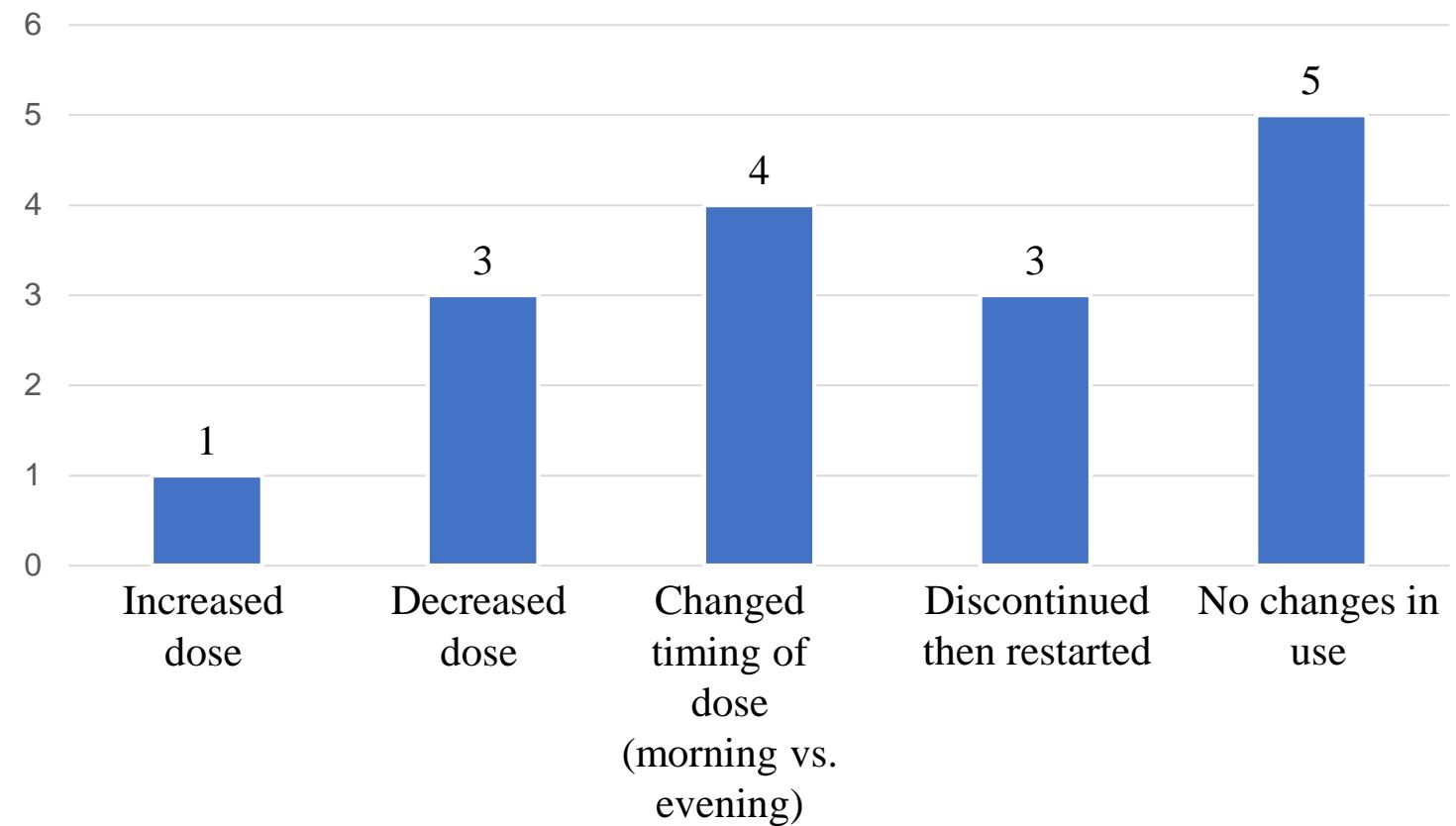
Cognitive Testing (N=23)*

CFTR Modulator Status



- Orkambi
- Kalydeco
- Trikafta
- Not on CFTR Modulator

Changes in CFTR Modulator Use



* 1 person had unusable data

GEMS Mod-SE Revisions *after* Cognitive Testing

Preliminary Validation of GEMS Mod-SE

Participants: N=54 from Phase 1

Results:

- **GEMS Mod-SE** yielded high internal consistency for exposure (KR-20 = 0.87), impact ratings (alpha = 0.90) and average domain-level reliability (alpha = 0.76).
- There was strong convergence found between *both GEMS-CF* and *GEMS-ModSE* with: PHQ-9, GAD-7, DSM-5 Cross-Cutting Symptom Measure (r 's = 0.62-0.82, $p < .001$).
- GEMS Mod-SE was *negatively* correlated with hope, resilience, and CFQR-composite scores (r 's = -0.33 to -0.49, p 's $< .05$).

Next Steps: National Validation



Results

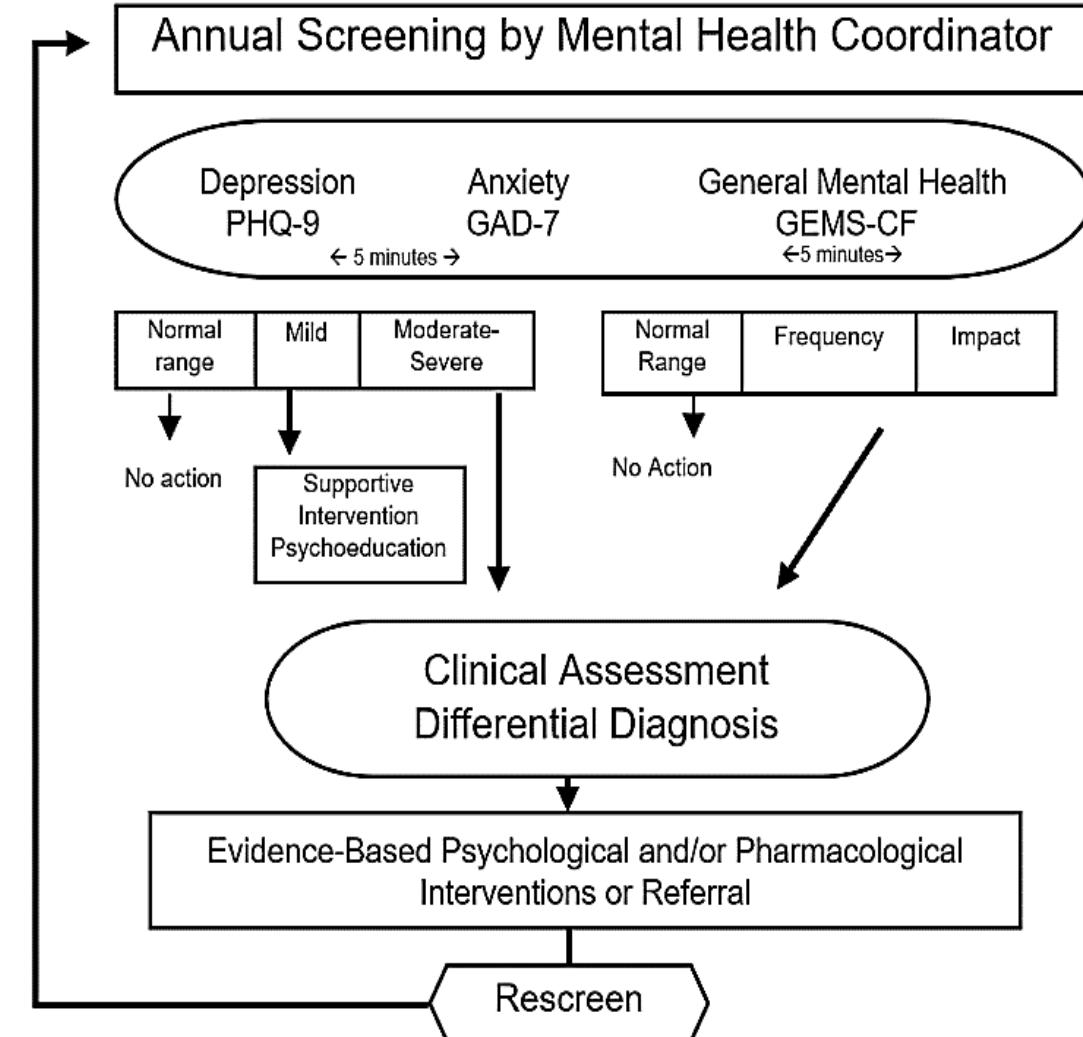
| N=54 | PHQ-9 | GAD-7 | SDMT | DSM-5 | Herth Hope Index | CD-RISC | GEMS-CF Impact | GEMS Mod-SE |
|-------------------------|----------|----------|-------|----------|------------------|----------|----------------|-------------|
| GAD-7 | 0.71*** | 1.00 | | | | | | |
| SDMT | -0.15 | 0.00 | 1.00 | | | | | |
| DSM-5 | 0.87*** | 0.81*** | -0.06 | 1.00 | | | | |
| Herth Hope Index | -0.32* | -0.22 | 0.06 | -0.29* | 1.00 | | | |
| CD-RISC | -0.50*** | -0.47*** | 0.09 | -0.57*** | 0.63*** | 1.00 | | |
| GEM-CF Impact | 0.70*** | 0.62*** | -0.09 | 0.65*** | -0.31* | -0.51*** | 1.00 | |
| GEMS Mod-SE | 0.82*** | 0.73*** | -0.18 | 0.79*** | -0.31* | -0.35* | 0.70*** | |
| CFQR¹ | -0.65*** | -0.47*** | 0.27* | -0.49*** | 0.39** | 0.46*** | -0.67*** | -0.49** |

¹CFQR composite: CFQ-R Role Functioning, Vitality and Health Perceptions; *p<.05, **p<.01, ***p<.001



Implementation: GEMS-CF & GEMS Mod-SE

- Qualitative results suggested that MH comorbidities and side-effects from ETI are ***highly prevalent***
- Strategies to recruit a diverse sample were ***very successful***
- Feasibility of annual administration of the GEMS screeners was rated as ***very feasible (85%)***
- Potential helpfulness of assessing these comorbidities was rated as ***very helpful (82%)***
- **Next steps: Grant for national psychometric validation *under review***



Conclusions



- We enrolled a highly diverse sample of AWCF to elicit their most serious mental health comorbidities, in addition to depression and generalized anxiety.
- GEMS-CF was associated with measures of psychological distress and negatively associated with hope, resilience, and health-related quality of life.
- A separate Mod-SE checklist (14 items) has been developed to assess modulator side-effects given that was a top comorbidity.
- Our next plan is a comprehensive national psychometric validation, with tests of moderation in a larger sample.
- Our long-term goal is to offer GEMS-CF as a screener for CF-specific mental health concerns and qualities of resilience in AWCF and the GEMS Mod-SE for monitoring individuals on modulators.

GEMS Mod-SE

- *For permission to use please contact:*

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Acknowledgements



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