FATIGUE IN SJÖGREN’S
A burden to patients and the society
a challenge for clinicians and scientists

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Trustee, British Sjögren’s Syndrome Association
Medical Board Member, Sjögren’s Europe
Fatigue is common among people with Sjögren’s syndrome

- Fatigue affects ~70% of people with Sjögren’s syndrome
- Over 40% of people with Sjögren’s syndrome rated fatigue being the most important symptom needing improvement
- Some people with Sjögren’s syndrome do not experience significant fatigue

N = 843 (AECG)  
37 UK centres
Fatigue is a common feature in many chronic diseases.
Fatigue is a huge burden to patients and the society

**Patient’s perspective**
- Among the most disabling symptoms needful of treatment
- Often among the first symptoms patients notice
- In IMID, fatigue persists even when in clinical remission
- Should be included among the Core Outcome measures

**Associated with**
- Impaired activities of daily living performance
- Sickness absence and job loss in IMIDs
- Poor health-related quality of life in IMIDs and PD
- Increased mortality and risk of several complex disorders and death

**Increased societal and healthcare costs**

- Sickness absence
- Job loss
- Disability claims
- Increased medical consultations
Why aren’t we doing more about fatigue?

What is fatigue?
What causes fatigue?
How to measure fatigue?
How to treat fatigue?
WHAT IS FATIGUE?

- Most (if not all) people would have had experience that we called “fatigue” or “tiredness”
- Is it the same fatigue that patients go to see their doctor for?
- Qualitative research studies typically suggest that the patients’ experience is different from their “usual” fatigue
  - More profound and prolonged
  - Unpredictable
  - Persists after rest
WHAT IS FATIGUE?
- ARE THERE DIFFERENT “TYPES” OF FATIGUE?

- Is fatigue the same across diseases or is it disease-specific?
- What about different “types” of fatigue such as “physical”, “mental”, “central”, “peripheral”, etc.? Are they truly distinct phenomena or are they different facets of the same phenomenon?
WHAT IS FATIGUE (in research)?

- No consensus definition
- Essentially defined by the fatigue measurement tool used in a particular research
- Even when the same tool is used, the “cut-off value” for defining fatigue varies between studies
WHAT IS FATIGUE?

- A multi-dimensional phenomenon in which the biophysiological, cognitive, motivational and emotional state of the body is affected resulting in significant impairment of the individual’s ability to function in their normal capacity"
WHAT “CAUSE” FATIGUE AND HOW TO MANAGE FATIGUE
The constellation of non-specific symptoms of sickness such as *weakness*, *malaise*, *fatigue*, *aches*, *inability to concentrate* and somewhat *depressed* and *lethargic*, is collectively referred to as “sickness behaviour” (Benjamin Hart, 1988)
SICKNESS BEHAVIOUR

- A highly organized strategy of the body to fight infections
- In humans, metabolic rate needs to be increased by 13% to raise 1 °C in body temperature.
- Also motivational interpretation of sickness behaviour

(Benjamin Hart, 1988)
“INDIRECT” EFFECTS OF INFLAMMATION

- Disrupts *circadian rhythms* (vice versa)
- Leads to *sleep disturbances* (e.g. reduced slow wave sleep, increase REM, subjective sleep “quality”)
- Increases *oxidative stress*
- May induce “*depression-like*” symptoms
- Chronic exposure to inflammatory cytokines blunts *Hypothalamus-Pituitary-Adrenal (HPA)* responses
Inflammation and fatigue in chronic immune-mediated inflammatory disease such as Sjögren’s syndrome

- Fatigue persists when patients in apparent clinical remission (i.e. no measurable systemic inflammation)
- Variability
- Many patients with clear evidence of systemic inflammation do not experience fatigue
Role of “conventional” inflammatory processes in fatigue in chronic disease remain to be defined.

Davies K, et al, 2019
SERUM PROINFLAMMATORY CYTOKINES IN PSS – REGRESSION MODEL

All parameters

Predicted fatigue levels

Observed fatigue levels

Pain, Depression, IP-10, IFN-Y

Full model

Reduced model

Correct = 67%

Howard-Tripp et al, 2016
Acute immune/inflammatory responses

Physiological model of fatigue

Chronic immune/inflammatory responses

Immune Regulatory or other adaptive mechanisms

Depression

Fatigue

PAIN
Mechanisms of fatigue

Inflammation
- HPA axis
- Circadian rhythms
- Sleep disorders
- Fatigue

CNS changes
- (Neuro networks, structural changes)

Neurotransmitter metabolism
- (Serotonin, dopamine)

Oxidative & nitrosative pathways
- (glutathione)

Autonomic dysfunction

Mitochondrial dysfunction

Cardio-respiratory fitness/muscle weakness

Pain

Anxiety

Depression

Circadian rhythms

Fatigue
Mechanisms of fatigue

- Oxidative & nitrosative pathways (glutathione)
- Neurotransmitter metabolism (Serotonin, dopamine)
- Mitochondrial dysfunction
- Cardiorespiratory fitness/muscle weakness
- Pain

Any (chronic) stressors

CNS changes (Neuro networks, structural changes)

Autonomic dysfunction

HPA axis

Circadian rhythms

Sleep disorders

Fatigue

Anxiety

Depression

Fibromyalgia, Cancers, CFS

Any (chronic) stressors
Fatigue

- Neurotransmitter metabolism (Serotonin, dopamine)
- Oxidative & nitrosative pathways (glutathione)
- mitochondrial dysfunction
- Cardio-respiratory fitness/muscle weakness
- Pain
- Anxiety
- Depression
- Autonomic dysfunction
- HPA axis
- Circadian rhythms
- Sleep disorders
- Fatigue subset
- CNS changes (Neuro networks, structural changes)
- Fatigue subset
TREATMENT OF FATIGUE

• Optimise immunomodulatory therapies to achieve clinical remission of the underlying inflammatory rheumatic disease
• Consider trial with hydroxychloroquine
• Avoid corticosteroid, especially long-term use or in non-inflammatory conditions

• ? Immunomodulatory therapies may be more useful in early disease or acute flares
TREATMENT OF FATIGUE

- Analgesics
- Pain modifying agents
- Pain management programmes
- Cognitive behavioural therapy
- Psychotherapies
- Other Mind-Body therapies (e.g. mindfulness, meditations)
- Acupuncture

- Anti-depressants
- Cognitive behavioural therapy
- Psychotherapies
- Other Mind-Body therapies (e.g. mindfulness, meditations)
- Acupuncture
TREATMENT OF FATIGUE

• Exercises
  • Aerobic*
  • Resistance
• Supplements
  • Anti-oxidants (e.g. Vit E)*
  • Coenzyme Q10
  • Miscellaneous (e.g. turmeric, garlic, zinc, fish oils etc)
TREATMENT OF FATIGUE

- Treat any underlying sleep disorders
- Sleep education
- CBT-Insomnia
- ? Hypnotics
- ? anti-depressants
- ? Melatonin
- ? Modafinil
- Physical activities and exercise training
TREATMENT OF FATIGUE

- Psychostimulants (e.g. methylphenidate, bupropion, amphetamine, ephedrine)
- Modafinil
- SSRIs
- Mind-body therapies

Neurotransmitter metabolism (Serotonin, dopamine)

CNS changes (Neuro networks, structural changes)
TREATMENT OF FATIGUE

HPA dysfunction
• ???
• ?? Low dose hydrocortisone/DHEA
• ?? Herbal medicine
• ?? Psychological medicine

Autonomic dysfunction
• ???
• Depending on symptoms, largely symptomatic
• For orthostatic symptoms (? Fludrocortisone, Midodrine, Droxidopa, Pyridostigmine)
• ? Vagus nerve stimulation
HOW TO MEASURE FATIGUE
CHALLENGES IN MEASURING FATIGUE

- Multi-dimensional
- “Severity” vs. “Impact”
- Variability
- “Momentary” vs. “average over a period of time”
- Confounders
- “Subjective” vs. “observed” or “objective” (“Perceived” vs “capacity” or “performance”)
### CHALLENGES IN MEASURING FATIGUE

#### FSS Questionnaire

During the past week, I have found that:

<table>
<thead>
<tr>
<th>Question</th>
<th>Agreement Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My motivation is lower when I am fatigued.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>2. Exercise brings on my fatigue.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>3. I am easily fatigued.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>4. Fatigue interferes with my physical functioning.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>5. Fatigue causes frequent problems for me.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>6. My fatigue prevents sustained physical functioning.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>7. Fatigue interferes with carrying out certain duties and responsibilities.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>8. Fatigue is among my three most disabling symptoms.</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>9. Fatigue interferes with my work, family, or social life.</td>
<td>1 2 3 4 5 6</td>
</tr>
</tbody>
</table>

#### Fatigue Severity Scale

Multi-dimensionality - No question assessing “mental fatigue”

Severity (Q8) vs Impact (Q9): - But “impact” may depend on factors other than fatigue!

Unable to capture variability often experienced by patients

Perhaps more accurately or reliably assessed “objectively”?

In this questionnaire, the average score for someone with depression is 4.5, whereas the average score for SLE patients with fatigue is 6.5
POTENTIAL NOVEL APPROACHES TO MEASURING FATIGUE

- Measure using e.g. trail making test, Stroop test?
- Measure using accelerometer?
- Measure using psychomotor vigilance test?
- Measure aerobic capacity? Tracking heart rate and respiratory rate?

Modified Fatigue Impact Scale

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I have been less alert.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>I have had difficulty paying attention for long periods of time.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3.</td>
<td>I have been unable to think clearly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td>I have been clumsy and uncoordinated.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5.</td>
<td>I have been forgetful.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6.</td>
<td>I have had to pace myself in my physical activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7.</td>
<td>I have been less motivated to do anything that requires physical effort.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8.</td>
<td>I have been less motivated to participate in social activities.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9.</td>
<td>I have been limited in my ability to do things away from home.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10.</td>
<td>I have trouble maintaining physical effort for long periods.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Several studies have shown impairment in neurocognitive performance in Sjögren’s syndrome and other rheumatic diseases. The results were not always consistent between studies. Sample size tended to be small. Most studies do not study the relationships between neuropsychological performance and fatigue. Confounders may not be adequately controlled.
NOVEL MEASURES FOR FATIGUE

- Kocer B et al showed impaired neuropsychological performance in Sjögren’s
- Neuropsychological performance did not correlate to FSS or SF-36 vitality

But
- FSS has no practically no item on “cognitive” or “mental” fatigue, same for SF-36 Vitality domain!

**SF-36 Vitality domain**

23. Did you feel full of pep?
   - Yes: 1, No: 2-6

27. Did you have a lot of energy?
   - Yes: 1, No: 2-6

29. Did you feel worn out?
   - Yes: 1, No: 2-6

31. Did you feel tired?
   - Yes: 1, No: 2-6

---

**Table 2: Values of neuropsychological test performances in PSS and healthy control groups**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient (n = 32)</th>
<th>Control (n = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSS</td>
<td>29.22±1.04</td>
<td>29.84±0.38</td>
<td>.021</td>
</tr>
<tr>
<td>Clock Drawing</td>
<td>6.44±0.80</td>
<td>6.89±0.32</td>
<td>.029</td>
</tr>
<tr>
<td>COWAT</td>
<td>25.59±10.19</td>
<td>33.74±9.72</td>
<td>.007</td>
</tr>
<tr>
<td>PASAT</td>
<td>46.97±8.49</td>
<td>51.84±3.64</td>
<td>.007</td>
</tr>
<tr>
<td>Stroop (second)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop1</td>
<td>33.91±9.23</td>
<td>30.09±3.09</td>
<td>.038</td>
</tr>
<tr>
<td>Stroop2</td>
<td>42.19±7.72</td>
<td>37.33±3.68</td>
<td>.004</td>
</tr>
<tr>
<td>Stroop3</td>
<td>32.80±6.79</td>
<td>31.86±4.50</td>
<td>.594</td>
</tr>
<tr>
<td>Stroop4</td>
<td>76.79±15.76</td>
<td>73.84±7.26</td>
<td>.368</td>
</tr>
<tr>
<td>SDLT</td>
<td>8.13±7.59</td>
<td>15.58±3.564</td>
<td>.000</td>
</tr>
<tr>
<td>AVLT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate (A1)</td>
<td>6.31±1.80</td>
<td>7.74±1.41</td>
<td>.003</td>
</tr>
<tr>
<td>Short term (A4)</td>
<td>11.41±2.00</td>
<td>11.84±1.17</td>
<td>.330</td>
</tr>
<tr>
<td>Short term (A5)</td>
<td>11.75±2.10</td>
<td>12.74±1.56</td>
<td>.081</td>
</tr>
<tr>
<td>Long term (A7)</td>
<td>10.34±2.28</td>
<td>11.42±1.31</td>
<td>.037</td>
</tr>
<tr>
<td>Recognition</td>
<td>41.63±4.49</td>
<td>41.95±2.35</td>
<td>.738</td>
</tr>
<tr>
<td>BNT</td>
<td>33.53±1.80</td>
<td>33.95±1.35</td>
<td>.387</td>
</tr>
<tr>
<td>BJLOT</td>
<td>21.03±3.82</td>
<td>24.63±2.19</td>
<td>.000</td>
</tr>
<tr>
<td>RCFT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>17.88±7.45</td>
<td>23.37±4.21</td>
<td>.001</td>
</tr>
<tr>
<td>30 seconds</td>
<td>17.34±7.58</td>
<td>22.16±4.89</td>
<td>.008</td>
</tr>
<tr>
<td>30 minutes</td>
<td>17.28±7.23</td>
<td>22.68±4.30</td>
<td>.002</td>
</tr>
<tr>
<td>Recognition</td>
<td>19.42±2.42</td>
<td>21.26±1.49</td>
<td>.004</td>
</tr>
</tbody>
</table>

NOVEL MEASURES FOR FATIGUE

• Impaired neuropsychological performance in Sjögren’s syndrome
• No correlation between neurological performance and Fatigue Severity Scale

However,
• There were correlations between Sjögren’s Mental fatigue score and Verbal memory (HVLT-R) and (close to statistical significant correlations) with attention, working memory and processing (DST, Trails B)
• HVLT-R is an independent predictor of the mental fatigue score.

Table 2 Cognitive performance in PSS patients and controls

<table>
<thead>
<tr>
<th>Test</th>
<th>All PSS Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>P-value</th>
<th>Effect size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails B</td>
<td>56.56 (5.56)</td>
<td>58.21 (9.73)</td>
<td>0.424</td>
<td>0.234</td>
</tr>
<tr>
<td>Stroop</td>
<td>53.50 (9.84)</td>
<td>58.13 (9.16)</td>
<td>0.114</td>
<td>0.472</td>
</tr>
<tr>
<td>WCST</td>
<td>47.91 (9.24)</td>
<td>50.07 (6.99)</td>
<td>0.422</td>
<td>0.248</td>
</tr>
<tr>
<td>Similarities</td>
<td>57.13 (8.446)</td>
<td>64.12 (8.703)</td>
<td>0.007</td>
<td>0.772</td>
</tr>
<tr>
<td>Boston naming test</td>
<td>54.08 (12.93)</td>
<td>56.94 (8.17)</td>
<td>0.406</td>
<td>0.245</td>
</tr>
<tr>
<td>DST</td>
<td>52.85 (8.52)</td>
<td>58.04 (6.02)</td>
<td>0.021</td>
<td>0.636</td>
</tr>
<tr>
<td>Controlled oral word association</td>
<td>44.21 (8.69)</td>
<td>47.95 (8.38)</td>
<td>0.143</td>
<td>0.398</td>
</tr>
</tbody>
</table>

Table 5 Linear regression model for cognitive SYMPTOMS (Prof-M) adjusted for age and depression in PSS patients

<table>
<thead>
<tr>
<th>Adjustors: age and depression (CES-D)</th>
<th>R²</th>
<th>R² change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.108</td>
<td>0.108</td>
<td>0.053</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal memory (HVLT-R) + adjustors</th>
<th>R²</th>
<th>R² change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.614</td>
<td>0.614</td>
<td>0.0000002</td>
<td></td>
</tr>
</tbody>
</table>

NOVEL MEASURES FOR FATIGUE

RSLV-132 is a First-in-Class Biologic (RNase fusion protein) to Eliminate Circulating Nucleic Acids

Posada J, et al, 2020

ProF: Improvement in mental fatigue score

Improvement in the performance of Digital Symbol Substitution Test

+2.8 sec.  p=0.024

-16.4 sec.  p=0.046
NOVEL MEASURES FOR FATIGUE

- Several studies have used accelerometers to measure physical activities in rheumatic diseases
- Several studies have also measure cardiorespiratory fitness and other assessment of physical capacity
- Relationship between fatigue was often not determined
- Confounders may not be adequately controlled
NOVEL MEASURES FOR FATIGUE


- FACIT-F and SF-36
- TUG negatively correlate with SF-36 Vitality
- Only bivariate correlation was carried out
- Only crude measures of accelerometer data were analysed
- FACIT-F/SF-36 VT may not be the best questionnaire to explore these objective measurements and fatigue

<table>
<thead>
<tr>
<th></th>
<th>pSS (n = 29)</th>
<th>CTRL (n = 20)</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary time (min/day)</td>
<td>493.8 ± 102.2</td>
<td>481.0 ± 103.5</td>
<td>-43.6 to 71.1</td>
<td>0.631</td>
</tr>
<tr>
<td>Sedentary time (% of wear time per day)</td>
<td>52.0 ± 10.9</td>
<td>56.4 ± 7.5</td>
<td>-9.3 to 1.5</td>
<td>0.161</td>
</tr>
<tr>
<td>Light PA (min/day)</td>
<td>375.1 ± 77.0</td>
<td>411.4 ± 106.2</td>
<td>-83.2 to 18.2</td>
<td>0.203</td>
</tr>
<tr>
<td>Light PA (% of wear time per day)</td>
<td>34.2 ± 7.7</td>
<td>31.6 ± 5.0</td>
<td>-1.2 to 6.2</td>
<td>0.186</td>
</tr>
<tr>
<td>Total MVPA (min/day)</td>
<td>26.3 ± 13.6</td>
<td>27.2 ± 12.2</td>
<td>-14.1 to 3.7</td>
<td>0.244</td>
</tr>
<tr>
<td>MVPA (min/day in ≥ 10-min bouts)</td>
<td>8.5 ± 8.5</td>
<td>6.0 ± 5.9</td>
<td>-88.9 to 35.9</td>
<td>0.409</td>
</tr>
<tr>
<td>Total MVPA (% of wear time per day)</td>
<td>13.7 ± 5.3</td>
<td>12.0 ± 4.3</td>
<td>-2.0 to 4.0</td>
<td>0.528</td>
</tr>
<tr>
<td>Total counts (counts/day)</td>
<td>653834 ± 161674</td>
<td>702106 ± 175975</td>
<td>-158198 to 31886</td>
<td>0.188</td>
</tr>
<tr>
<td>Mean accelerometer wear time (hours/day)</td>
<td>14.9 ± 1.1</td>
<td>15.3 ± 1.6</td>
<td>-1.3 to 0.4</td>
<td>0.338</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>pSS (n = 29)</th>
<th>CTRL (n = 20)</th>
<th>CI (95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO_{peak} (ml/kg/min)</td>
<td>22.5 ± 3.5</td>
<td>24.6 ± 3.6</td>
<td>-4.2 to 0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>HR_{peak} (bpm)</td>
<td>164 ± 14</td>
<td>172 ± 10</td>
<td>-15.6 to -0.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Time to exhaustion (min)</td>
<td>12.3 ± 2.3</td>
<td>13.4 ± 2.1</td>
<td>-2.4 to -0.2</td>
<td>0.085</td>
</tr>
<tr>
<td>Leg press (kg)</td>
<td>105.2 ± 28.5</td>
<td>135.8 ± 54.6</td>
<td>-54.5 to -6.5</td>
<td>0.014</td>
</tr>
<tr>
<td>Bench press (kg)</td>
<td>19.9 ± 3.8</td>
<td>23.8 ± 6.1</td>
<td>-6.7 to -0.9</td>
<td>0.010</td>
</tr>
<tr>
<td>Hand grip (kg)</td>
<td>23.8 ± 4.5</td>
<td>26.6 ± 3.2</td>
<td>-5.1 to -0.4</td>
<td>0.021</td>
</tr>
<tr>
<td>Timed-Stands Test (reps)</td>
<td>14.8 ± 2.8</td>
<td>16.2 ± 2.6</td>
<td>-2.9 to -0.3</td>
<td>0.099</td>
</tr>
<tr>
<td>Timed Up &amp; Go (s)</td>
<td>6.4 ± 0.8</td>
<td>6.0 ± 0.4</td>
<td>0.0 to 0.85</td>
<td>0.034</td>
</tr>
</tbody>
</table>
• Multi-dimensional
• Different questions

Similarly,

• Different objective measurements to capture different dimension/aspects of fatigue might be needed
NOVEL MEASURES OF FATIGUE

Figure 1: An overview of our fatigue assessment system

Yang B, et al, IWSC, 2020

Luo H, et al, Digital Biomarkers, 2020
IDENTIFYING DIGITAL ENDPOINTS TO ASSESS FATIGUE, SLEEP AND ACTIVITIES OF DAILY LIVING IN NEURODEGENERATIVE DISORDERS AND IMMUNE-MEDIATED INFLAMMATORY DISEASES

WWW.IDEA-FAST.EU
Identifying Digital Endpoints to Assess FAatigue, Sleep, acTivities of daily living in neurodegenerative and immune-mediated diseases

Disease of interests
- Immune-mediated Inflammatory Disease
- Neurodegenerative Disease

Lasting impact
- Real world clinical & digital datasets of 2200 subjects

IDEA FAST
- 18 Clinical / academic organisations
- 6 Not-for profit organisations
- 10 SMEs
- 3 Patient organisations
- 10 EFPIA and associated partners
- 15 European countries

€ 42M
Concept and Approach

Clinical Trials Transformation Initiative (CTTI)

- Fatigue
- Sleep Disturbance

5 Digitalisable Concepts of Interests (COI)

Digital devices & technologies that measures these 5 COIs

Clinical Validation Study (N=2000)

Feasibility Study (N=148)

EMA Advice on Digital Endpoint

Impact
Feasibility Study protocol

**Device use period (5 days per period)**
- At least 1 device for each of the 5 COI
- 4 times daily symptom scores
- Patient diary

2 x 5-day periods

4-6 weeks

2 x 5-day periods

First Study visit
- Patient reported outcomes
- Detailed clinical assessment
- Issue Digital technology
- Digital technology instruction
- Biobanking (Optional)
  - Blood, urine, stool

End of Study visit (Optional)
- Exit interview (Qualitative)
- Patient reported outcomes

Change Device combination

Blood, urine, stool
a) An example device combination across the timeline

<table>
<thead>
<tr>
<th></th>
<th>Cat\wk</th>
<th>1 (or 3)</th>
<th>2 (or 4)</th>
<th>3 (or 1)</th>
<th>4 (or 2)</th>
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<tr>
<td><strong>“Permanent”</strong></td>
<td>A</td>
<td>3</td>
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<tr>
<td></td>
<td>B</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
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<td></td>
<td>E</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Alternating sets</strong></td>
<td>A</td>
<td>1 or 2</td>
<td>1 or 2</td>
<td>2 &amp; 4 or 1 &amp; 4</td>
<td>2 &amp; 4 or 1 &amp; 4</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1 (&amp;2)</td>
<td>1 (&amp;2)</td>
<td>4</td>
<td>4</td>
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<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

b) Device locations

1. Dreem
2. Byteflies
2. Biovotion
3. RF-sensing

1. Vitalpatch
2. AX6
1. CANTAB/App
1. VTT App
3. Bed Sensor
CONCLUSIONS

- Fatigue is a syndrome that often coexist with other symptoms and there may be different “types” of fatigue or fatigue has different facets or dimensions
- Many questionnaires for fatigue exists, careful selection of appropriate questionnaire(s) to use in individual studies is important
- Considerations of confounding factors are critical in fatigue assessment and research
- Repeat/longitudinal measurement is useful (both in clinic and in research)
- Potentials for objective measurements of fatigue using non-invasive digital technology to complement questionnaire-based assessment.
CONCLUSIONS

- Management of fatigue remains a challenge
- Acknowledge the symptom and its impact is an important first step
- Multi-disciplinary, personalized and holistic approach is most likely required
- Begin with assessing potential contributing factors and devise targeted therapies accordingly
- Treat relevant comorbidities (e.g. anaemia, hypothyroidism)
- Effective treatments for most contributing factors remain elusive
ACKNOWLEDGEMENT
Acknowledgement

Patients & healthy volunteers

Sir Samuel Scott of Yews Trust
Thank you for listening