

Implications of Multiple Comorbidities for the Design of Chronic Pain Clinical Trials

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The Challenge of Comorbidity: One Day in the Fibromyalgia Clinic

- 65 year old married woman with 4- year history of fibromyalgia (follow-up)
 - Medical comorbidity: obesity, asthma, hypertension, sleep apnea, osteoarthritis, shoulder impingement, sciatica, hip pain, carpal tunnel syndrome
 - Psychiatric comorbidity: generalized anxiety disorder
- 53 year old single woman with 12-year history of fibromyalgia (follow-up)
 - Medical comorbidity: obesity, degenerative disc disease, chronic low back pain from fall at work 12 years ago (workman's comp for chronic back pain), osteoarthritis, sciatica, migraine, gastroesophageal reflux disease.
 - Psychiatric comorbidity: attention deficit disorder

The Challenge of Comorbidity: One Day in the Fibromyalgia Clinic

- 48 year old single woman with 2- year history of fibromyalgia (new patient visit)
 - Medical comorbidity: obesity, migraine, plantar fasciitis, interstitial cystitis
 - Psychiatric comorbidity: generalized anxiety disorder, major depression
- 36 year old married woman with 5- year history of fibromyalgia (follow-up)
 - Medical comorbidity: osteoarthritis (knees, back), migraines, endometriosis
 - Psychiatric comorbidity: major depression

The Challenge of Comorbidity: One Day in the Fibromyalgia Clinic

- 55 year old married woman with 3- year history of fibromyalgia (follow-up)
 - Medical comorbidity: Degenerative disc disease, chronic low back pain, cervical radiculopathy, hypothyroidism
 - Psychiatric comorbidity: Post-traumatic stress disorder (childhood physical and sexual abuse), major depression
- 18 year old single young woman with 4 -year history of fibromyalgia (follow-up)
 - Medical comorbidity: migraine
 - Psychiatric comorbidity: social anxiety disorder, major depression

The Challenge of Comorbidity: One Day in the Fibromyalgia Clinic

- 74 year old widowed woman with 8- year history of fibromyalgia (follow-up)
 - Medical comorbidity: overweight, osteoarthritis (hips, neck, shoulders), coronary artery disease, Type II diabetes, diabetic peripheral neuropathic pain, chronic foot fungus (1 year)
 - Psychiatric comorbidity: major depression
- 25 year old single woman with recent (1 year history of symptoms) diagnosis of fibromyalgia by rheumatologist (new patient visit)
 - Medical comorbidity: obesity, spondylolisthesis, sciatica, irritable bowel syndrome, temporomandibular disorder
 - Psychiatric comorbidity: generalized anxiety disorder, bulimia

Common Comorbid Pain Disorders in Fibromyalgia

- Common comorbid regional pain disorders:
 - Irritable bowel syndrome
 - Chronic headache/migraine
 - Interstitial cystitis or painful bladder syndrome
 - Temporomandibular disorder
 - Chronic pelvic pain
 - Chronic low back pain
 - Other “Chronic Overlapping Pain Conditions” or COPCs.

Common Comorbid Pain Disorders in Fibromyalgia, continued

- Other common comorbid disorders associated with pain:
 - Osteoarthritis, degenerative disc disorder, spinal stenosis, other spinal disorders
 - Neuropathy (multiple etiologies)
 - Radiculopathy
 - Other rheumatologic disorders (e.g., rheumatoid arthritis, lupus, psoriatic arthritis)
 - Ehler's Danlos syndrome
 - Obesity
 - Obstructive sleep apnea
 - Depression/anxiety

The Challenge of Comorbidity in Fibromyalgia Clinical Trials

Typical exclusion criteria for fibromyalgia trials related to comorbidity:

❖ Other pain conditions:

- Pain due to diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome, or **other*** source of pain that, **in the investigator's opinion, would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the subject's study participation**
- Infectious or inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout), autoimmune disease (e.g., systemic lupus erythematosus), or other **widespread rheumatic disease** other than fibromyalgia.

* Does not specifically exclude COPCs but up to investigator judgment

The Challenge of Comorbidity in Fibromyalgia Clinical Trials

Typical exclusion criteria for fibromyalgia trials related to comorbidity, continued:

❖ Psychiatric disorders:

- Current, untreated, moderate to severe major depression and/or anxiety disorders.
- History of any psychotic and/or bipolar disorder
- History of suicide attempt or behavior or suicidal ideation within the last 12 months.
- Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid and/or alcohol use disorders.

The Challenge of Comorbidity in Fibromyalgia Clinical Trials

Typical exclusion criteria for fibromyalgia trials related to comorbidity, continued:

❖ Other disorders:

- Body mass index (BMI) ≥ 40 -45 kg/m² (varies by study)
- Evidence of any **clinically significant, uncontrolled** cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary (including obstructive sleep apnea not controlled by a CPAP device), neurologic, dermatologic, psychiatric, renal, and/or other major disease (exclusive of fibromyalgia), **as assessed by the investigator.**

The Challenge of Comorbidity in Fibromyalgia Clinical Trials

- Pain assessment (primary outcome)
 - Average pain severity, measured once daily (evening or morning)
 - 0-10 average pain severity over the past 24 hours (0=“no pain”; 10=“worst possible pain” or “pain as bad as you can imagine”)
 - Does not typically specify the bodily area or pain condition to be rated.
 - Unclear how comorbid disorders might contribute to pain ratings.
 - May introduce between-patient variation in the pain scores¹

1. Smith et al. J Pain 2015;16:299-305

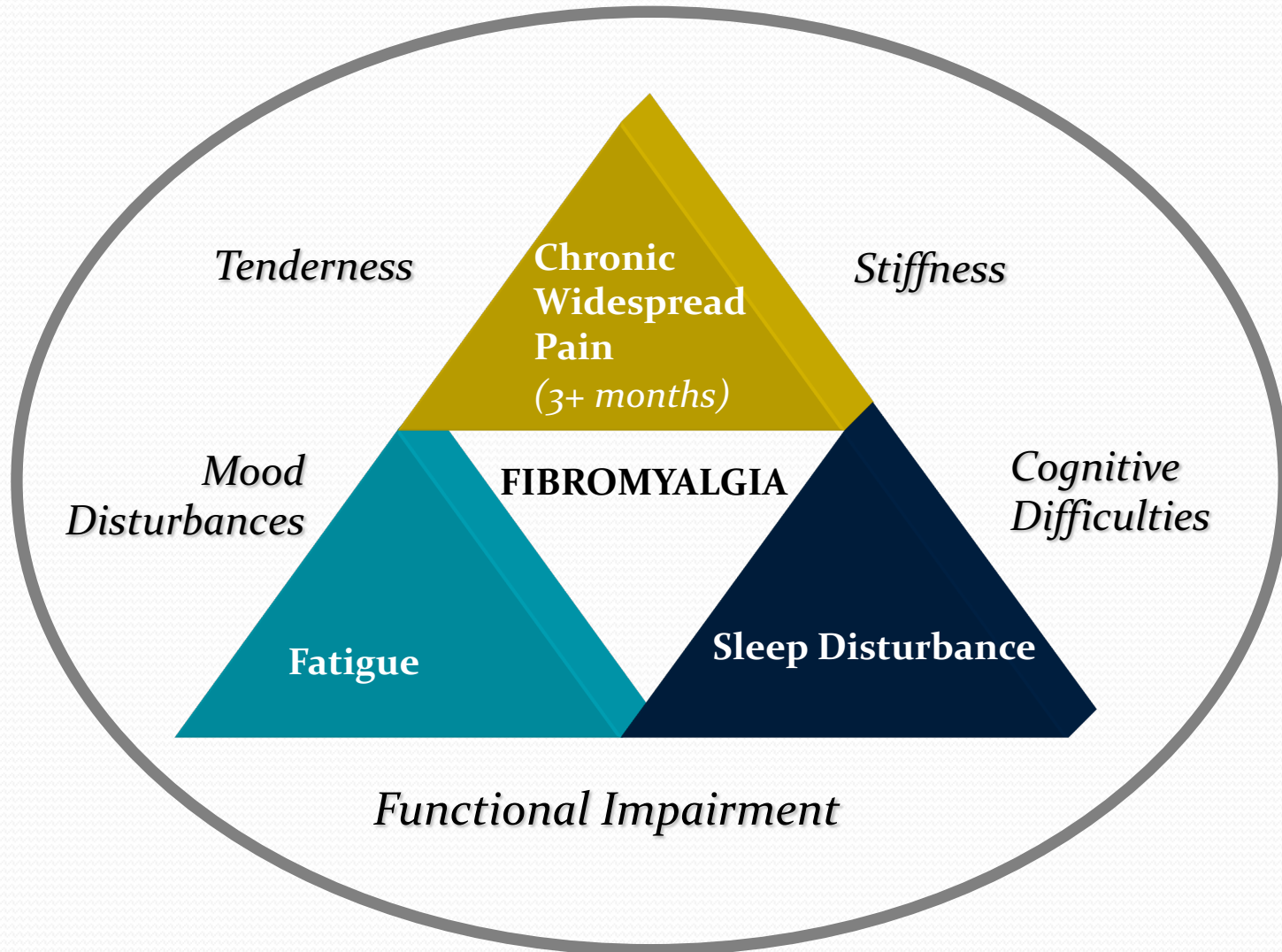
Designing Chronic Pain Clinical Trials

- Proposal
 - Consider fibromyalgia as representing centralized pain (i.e., the end of the continuum)
 - Other COPCs are related based on the presence of centralization (or fibromyalgia)
 - Per Dan Clauw:

“The phenotype for this underlying mechanism is quite clear:

 - Multifocal pain at present (and in past)
 - Other CNS symptoms (sleep, fatigue, memory, mood)
 - Hypersensitivity to other sensory stimuli (manifest as auditory or visual hyper-responsiveness, drug side effects)”

Summary of Hallmark Symptoms of Fibromyalgia



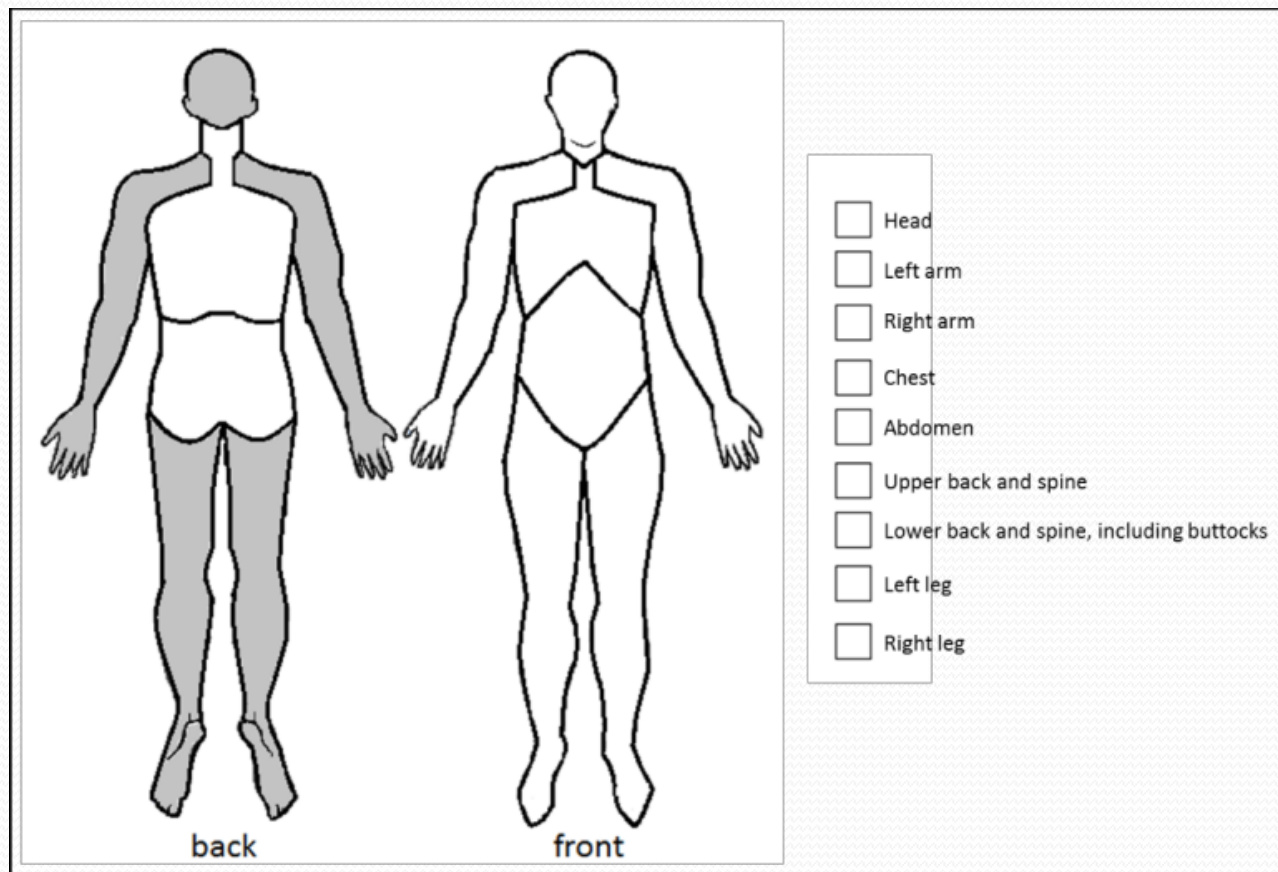
2019 AAPT Fibromyalgia Criteria

Table 1. AAPT Diagnostic Criteria for Fibromyalgia

Dimension 1: Core Diagnostic Criteria

1. MSP defined as 6 or more pain sites from a total of 9 possible sites (see Fig 1)
 2. Moderate to severe sleep problems OR fatigue
 3. MSP plus fatigue or sleep problems must have been present for at least 3 months
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NOTE. The presence of another pain disorder or related symptoms does not rule out a diagnosis of FM. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms.



Number of pain sites (out of 9 possible areas) _____

Designing Chronic Pain Clinical Trials, continued

- Patients with other chronic pain disorders (e.g. TMD, chronic migraine, etc) may also have fibromyalgia (or centralized pain).
- Trials may need to identify the extent of centralization (or presence of fibromyalgia symptoms) in the patients under study.
- Treatment response may differ in patients with evidence of centralized pain/fibromyalgia.

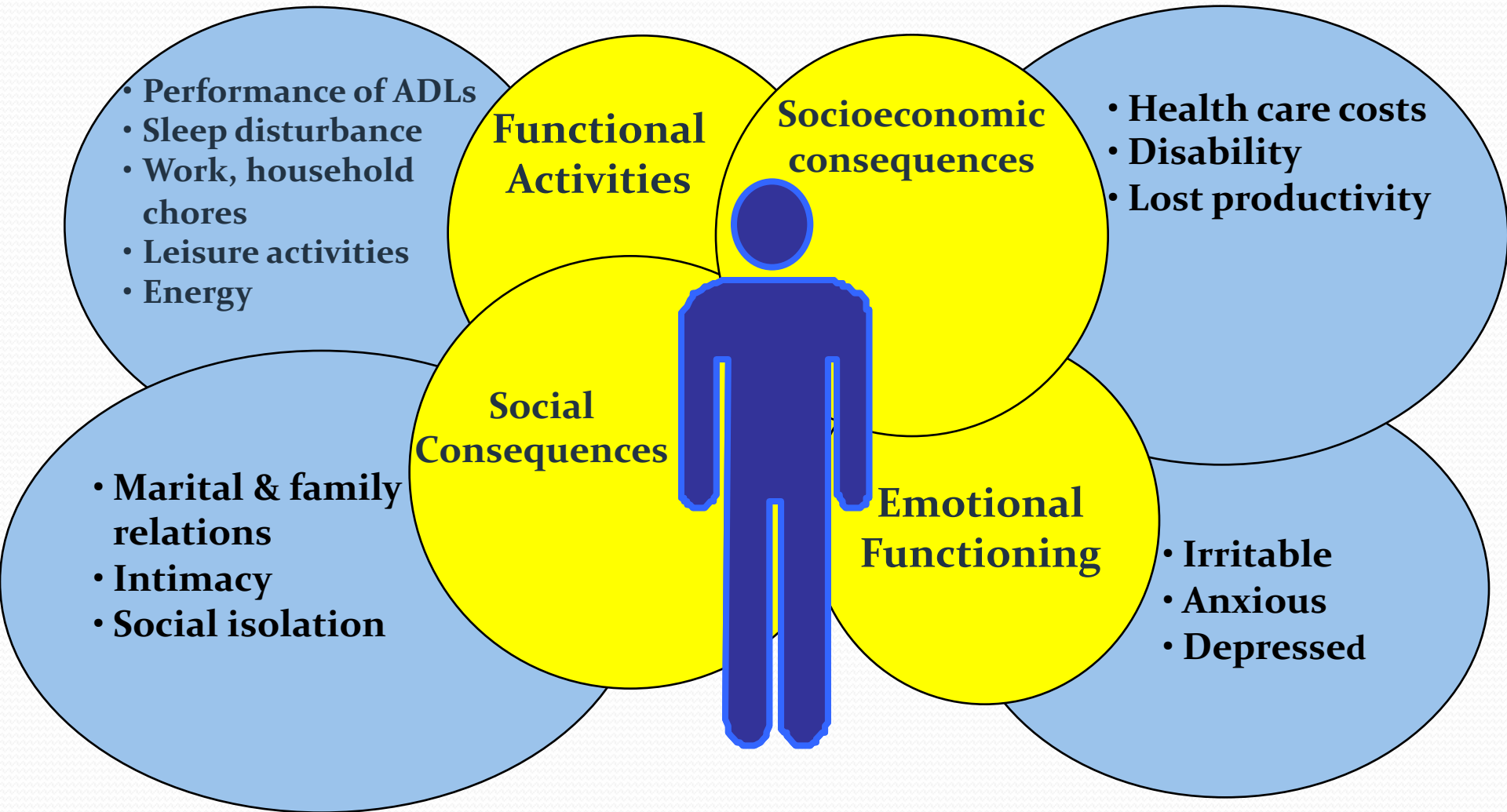
Proposal for the Design of Chronic Pain Trials

- Fibromyalgia trials
 - Identify other chronic pain disorders (e.g., COPCs such as TMD, IBS, etc) and monitor the response of all pain disorders to treatment
 - Need to develop outcomes that address all pain disorders and associated symptoms
 - Evaluate overall pain severity vs. more specific pain scores based on comorbidity
 - Possible phenotyping of subjects to identify subgroups based on comorbidity, QST, imaging.
- Other chronic pain disorders
 - Phenotyping as above, and include assessment of the degree of centralization of pain (e.g, presence of syndromal or subsyndromal fibromyalgia).

Chronic Pain Trials

- Other issues to consider in the design of clinical trials:
 - Current and lifetime history of mood and anxiety disorders and other psychiatric disorders
 - Presence of catastrophizing
 - Rheumatologic disorders (including osteoarthritis)
 - Other common pain disorders (neuropathy, radiculopathy)
 - Obesity
 - Sleep disorders
 - Lifestyle factors, psychosocial stressors, disability, function

The Impact and Burden of Fibromyalgia



Summary

- Fibromyalgia is the prototypic centralized pain state
- Assessment for the presence of fibromyalgia symptoms (i.e. centralized pain) may be important in trials of chronic pain disorders
- Identifying COPCs and tracking response to treatment may be helpful in establishing new therapies
- Phenotyping based on the presence of comorbidity and use of advanced techniques (e.g., imaging) may help to identify individuals most likely to response to a particular therapy.