Treat-to-target strategy for fibromyalgia: opening the dialogue

Winfried Häuser[1,2] , Daniel J. Clauw[3], Mary-Ann Fitzcharles[4,5]

[1] Department Internal Medicine I, Klinikum Saarbrücken, Saarbrücken, Germany, [2] Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, München, Germany, [3]Department of Anaesthesiology, Chronic Pain and Fatigue Research Center, University of Michigan Medical Center, Michigan, United States of America, [4] Division of Rheumatology, McGill University Health Centre, Quebec, Canada, [5]Alan Edwards Pain Management Unit, McGill University Health Centre, Quebec, Canada,

Winfried Häuser Dr.med., Daniel J. Clauw MD, Mary-Ann Fitzcharles MB.ChB

Address corresponding author: Mary-Ann Fitzcharles, Montreal General Hospital, McGill University Health Centre, 1650 Cedar ave, Montreal, Quebec, H3G 1A4
Tel no: (514)-934-1934#44176
Fax no: (514)-934-8239
E-mail:mary-ann.fitzcharles@muhc.mcgill.ca

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Illness represents a dysregulation of body homeostasis with consequences to physical and mental well-being, negative impact on functionality and life expectancy, prompting the concept of treat to target for many conditions. This strategy has however not yet been operationalized for the care of persons with fibromyalgia (FM). FM, defined by the American College of Rheumatology (ACR) preliminary 2010 diagnostic criteria and modified 2011 criteria, is characterized by widespread body pain and associated core symptoms of sleep disturbance, fatigue and cognitive problems as well as other somatic and mood complaints, has immediate effect on health-related quality of life (HRQoL), but with lesser known long standing effects (1-3). Although not yet fully understood, the pathogenesis of FM is likely centered in the nervous system rather than the musculoskeletal system as the taxonomy "fibromyalgia" implies (4). FM may occur as a unique diagnosis, but the association with other somatic and mental disorders broadens the impact of this condition (3).

The treat to target principle should be considered for FM care even though numerous uncertainties exist. In order to adhere to these principles the following need clarification: choice of ideal health care setting; a standard for clinical diagnosis; and a universal treatment algorithm. A move towards treat to target in FM is important for several reasons. Firstly, FM is common, with disease prevalence worldwide of at least 2%, and with prolonged persistence of symptoms (5). Secondly, FM impacts HRQoL, personal and social functioning, and incurs both direct and indirect health costs (4). Thirdly, the co-association with other inflammatory rheumatic diseases will impact treatment decisions and outcome for these illnesses (6). Therefore a more structured approach to management of FM should replace the current treatment paradigm that is often haphazard and is largely based on individual physician preferences (7).

What is needed?

The premise for "treat to target" is to apply a treatment strategy that improves patient outcome assessed with a pre-specified measure that captures illness severity. Beyond current symptom control, the overriding objective is to improve long-term functional outcomes with prevention of adverse consequences to health by applying an effective treatment algorithm, supported by evidence from randomised clinical trials, with objective of disease remission or very low disease activity (8).

Treat to target should adhere to a number of elementary steps including: clear disease definition, knowledge of long-term consequences of inadequate treatment, substantial effect for treatments and known duration of treatment, defined meaningful outcome measurements and accepted response criteria. Furthermore, an understanding of the underlying pathophysiologic processes will help identify prognostic and prevention factors. In this context we will address concepts of treat to target pertaining to FM by examining the current evidence with the aim of initiating dialogue.

How does fibromyalgia measure up to the critical elements that comprise a treat-to-target strategy?

1. Is fibromyalgia a clearly defined condition?

FM is a recognized medical condition, with ACR defined preliminary criteria and severity scales (2). The precise diagnosis in an individual patient may however be elusive, with symptoms present for years leading to many health care encounters and diagnostic delay possibly adversely affecting outcome (9). Those familiar with treating FM contend that "they can recognise FM", but experts still debate practical clinical diagnostic criteria (7, 10). Issues include the precise definition of widespread pain, and the relevance of co-associated symptoms, that vary both within a patient over time as well as between patients (11).

Widespread pain is universally recognized as the cardinal symptom of FM, with variability in the presence of other core symptoms as identified by the OMERACT working group (11). Core symptoms may be expressed differently between patients, contributing different weights to global health status. Therefore weighting symptoms for an individual, in line with the general concepts of using patient reported outcomes (PROs), may more accurately reflect global health status than using a generic measurement The importance of such PROs probing of many relevant domains has influenced assessment in clinical trials, observational studies and clinical practice (12). Therefore identifying the symptom of greatest importance can anchor treatment in a patient-tailored approach, prompting attempts to subgroup patients to help direct treatments (13).

2. Can fibromyalgia be prevented?

Prediction, prevention and early detection of disease represent an ideal. Factors predicting onset of FM are largely unknown, although genetic predisposition, adverse psychosocial lifetime experience, poor stress response system and triggering events may play a role (3, 4). Some regional pains may even evolve into more widespread pain. It is largely unknown whether early FM detection will influence outcome, but intuitively prompt recognition of FM or of a symptom pattern that suggests a diathesis towards developing FM might lead to earlier intervention with non-pharmacological approaches. Earlier detection of FM may be facilitated by education of and a heightened awareness by primary health care providers, and/or by using screening measures for the core symptoms of (or risk factors for) fibromyalgia in routine practice. Various screening questionnaires have been proposed to help identify FM or discriminate FM from other rheumatic conditions, but have not to date demonstrated an effect on outcome. (10, 14-16). At this time, the ACR criteria and current evidence-based guidelines strongly recommend against assigning a diagnosis of FM based only on completion of a questionnaire as the clinical encounter and narrative report of the patient must still remain the gold standard for diagnosis (1, 17).

3. Are the long term consequences of fibromyalgia known?

Long-term observational studies give insight into disease natural history, with poor control adversely affecting outcome. Although FM is associated with poor HRQoL and considerable functional impairment in the present, long term effects are largely unknown, but with indications that symptoms persist over time (3, 4). Adolescents with juvenile-onset FM had a high likelihood of continued symptoms into adulthood, with consequent physical and emotional impairment, and poorer educational achievement (18). It is reasonable to believe that outcome may be affected by variables such as delayed diagnosis, symptom duration, other comorbidities, and environmental and social factors. It is also possible that cognitive styles such as catastrophizing, known to be associated with poorer outcomes in all chronic pain conditions, could be prevented or reduced by earlier (especially non-pharmacological) interventions that enable active participation by the patient in preventing symptoms and associated dysfunction rather than being the passive victim (19). It is also not known whether patients maintain their characteristic phenotype and disease expression with time, or whether disease expression changes. For example, it is possible that an individual core symptom may emerge or decline as a predominant symptom.

Reports on all-cause mortality for FM are conflicting, with reports of no difference or increased mortality rates compared to population norms. Wolfe and colleagues reported similar standardised mortality ratios for FM compared to the US population, but with FM associated with an increased standardized mortality odds ratio (OR) for suicide (OR 3.31, 95% CI 2.15-5.11), and for accidental deaths (OR 1.45, 95% CI 1.02-2.06), but not for malignancy (20). Similarly, overall mortality was not increased for a Danish FM cohort followed for a total of 5,295 person-years, but with increased risk of death from suicide, liver disease and cardiovascular disease (21). Suicidal ideation is reported to occur in almost half of FM patients, and risk of suicide was greater for FM patients than those with low back pain (22).

Another factor that influences life expectancy is injury. The incidence rate ratio for motor vehicle accidents for adults with FM living in Ontario, Canada, where the driver required a visit to an emergency room, was 2.44 compared with the population norm (95% CI 2.27-2.63, $p< 0.001$) (23). Therefore there is a picture emerging of a possible increased rate of accidental death (possibly related to cognitive difficulties innate to FM or medications) as well as suicidal deaths related to associated depression (22). An intriguing concept is that biological age may be affected by FM. Leucocyte telomere length was shorter in FM patients than controls, but with a significant effect observed for those FM patients with both high pain and high depression levels (24).

Finally, the long-term socioeconomic consequences for the individual and society must be acknowledged. Costs to society include the direct and indirect health related costs, employment status, productivity and disablement (25).

4. Are there effective treatments for fibromyalgia?

At this time, a treatment plan for FM must begin with non-pharmacologic strategies including education, establishing individualized and realistic goals of therapy, patient engagement, and implementation of self-management techniques. Selective drug treatments may also we used with diligent monitoring of efficacy and side effect profile. Contrary to conditions where treatments are known to substantially alter or control disease, management strategies for FM fall short of the mark, without a recommended ideal health care setting, or universally accepted treatment algorithm or "gold standard", or suggested duration of treatments. Therefore the concept of intensive treatments or "tight control" is at this time outside the scope of this dialogue. Although many interventions show statistical significance, clinically meaningful and continued effect remains questionable. A stepwise treatment approach has recently been recommended by German, Canadian and Israeli interdisciplinary guidelines, beginning with non-pharmacologic strategies of active patient participation championing self-management strategies, and with discretionary medication use to ensure that side effects do not eclipse the positive effects (26).

Current drug treatments for FM are imperfect, offering mostly modest benefit for the majority of patients, with only a few experiencing substantial effect. For example, a Cochrane review of the effect of serotonin norepinephrine reuptake inhibitors (SNRI's) for FM reported that the average effect of drug treatments (compared to controls) was small (27). The risk ratio (RR) was about 1.5 for 50% or more pain relief compared to placebo for most, and the number needed to treat to benefit (NNTB) and number needed to harm (NNTH) was in the order of 10 for each (27). Only very few patients in trial settings reach a pain level of <4 (low pain) on a visual analogue scale. Non pharmacological treatments including multidisciplinary approaches and those that have a mind-body component hold promise, but may not be universally available (28, 29). Acceptance-based CBT had a NNTB of 2 for 20% improvement for HRQoL compared to best available drug treatment (duloxetine, pregabalin)(29). A recent network meta-analysis of all treatments for FM reported that the average benefits of pharmacologic treatments was of questionable clinical relevance and that the evidence for non-pharmacological interventions is limited (30). Moreover, although there is a growing body of published scientific evidence for complementary and alternative therapies for FM, methodological flaws identified in systematic reviews preclude conclusions about efficacy and safety for many (30, 31).

How then can this inform FM care? As a first step, a treatment algorithm, with a sound evidence base, must be developed and agreed upon by the international health community. Current algorithms, such as that developed in Germany, could be examined for universal applicability (32). Taking into account the current evidence and combined with clinical judgement, strategies that promote physical activity and stress reduction, and require active patient engagement have value and should be encouraged. With only three drugs, pregabalin, duloxetine and milnacipran, approved for treatment of FM in the United States and with more limited approval worldwide, pharmacologic treatment options are limited. Selected pharmacotherapy may be chosen according to the most prominent symptom with tricyclic drugs, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids identified as classes of drugs with the greatest benefits. Fatigue is a challenging symptom, with no consistent evidence for pharmacologic treatment, but evidence for physical activity and cognitive behavioral therapies as the best current strategy (33, 34) . With the exception of a single study each of tramadol and tramadol/paracetamol, there are no randomized controlled trials of opioids in FM, and there is virtually unanimity that this class of drugs should be avoided (26). In this setting of symptom heterogeneity, FM represents the prototype condition that calls for patient tailored individualized treatments. A starting treatment algorithm is suggested (Figure 1. Algorithm for Fibromyalgia care).

5. Is there a target for disease outcome for fibromyalgia?

A target should be a standard outcome measurement that is reliable, easy to perform, clinically meaningful, captures disease severity and has a defined minimal threshold for improvement. Consideration could even be given to a simple concept of disease status as active, or partial or complete remission, but simply focussing on a single symptom such as pain intensity is no longer a tenable outcome measure (32, 35). Unique target challenges posed by FM include the heterogeneity of symptoms and possible differing outcome goals for patient or physician. Subgrouping patients may help focus towards a specific symptom or target, such as categorizing patients according to psychological factors, i.e. low or high psychological problems, with those with mostly physical symptoms likely easier to manage compared to those with a high burden of psychological distress (13). The latter could theoretically benefit from more focussed psychologically directed treatments

Simplistically, remission may be defined by the patient stating that "I am no longer a patient and no longer suffer due to my pain (which may still be present) (30)". As patient narrative may be difficult to anchor multiple complaints, the patient global assessment (PGA), encompassing all domains may have use. Although confounded by short term fluctuating symptoms, and longer term recall bias, the PGA is a simple and reliable clinical assessment, whereas a physician global assessment may be less reliable for subjective complaints (36).

Another target could be to achieve a threshold value on a composite measure. Questionnaires reflecting outcomes include the Fibromyalgia Impact Questionnaire (FIQ) or the updated revised FIQ (FIQR), the 2011 Fibromyalgia Survey Criteria and the Patient Health Questionnaire 15 (PHQ15) (2, 37-39). These composite measures mostly address various dimensions of disease, with some assessing function, but with risk that the final score may not sufficiently reflect the effect of a specific domain within a group. The FIQ, or FIQR are the most widely used measures, but score calculation is complex and less applicable to clinical care. A target may however be defined by a FIQ total score <39. However, in a clinical study of group acceptance and commitment therapy which used the FIQ, no patient reached a FIQ score <39 (29). Some participants in multicomponent trials reported to be "no patients any more" (28). A recent modification of the FIQR, the Symptom Impact Questionnaire (SIQR), similarly complex to calculate, has been proposed as a disease-neutral measurement (16). The FM Survey Criteria in contrast, focuses specifically on symptoms without reference to functional status, quality of life or life participation, and

with a target defined as a total score of <12. The PHQ15 as a generic measure of somatic symptom burden is easy to complete and calculate, and a threshold of <5 could may represent a remission (39).

An individualized personal target that may be applied in real world clinical practice may be an identified improvement in daily function, rather than specifically focussing on individual symptoms. Some standardized measurements do exist, but have not yet been applied to FM. Similarly, focussing towards short term goals that are readily tangible may be more meaningful to the patient than a calculated number on a questionnaire. Defining individual and realistic outcome goals, such as a 30% symptom relief and a specified goal for daily functional improvement, in a setting of shared-decision making, is an achievable and reasonable target that can be easily clinically applied (39).

Can a treat to target strategy for fibromyalgia be suggested?

The gaps in FM that must be closed to truly move towards a treat-to-target approach include the following: validation of existing diagnostic and treatment algorithms in different settings (primary care, rheumatology, pain medicine, and less developed countries); validation of individual tailored treatments versus a standard approach based on defined patient subgroups, and consensus on responder criteria to be used to assess treatment effects, especially for non-drug treatments. Poorly treated FM has immediate impact on physical and psychological well-being, with long-term consequences an emerging reality. Future study should be focussed to identifying persons at risk for FM to consider prevention strategies, examination of patient-tailored specific therapies, with the treatment goal of symptom relief and maintained function. These considerations should prompt management of FM beyond the immediate towards a wider vision of future health status, and that these principles should guide the research agenda.

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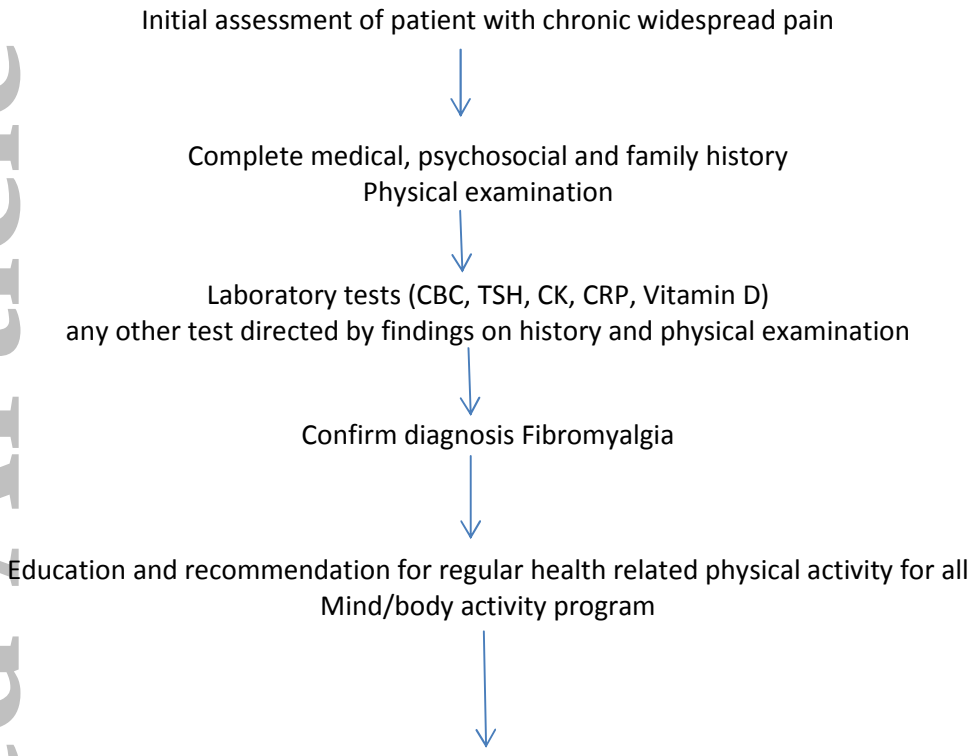

Pain	Sleep disturbance	Mood disturbance	Fatigue	Impaired function
Simple analgesic, acetaminophen	Sleep hygiene	Aerobic exercise	Address sleep problems	Multimodal therapy
Tricyclic agent, amitriptyline	Tricyclic agent, amitriptyline	Mental health specialist	Physical activity	Rehabilitation program
Gabapentinoid, pregabalin	Gabapentinoid, pregabalin	Psychological therapies, e.g. CBT	Psychological therapies, e.g. CBT	
SNRI, duloxetine, milnacipran	Cyclobenzaprine	SNRI duloxetine, milnacipran	SNRI, duloxetine, milnacipran	
		SSRI, fluoxetine, paroxetine		

CBC=complete blood count, TSH= thyroid stimulating hormone, CK=creatine kinase, CRP=C-reactive protein, SNRI=serotonin norepinephrine reuptake inhibitor, CBT=cognitive behavioural therapy, SSRI=selective serotonin reuptake inhibitor.

Figure 1. Algorithm for Fibromyalgia care