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Patients with refractory musculoskeletal pain syndromes undergoing a multimodal assessment and therapy programme: a cross-sectional study

Tiffany Prétat[a], Thomas Hügle[a], Johanna Mettler[a], Marc Suter[b], Sandy Jean Scherb[b], Reine-Laure Taily[a], Charlotte Hans[a], Marielle Hoarau[c], Laurent Monod[d], Pierre Frossard[a], Sonia Turchi[e], Guillaume Marillier[f], Nastasya Delavignette[f], Marc Blanchard[a], Antonio Le Thanh[f], Pedro Ming Azevedo[a]

[a] Department of Rheumatology, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[b] Pain Center, Department of Anesthesiology, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[c] Musculoskeletal department, Chiropractic Unit, University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[d] School of Health Sciences Fribourg (HEdS-FR), HES-SO University of Applied Sciences and Arts Western, Fribourg, Switzerland
[e] Musculoskeletal department, Occupational therapy Unit, University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[f] Department of Psychiatry, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

Summary

BACKGROUND: Chronic musculoskeletal pain syndromes, including fibromyalgia, are heterogeneous entities with a major socioeconomic burden. Multimodal treatment programmes have shown greater efficacy than conventional approaches for these patients, at least in the short term. A profound understanding of chronic musculoskeletal pain syndrome patients treated in multimodal treatment programmes is important for their development and to provide insight into these conditions.

AIM: To provide a comprehensive and objective description of medical, psychosocial and sleep characteristics of the treatment-refractory chronic musculoskeletal pain syndrome patients treated at the multimodal treatment programmes provided by our tertiary service in Switzerland.

METHODS: This was a cross-sectional analysis of 202 refractory chronic musculoskeletal pain syndrome patients with or without a concomitant autoimmune disorder hospitalised between 2018 and 2022 in a 12-day Swiss multimodal treatment programme. They underwent a comprehensive self-assessment with eight different questionnaires and assessments by a psychiatrist, rheumatologist, pain specialist, occupational therapist and physiotherapist. Sleep assessment was performed via actigraphy. Clinical and demographic variables were selected by consensus of three experienced rheumatologists and chronic pain specialists. The Fibromyalgia Rapid Screening Test (FiRST), American College of Rheumatology (ACR)-2010 criteria (ACR2010) and Toronto Alexithymia Scale-20 (TAS-20) were also applied.

RESULTS: The mean age of the patients was 47 years (SD = 10), 73% were female, and 30% were obese. Half (50%) were not from Switzerland, and 12% came from conflict zones. Almost half (40%) lived alone. Back pain was the principal site (90%). Of the patients, 78% fulfilled the ACR2010 criteria for fibromyalgia, and 17% were diagnosed with an underlying immune-mediated disorder, mostly spondylarthritis. Pain since childhood occurred in 45% of the patients, and 68% had pain since adolescence. Disability financial aid had been pursued by 69%, and 46% were still awaiting a response. Psychiatric comorbidities were highly prevalent (73%), of which 56% consisted of depression. Of all patients, 15% were diagnosed with enduring personality changes after a catastrophic experience (EPCACE), and 10% had post-traumatic stress disorder. Alexithymia affected 34% of patients. Objective sleep disorder was observed in 78% of patients, and 41% were under opioid therapy.

CONCLUSION: This analysis reveals the complex psychosomatic and socioeconomic patterns of the patients treated in Switzerland with refractory chronic musculoskeletal pain syndromes, often originating in childhood and adolescence. Obesity, immigration, social isolation, psychiatric comorbidities, sleep deprivation and opiate use, among others, stood out as target characteristics for further research.

Dr. Pedro Ming Azevedo
Department of Rheumatology
University Hospital Lausanne (CHUV)
CH-1011 Lausanne
pedro.ming-azevedo[at]chuv.ch

Introduction

Chronic pain is the leading cause of years lived with disability in the world [1] and the leading reason for seeking medical help in the United States [2]. It can have a profound impact on individuals' quality of life, leading to depression, anxiety, social isolation and reduced function. Chronic pain can also impose a significant economic burden. Studies in the United States have estimated the annual cost of chronic pain to be in the range of $560 to $635 billion, with a substantial portion attributed to indirect costs such as lost productivity and disability [3]. Additionally, chronic pain is associated with higher healthcare costs, including increased use of medications, hospitalisation and outpatient consultations [4]. It is a major problem in Switzerland as it is worldwide. In 2006, a European telephonic survey found that 16% of Swiss participants had chronic musculoskeletal pain syndromes (CMPS), of

which 32% were reported as severe. Most participants (54%) thought that their pain was inadequately controlled, with direct consequences on their quality of life, work and social life [5].

The impact of chronic pain highlights the need for effective prevention and management strategies to reduce the burden on individuals and society. The effectiveness of interventions may vary depending on the underlying cause and characteristics of the pain, making personalised treatment plans essential [6]. Despite uncertainties about optimal treatment, the need for a personalised and multidisciplinary approach is a consensus. In this context, multimodal treatment programmes (MMPs) emerge as the most effective intervention, at least in the short term [7–9]. Significant benefits of multicomponent treatment have been documented in a meta-analysis [9], and multimodal programmes are proposed in most guidelines for resistant cases [10, 11].

Since 2018, the department of rheumatology of our institution (Centre Hospitalier Universitaire [CHUV], Lausanne, Switzerland) has provided a multimodal treatment programme for patients with chronic pain and fatigue syndromes. This 2-week inpatient programme includes patient evaluations by several health professionals, including rheumatologists, anaesthesiologists, physiotherapists, occupational therapists, chiropractors, osteopaths and psychiatrists. It aims to rediscuss the diagnoses, build an overall action plan for the patient and find solutions concerning health insurance-related issues.

Multimodal programmes are implemented globally, yet no agreed best approach exists for individual patients. Understanding the typical profiles of patients who attend these programmes is crucial to effectively customising care, optimising both the costs and benefits of these interventions.

The present work is part of a larger research project aimed at optimising the effectiveness and cost-effectiveness of the multimodal treatment programme provided by our institution for chronic pain syndromes. The priorities of the project are defining and investigating (a) the most relevant endpoints to be studied prospectively and (b) the clinical, social and psycho-behavioural characteristics that seem to influence such endpoints and can be used to separate patients in clusters.

Study aims

The study goal was to provide a comprehensive and objective description of medical, psychosocial and sleep characteristics of the treatment-refractory chronic musculoskeletal pain syndrome patients treated at the multimodal programme provided by our tertiary service in Switzerland.

Methods

This was a cross-sectional study involving 207 patients who completed the 2-week inpatient multimodal treatment programme for chronic musculoskeletal pain syndromes provided by CHUV from its beginning in March 2018 up to November 2022. The exclusion criteria for the study were refusing to sign the informed consent, failing to complete the multimodal treatment programme and missing data. The population targeted by the MMP consists of adult chronic musculoskeletal pain syndrome and chronic fatigue syndrome patients who have failed ambulatory treatment and are therefore sent to this tertiary university MMP by their physicians in secondary or primary care. The inclusion criteria are age between 18 and 70 years and the ability to fluently speak French. The exclusion criteria for the MMP are the existence of cognitive, physical, cultural or psychiatric difficulties that prevent patients from understanding or adhering to MMP procedures. We estimate that one in every five patients sent to a pre-MMP consultation is excluded because of these criteria.

Clinical questionnaires

The questionnaires used were chosen beforehand by a group of physician specialists in the treatment of chronic musculoskeletal pain syndromes when designing the multimodal treatment programme. The questionnaires are the validated and traditionally used French versions for patients with chronic pain. They assess various aspects of these conditions, including cognitive-behavioural factors (kinesiophobia, catastrophism, avoidance beliefs regarding work and physical activity, and patterns of activities), emotional distress (anxiety and depression), physical functioning and pain severity.

Patients were asked to complete the clinical questionnaires at the start of hospitalisation and before discharge. The questionnaires were completed online using secure software (REDCap®), and patients' identities were replaced by a security code. Access to the questionnaires was given to patients 3 days before hospitalisation. Patients who did not complete the electronic forms alone did so with assistance at entry and discharge.

Evaluation of cognitive-behavioural factors

Kinesiophobia

The Tampa Scale for Kinesiophobia (TSK) is a psychological assessment tool used to measure kinesiophobia, or fear of movement, through 17 items that gauge participants' feelings about pain and movement. Commonly used in clinical settings, the TSK helps determine how fear influences a patient's avoidance of physical activity, guiding treatment strategies and interventions [12].

Catastrophism

The Pain Catastrophizing Scale (PCS) is a psychological tool used to measure an individual's tendency to catastrophise pain, a process where pain is anticipated or experienced with exaggerated negative mental responses. The PCS evaluates thoughts and feelings about pain across three dimensions: rumination, magnification and helplessness. Widely used in both clinical and research settings, the PCS helps assess the impact of pain catastrophising on pain experiences and outcomes, especially in managing chronic pain [13].

Avoidance beliefs regarding work and physical activity

The Fear-Avoidance Beliefs Questionnaire (FABQ) is a tool designed to evaluate individuals' beliefs about how physical activity and work might cause or worsen pain. It is frequently used to understand how these beliefs contribute

to the avoidance of physical activity and the resulting disability in chronic pain conditions [14].

Patterns of activities

The Patterns of Activity Measure (POAM) questionnaire is designed to evaluate daily activity behaviours in individuals with chronic pain. It identifies three main behavioural strategies: pacing (POAM-P), which is adaptive, and avoidance (POAM-A) and overdoing (POAM-O), which are often maladaptive and linked to the development and persistence of chronic pain. The POAM-A measures the extent to which individuals avoid activities due to fear of pain or re-injury. The POAM-O assesses how individuals exceed their physical limits during activities, often ignoring pain signals, which may lead to increased pain and a cycle of overactivity followed by enforced rest [15].

Evaluation of emotional distress

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is a common screening tool used to detect potential anxiety disorders and depression. It is especially valuable for assessing patients with ongoing physical discomfort, such as chronic musculoskeletal pain syndromes [16].

Evaluation of pain severity, physical functioning and quality of life

The Brief Pain Inventory (BPI) is a standardised tool often used to measure pain severity and its effects on daily activities in individuals with chronic pain. The BPI-Severity (BPI-S) section has patients rate their pain from 0 (no pain) to 10 (worst pain imaginable), and the BPI-Impact (BPI-I) section assesses how pain affects aspects of daily life such as general activity, mood, mobility, work, social interactions, sleep and enjoyment of life. In the study's longitudinal component, not discussed in this paper, BPI-Impact variation was selected as the primary outcome for multimodal treatment programmes, with other questionnaires serving as secondary measures [17].

Clinical and demographic variables

Three experienced rheumatologists and chronic pain specialists selected clinical and demographic variables to understand chronic musculoskeletal pain syndromes and patient treatment responses. These included demographics (age, sex, origin, family status, disability insurance), BMI, clinical and psychiatric diagnoses, comorbidities, pain types (nociceptive, nociplastic, neuropathic), sleep patterns (assessed over 5 nights with actigraphy), medication use and lab results. Details on the variables chosen and their definitions are shown in tables S1 to S4 (see appendix).

"Fibromyalginess", the extent of central fibromyalgia features, was evaluated using the ACR 2010 and FiRST criteria. Alexithymia was assessed with the TAS-20 scale and two psychiatric evaluations.

Data analysis

Measures of central tendency and dispersion were assessed for all numerical data. The mean and standard deviation (SD) are shown for variables with approximately normal distribution. The median, mode and range are shown where the distribution was not normal. Normality was evaluated with normal probability plots. To account for missing data, we used proportions to make the different clinical variables comparable, while systematically specifying the total number of non-missing data.

The data were analysed with Microsoft Office Excel 2019 and Stata/MP 13.

Ethics approval

Ethics approval was granted by the Commission Cantonale d'Éthique de la Recherche sur l'Être Humain (CER-VD) on 06 December 2021 (Project ID 2021-00853). Some of the patients signed a specific informed consent form for this research, and all signed the hospital's general consent form, allowing the use of their clinical and epidemiological data as long as their identity was kept secret. The study was performed without a preregistered protocol.

Results

Demographic data

Two hundred and seven patients initially participated in the study, but 5 were excluded – 3 for not completing the multimodal treatment programme and two for not completing the questionnaires – leaving a final sample of 202 patients. The sample comprised 73% women and 27% men, with an average age of 47 years, ranging from 23 to 74 years (figure 1). Demographic details are available in table S1.

The country of origin was identified for 94% (190/202) of the patients, with distributions depicted in figure 1. Regarding living arrangements, around 60% of patients lived with a partner (57% women, 67% men), and the majority (68%) had children. Disability insurance status, reported by 98% of patients, showed that 69% had applied for it, 13% had been granted, 8% were denied and 45% were awaiting for a decision (figure 1).

Clinical characteristics

The clinical characteristics of patients are represented in tables 1 and 2.

Body Mass Index and main clinical comorbidities

The overweight and obese categories accounted for 33% and 30% of the patients, respectively. Four and a half per cent of the patients were underweight. The main comorbidities observed included sleep obstructive apnoea (9.4%), chronic obstructive pulmonary disease (3%), asthma (9%), diabetes (6%) and microcrystalline disease (3%).

Pain characterisation and diagnosis

The vast majority of patients reported back pain. The lumbar region was painful for 82% of all patients. Cervical pain affected 67% of patients. Axial pain was considered to have a nociplastic component in 65% (pain characteristics could not be attributed to a neuropathic or nociceptive process). Nevertheless, the Waddell score (proposed as a

marker of "non-organic" pain) showed a median of 1 for all patients.

The characterisation of peripheral pain sites led to too many variables of questionable importance and was abandoned. Shoulder pain was retained because it was a frequent complaint (reported by 45% of all patients) that can be associated with neck pain and biomechanical processes. Nociplastic pain was the most represented type of peripheral pain, diagnosed in 75% of all patients (82% of women and 56% of men). Fibromyalgia, based on the 2010 ACR and FiRST criteria, was present in 78% and 81% of patients, respectively. Peripheral nociceptive pain was prevalent among 61% of all patients. Peripheral osteoarthritis was observed in 28% of patients (32% of women and 17% of men). Tendinopathy was present in 37% of patients. Peripheral neuropathy was reported by 20% of all patients. Inflammatory pain was rare.

A detailed personal pain history was collected from 2021 onwards. In 45% of the investigated cases (n = 86, representing 43% of the total sample), persistent or recurrent pain was reported in childhood, and in 68.2%, from adolescence. All patients experiencing pain in childhood also reported pain in adolescence, and 40% of the latter did not recall pain in childhood.

Among the entire sample, 34% of patients received a diagnosis implicating an intrinsic biomechanical mechanism (36% of women and 26% of men).

Clinically diagnosed hypermobility was present in 27.6% of patients for whom data were available (33% of women and 14% of men). Beighton scores were measured in 101

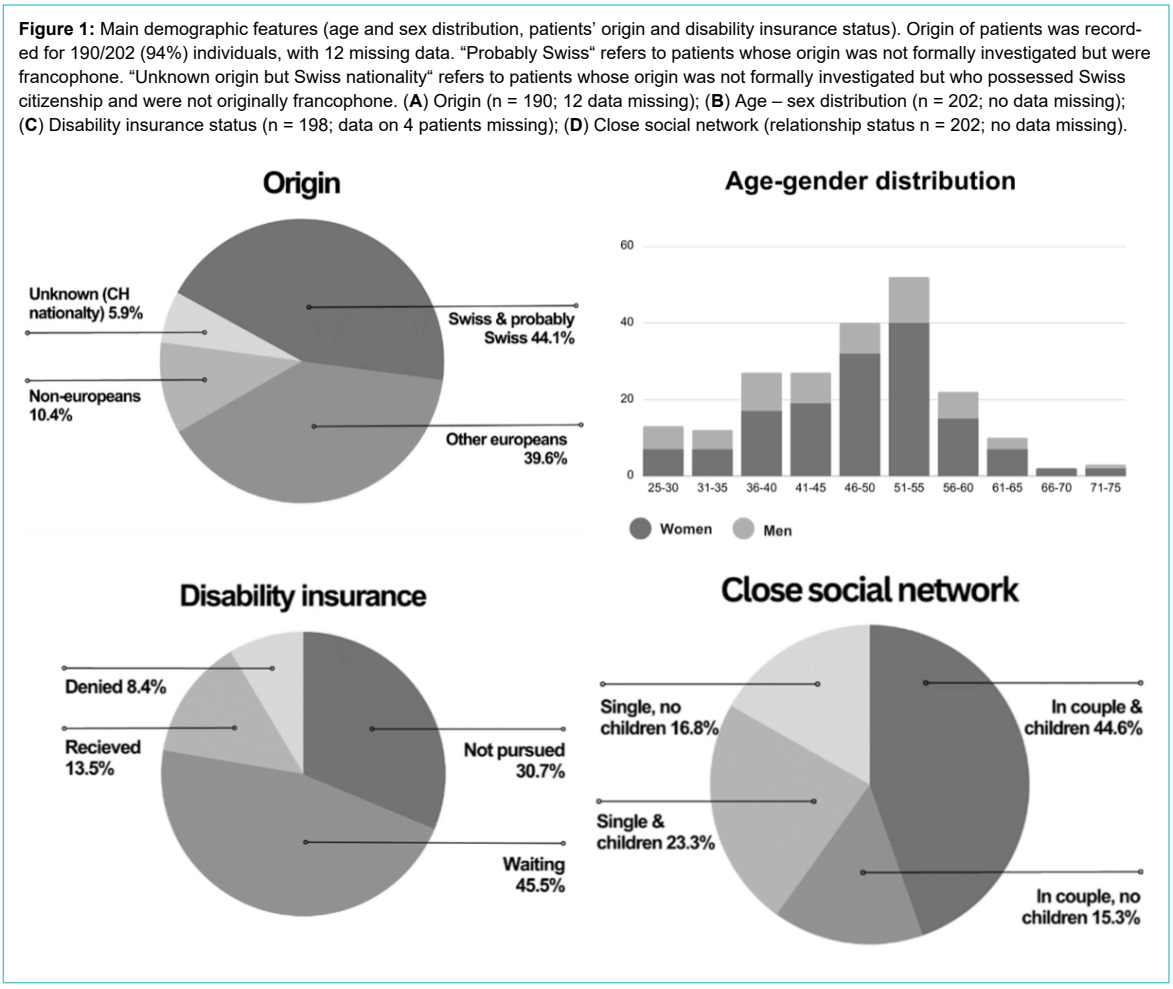

Figure 1: Main demographic features (age and sex distribution, patients' origin and disability insurance status). Origin of patients was recorded for 190/202 (94%) individuals, with 12 missing data. "Probably Swiss" refers to patients whose origin was not formally investigated but were francophone. "Unknown origin but Swiss nationality" refers to patients whose origin was not formally investigated but who possessed Swiss citizenship and were not originally francophone. (**A**) Origin (n = 190; 12 data missing); (**B**) Age – sex distribution (n = 202; no data missing); (**C**) Disability insurance status (n = 198; data on 4 patients missing); (**D**) Close social network (relationship status n = 202; no data missing).

Table 1:
Patients' body mass index (BMI) and main clinical comorbidities. Missing data is indicated where the total number is different from 202.

Clinical characteristic		All patients	Women	Men
Weight	BMI	Median = 27, mode = 25, range: 16.3–50	Median = 27.5, mode = 25, range: 16.3–46.9	Median = 26.2, mode = 28.4, range: 16.5–50
	Underweight: n/total (%)	7/158 (4%)	5/115 (4%)	2/43 (4%)
	Healthy weight: n/total (%)	49/158 (31%)	35/115 (30%)	14/43 (33%)
	Overweight: n/total (%)	53/158 (33%)	35/115 (30%)	18/43 (423%)
	Obese: n/total (%)	48/158 (30%)	39/115 (34%)	9/43 (21%)
Main comorbidities n/total (%)	Obstructive sleep apnoea: n, total (%)	19/202 (9%)	11/148 (7%)	8/54 (15%)
	COPD: n, total (%)	6/202 (3%)	2/148 (1%)	4/54 (7%)
	Asthma: n, total (%)	18, 202 (9%)	12, 148 (8%)	6, 54 (11%)
	Diabetes: n, total (%)	12, 202 (6%)	9, 148 (6%)	3, 54 (6%)

patients, with a median of 2. When patients were diagnosed with hypermobility, the median score was 6 for women and 4 for men.

Autoimmune rheumatic diseases at entry to the programme were reported by 22% of the total sample, but this diagnosis was not confirmed by our investigation in 23% of cases. Active peripheral autoimmune inflammation was present in 6% of all patients.

Psychiatric comorbidities

The psychiatric comorbidities of patients are detailed in table 3.

Among all patients, 73% had at least one psychiatric disorder.

Clinically diagnosed depression was observed in 56% of all patients, with a comparable prevalence between genders. According to the HDS, depression affected 39% of patients (38% of women and 41% of men).

Clinically diagnosed anxiety was found in 31% of all patients, evenly distributed between genders. Additionally, 57.5% of all patients had a high anxiety score, with a HAS of >10 (54% of women and 67% of men).

Post-traumatic stress disorder (PTSD) was found in 10% of patients (11% of women and 6% of men), with enduring personality changes after a catastrophic experience (EPCACE) in 15% (18% of women and 9% of men). Most (85%) post-traumatic stress disorder patients had concomitant enduring personality changes after a catastrophic experience, and 85% were Europeans, including 60% Swiss patients. Twenty per cent of post-traumatic stress disorder patients came from conflict zones. Conversely, 8% of patients coming from a conflict zone demonstrated post-traumatic stress disorder. Eighty-four per cent of patients with enduring personality changes after a catastrophic experience were Europeans, including 45% Swiss patients. Approximately one third originated from a conflict zone. Conversely, 21% of patients coming from a conflict zone demonstrated enduring personality changes after a catastrophic experience.

Clinical alexithymia was present in 34% of all patients (32% of women and 41% of men). Alexithymia can be assessed through the TAS-20 score; 15% of the sample completed this, of whom 30% had a score of ≥61 (probable alexithymia).

Medications

Medication details are provided in table 4.

The most used medications were non-opioid analgesics such as paracetamol and metamizole (64%), followed by

Table 2:
Pain characterisation and diagnosis. Missing data is indicated where the total number is different from 202.

Clinical characteristic				All patients	Women	Men
				n/total (%)	n/total (%)	n/total (%)
Pain site	Back pain	Any back pain		182/202 (90%)	135/148 (91%)	47/54 (87%)
		Buttock		65/202 (32%)	50/148 (34%)	15/54 (28%)
		Lumbar		166/202 (82%)	128/148 (86%)	38/54 (70%)
		Dorsal		63/202 (31%)	51/148 (3%)	12/54 (22%)
	Cervical pain			136/202 (67%)	105/148 (71%)	31/54 (57%)
	Shoulder pain			92/202 (45%)	69/148 (47%)	23/54 (43%)
Pain type	Peripheral	Nociplastic		152/202 (75%)	122/148 (83%)	30/54 (56%)
		Nociceptive	Mechanical	124/202 (61%)	91/148 (61%)	33/54 (61%)
			Inflammatory	12/202 (6%)	7/148 (5%)	5/54 (9%)
		Neuropathic		40/202 (20%)	29/148 (20%)	11/54 (20%)
	Axial	Nociplastic (functional) component	Clinical diagnosis	131/202 (65%)	100/148 (68%)	31/54 (57%)
			Waddell score	n = 84 (42%), mode = 1, SD = 1.5	n = 65 (43%), mode = 1.5, SD = 2	n = 19 (35%), mode = 1, SD = 1.6
		Nociceptive	Mechanical	139/202 (69%)	108/148 (73%)	31/54 (57%)
			Inflammatory	8/202 (4%)	4/148 (3%)	4/54 (7%)
		Neuropathic (radiculopathy)		34/202 (17%)	19/148 (13%)	15/54 (28%)
Pain history	Pain in childhood			39/86 (45%)	32/70 (46%)	7/16 (44%)
	Pain in adolescence			58/85 (68%)	52/71 (73%)	6/14 (43%)
	Pain in adolescence but not childhood			23/58 (40%)	21/52 (40%)	2/5 (40%)
Biomechanical disorders				68/202 (34%)	54/148 (36%)	14/54 (26%)
Spine surgery >1				14/100 (14%)	9/75 (12%)	5/25 (20%)
Hypermobility		Clinical diagnosis		50/181 (28%)	43/130 (33%)	7/51 (14%)
		Abnormal Beighton score		n = 40, median = 6, mode = 7, range: 0–9	n = 33, median = 6, mode = 7, range: 1–9	n = 7, median = 4, mode = 4, range: 0–7
Clinical diagnosis associated with peripheral pain		Autoimmune rheumatic diseases		34/202 (17%)	25/148 (17%)	9/54 (17%)
		Significant osteoarthritis		57/202 (28%)	48/148 (32%)	9/54 (17%)
		Bursitis		12/202 (6%)	11/148 (7%)	1/54 (2%)
		Enthesopathy		53/202 (26%)	37/148 (25%)	16/54 (30%)
		Tendinopathy		62/202 (37%)	46/148 (31%)	16/54 (30%)
		Microcrystalline disease		7/202 (3%)	7/148 (5%)	0/54 (0%)
		Fibromyalgia	FM ACR 2010 fulfilled	36/46 (78%)	29/36 (81%)	7/10 (70%)
			FM FiRST criteria fulfilled	47/58 (81%)	38/47 (81%)	9/11 (82%)

NSAIDs (56%). A total of 41% were taking opiates, with 4% taking strong opiates.

Laboratory results

Details of laboratory results can be found in supplementary table S3.

The median C-reactive protein (CRP) level was 1 mmol/l (2 mmol/l women, 1 mmol/l men) with a range of 0 to 37. It was tested in approximately 69% of our sample, of which 14% showed higher than 5 mmol/l (the laboratory normality cutoff). The median sedimentation rate was 7 mm/h (11 mm/h in women, 4 mm/h in men) with a range from 1 to 63.

Sleep analysis

Details of the sleep analysis can be found in supplementary table S4.

The median total sleep time was 7 hours and 44 minutes (07:44), with a range of 04:39–11:14. When considering sleep efficacy (percentage of time spent asleep), 47% of the patients had an efficacy below the cutoff of 85%.

Regarding the sleep fragmentation index, 78% of patients showed a value greater than the cutoff of 20, indicating regular sleep interruptions. The overall percentage of individuals with a delayed sleep phase (defined as turning off the lights after midnight) was 21%.

Discussion

We present here a detailed panel of the clinical, psychiatric and epidemiological characteristics of patients with refractory chronic musculoskeletal pain syndromes seen in tertiary centres in French Switzerland. This characterisation is important because it provides insights allowing for possible improvements in the treatment and prevention of such cases.

Table 3:
Psychiatric comorbidities.

Psychiatric comorbidity			All patients	Women	Men
			n/total (%)	n/total (%)	n/total (%)
At least one psychiatric disorder			147/202 (73%)	108/148 (73%)	41/54 (76%)
Depression	Clinically diagnosed		114/202 (56%)	84/148 (57%)	30/54 (56%)
	HDS 10		75/194 (39%)	55/145 (38%)	20/49 (41%)
Anxiety	Clinically diagnosed		62/202 (31%)	45/148 (30%)	17/54 (31%)
	HAS >10		111/193 (57%)	78/144 (54%)	33/49 (67%)
Post-traumatic stress disorder			20/202 (10%)	17/148 (11%)	3/54 (6%)
Enduring personality change after disaster experience			31/202 (15%)	26/148 (18%)	5/54 (9%)
Alexithymia	Clinical diagnosis		69/202 (34%)	47/148 (32%)	22/54 (41%)
	TAS-20	TAS-20 total:	n = 30 (15%), mean = 53.5, SD = 16, range: 31–82	n = 24 (16%), mean = 53.7, SD = 16.9, range: 31–82	n = 6 (11%), mean = 52.5, SD = 13.4, range: 38–72
		TAS-20 ≥52	17/30 (57%)	14/24 (58%)	3/6 (50%)
		TAS-20 >60	9/30 (30%)	8/24 (33%)	1/6 (17%)
Personality disorder			54/202 (27%)	42/148 (28%)	12/54 (22%)
Bipolar disorder			7/202 (3%)	4/148 (3%)	3/54 (6%)

HDS: Hospital Depression Scale; HAS: Hospital Anxiety Scale; TAS-20 ≥52: possible alexithymia; TAS-20 >60: probable alexithymia.

Table 4:
Medications.

Medication		All patients	Women	Men
		n/total (%)	n/total (%)	n/total (%)
Opiates	Total	83/202 (41%)	62/148 (42%)	21/54 (39%)
	Strong	28/202 (14%)	22/148 (15%)	6/54 (11%)
	Weak	55/202 (27%)	40/148 (27%)	15/54 (28%)
Antidepressants (AD)	Total	95/202 (47%)	77/148 (52%)	18/54 (33%)
	Tricyclic or tetracyclic	22/202 (11%)	15/148 (10%)	7/54 (13%)
	Dual	31/202 (15%)	27/148 (18%)	4/54 (7%)
	Vilazodone	5/202 (2%)	4/148 (3%)	1/54 (2%)
	Mirtazapine	2/202 (1%)	2/148 (1%)	0/54 (0%)
	Trazodone	23/202 (11%)	20/148 (13%)	3/54 (6%)
Gabapentinoid drugs		37/202 (18%)	25/148 (17%)	12/54 (22%)
Anti-seizure medication (ASM)		8/202 (4%)	7/148 (5%)	1/54 (2%)
Neuroleptics		12/202 (6%)	11/148 (7%)	1/54 (2%)
Benzodiazepines		59/202 (29%)	46/148 (31%)	13/54 (24%)
Nonbenzodiazepines (Z-drugs)		26/202 (13%)	20/148 (13%)	6/54 (11%)
Nonsteroidal anti-inflammatory drugs (NSAIDs)		113/202 (56%)	82/148 (55%)	31/54 (57%)
Paracetamol/metamizole		130/202 (64%)	90/148 (61%)	40 54 (74%)
Myorelaxants		28/202 (14%)	21/148 (14%)	7/54 (13%)
Cannabidiol (CBD)		3/202 (1%)	0/70 (0%)	3/25 (12%)
Prednisone		9/202 (4%)	8/148 (5%)	1/54 (2%)
Biologics		10/202 (5%)	8/148 (5%)	2/54 (4%)

In 2019, a study measured the effects of a Swiss multimodal treatment programme aimed at improving chronic pain among Italian- or German-speaking patients [18]. Despite similar average ages and sex distributions across their cohort and our French-speaking population, social networks varied. Specifically, 17% of our patients were single and without children, compared to 22–27% of German speakers and 3–12% of Italian speakers. Additionally, 36–66% of German-speaking patients were unemployed, and 28–43% were working part-time. For Italian-speaking patients, 68–80% were unemployed, and 14–23% worked part-time. We did not directly measure the employment rate, but we were interested in the need to resort to disability insurance, which indirectly indicates difficulties in maintaining full-time employment. This concerned 69% of our population, which is then closer to the Italian cohort in this matter. The authors of that study only reported the number of comorbidities of their patients, ranging from 0 to >6, and did not characterise the pain types and mechanisms, nor patient behavioural, psychiatric or sleep characteristics. We believe that a need exists to specify and list these aspects as objectively and exhaustively as possible to better understand these complex patients.

Socioeconomic characteristics

We highlight the relatively young age of our patients, the predominance of women, the higher proportion of patients living alone, and the high proportion of immigrants and obesity.

The young age of our patients is partially related to the programme's age limits (18 to 70 years). Nevertheless, the distribution curve was close to normal, with no tendency to deviate towards older ages, which suggests a low influence of selection bias on this result. The peak incidence was concentrated between the ages of 45 and 55 years. The reasons for this are unclear. Menopause and perimenopause are probably factors associated with this phenomenon, but the same distribution was observed in men. Interestingly, 33% (n = 67) of our patients showed a predominant "overdoing" behavioural response profile (POAM-O). It could be argued that this adaptive strategy fails around the age of 45 years, when physical endurance begins to diminish. The need for performance, however, continues to be demanded by society and the patients themselves, which leads to crisis.

The female predominance is not a surprise. Around half of chronic pain conditions are more common in women, including fibromyalgia, with only 20% having a higher prevalence in men [19]. This reinforces that women are more exposed and should be a priority target for prevention.

The sample demonstrated a high proportion of patients living alone. Based on 2018 data from the SFSO [20],approximately 17% of women and 16% of men aged 34–54 years in Switzerland are single. In comparison, 36% of patients for the same age group in our sample were single. Nevertheless, our patients had children more often than the paired population in Switzerland (88% versus 75% in the 50–59 years age group) [21]. Higher singlehood levels coupled with more children might suggest a higher rate of divorce or single parenthood. Furthermore, a lower education level is linked to having more children, especially for women [22].

Social isolation in chronic pain is multifactorial. Mobility restrictions limit social interactions, as do the disbelief and stigmatisation of chronic pain patients [23]. High rates of fatigue, depression and other psychiatric conditions likewise play a role. If chronic pain triggers isolation, isolation might also be a risk factor for chronic pain [24, 25]. One benefit of the in-hospital multimodal treatment programme is that it enables patients to bond over shared experiences and offer each other support. Additionally, the inpatient setting isolates patients from their normal environments, which often contribute to their conditions, facilitating behavioural and social change. Furthermore, this setting generally allows for extended screening time, giving healthcare providers better opportunities to monitor progress, conduct diagnostic tests and tailor treatments accordingly.

At least 56% of patients were not originally from Switzerland, a higher proportion than that found in the population of Lausanne (estimated at 43% in 2019). The excess could be attributed to immigration stress, adaptation difficulties and economic factors. The living conditions before immigration are an issue, of course. Accordingly, 12% of the sample came from conflict areas. Nevertheless, post-traumatic stress disorder and enduring personality changes after a catastrophic experience were not more prevalent among war refugees and immigrants than among Swiss patients.

We observed a higher prevalence of obesity compared to the general Swiss population. According to a 2017 report by the Swiss Federal Statistical Office (SFSO) [26], 11% of women and 13% of men in the 35–54 years age range in Switzerland are obese, against29% of women and 21% of men with this age in our sample. The link between socioeconomic status, obesity and chronic pain is well established [27]: a low socioeconomic status is associated with a higher risk of developing chronic pain, and it is also associated with a higher risk of obesity [28]. This seems to be especially true for women living in high-income countries [29].

Psychiatric features

Approximately 73% of patients had at least one psychiatric disorder, and a notably high proportion was affected by post-traumatic stress disorder and enduring personality changes after a catastrophic experience. The latter diagnoses were more prevalent among women, which could be explained by the common presence of domestic violence and sexual abuse [30]. Notably, patients from territories in conflict did not show higher proportions of post-traumatic stress disorder or enduring personality changes after a catastrophic experience, and at least half of the patients with these diagnoses were from Switzerland.

Irrespective of sex, 56% of patients presented clinically diagnosed depression. However, when assessed using the HDS, depression was reported in 38% of women and 41% of men. A potential gender bias in the HDS assessment has been recognised, with several studies tackling this topic [31, 32].

Similarly, anxiety disorders were clinically diagnosed in 31% of the sample and evenly distributed between gen-

ders. Nonetheless, 54% of women and 67% of men were considered anxious according to the HAS. We conclude that, as for the HDS, the HAS seems to be more useful as a monitoring tool than a diagnostic one. Further research is needed to assess the ideal HAS cutoff, as well as gendered tendencies for the chronic musculoskeletal pain syndrome population.

Alexithymia, defined by difficulties in identifying and expressing emotions, was also a prevalent disorder, with a higher prevalence among men. Meta-analysis findings have indicated that chronic pain samples had significantly higher mean alexithymia scores compared with controls. In chronic musculoskeletal pain syndromes, alexithymia was significantly positively associated with anxiety, depression, pain intensity and interference, although the latter relationships may be accounted for by negative affect [33]. Only 30 patients answered the TAS-20 that was introduced later in the programme. All nine patients with TAS-20 scores of >60 were diagnosed with alexithymia, but 15 alexithymic patients had a TAS-20 of ≤60. In conclusion, the positive predictive value for this test seems to be good for this cutoff but at the expense of a poor negative predictive value.

Clinical characteristics

Among the clinical characteristics presented by this population, some stand out for their high incidence or for suggesting pathophysiological mechanisms, including the presence of peripheral arthritis, pain since childhood or adolescence, the use of opioids, the presence of fibromyalgia, the presence of sleep disorders and the coexistence of autoimmune rheumatic diseases.

Twenty-eight per cent of our sample had clinically significant peripheral osteoarthritis. Age, weight, hypermobility and biomechanical disorders are among the known causes of osteoarthritis. The mean age of patients diagnosed with osteoarthritis was 51 years, 29% were overweight, 38.2% were obese, 32% were diagnosed with hypermobility and 42% were classified as having a biomechanical disorder. In comparison, the entire sample was younger on average and displayed lower rates of each of these factors.

Remarkably, almost half of the patients had experienced pain since childhood or adolescence. Evidence suggests that chronic pain in childhood is likely to continue in adulthood, with more risk of depression, anxiety or opioid misuse [34, 35]. In our sample, the proportion of opiate usage between all patients (41%) and patients with pain since childhood or adolescence was similar (36%). A chi-square test did not reveal any significant association between the two conditions, nor with depression or anxiety. Nevertheless, we found a significant association between pain impact (according to the BPI) and the presence of pain since childhood or adolescence ($p = 0.034$) but not with pain severity ($p = 0.097$). Musculoskeletal pain in children and adolescents may be a highly underestimated problem,and questions remain about its causes and whether early intervention could help prevent the development of chronic pain [36].

Evidence suggests that long-term opiates do not improve the quality of life for patients with chronic musculoskeletal pain syndromes, while posing risks of addiction, opiate-induced hyperalgesia, myocardial infarction and fractures [37, 38]. Despite recommendations, 40.9% of our patients reported the use of these medications. Opioid consumption is increasing worldwide, and Switzerland ranked second in 2019 in terms of opioid use per habitant [39].

Fibromyalgia was formally tested in only 29% of the patients. Nevertheless, it was diagnosed in 78% of patients tested with the ACR 2010 criteria and in 81% of patients tested with the FiRST criteria. Most patients tested by both (92%) fulfilled both tests. Studies directly comparing the 2010 ACR criteria and FiRST are scarce, but sensitivities of 83% and 74% were found when using the modified 2010 ACR criteria and FiRST compared to the 1990 criteria, respectively [40, 41]. Fibromyalgia as a diagnosis has been criticised as artificial and not anchored by pathophysiology. The more recent concept of nociplasty is now largely accepted and better represents the increasingly understood pathophysiological mechanisms behind non-nociceptive and non-neurological pain [42]. By definition, fibromyalgia always implies peripheric nociplastic pain, but not all peripheral nociplastic pain is fibromyalgia. In our sample, 81% of patients considered to have peripheral nociplastic pain fulfilled the ACR 2010 criteria, and 88% fulfilled the FiRST criteria. Pure nociplastic pain was rare (only 7% of patients).

Many patients experienced fragmented sleep (78%), decreased sleep efficacy (47%) and sleep delay (20%). These results align with a recent systematic review and meta-analysis revealing that between 73% and 75% of patients with chronic pain experienced sleep disturbances [43]. The relationship between pain and sleep disorders is bidirectional, with each exacerbating the other [44]. This puts sleep as a priority target for future research and care management. Medications generally only offer partial relief and are not without side effects, especially with prolonged use. Non-pharmacological interventions exist, such as mindfulness, relaxation techniques, exercise and cognitive-behavioural therapy (CBT). More specifically, CBT approaches for insomnia, pain or both have shown good efficacy [45].

In 23% of cases, the pre-multimodal treatment programme diagnosis of autoimmune rheumatic diseases was abandoned upon evaluation. This was primarily due to the confusion between fibromyalgia-induced allodynia and polyenthesopathy associated with spondylarthritis (SpA) or hypermobility, especially in post-menopause women. In total, 40% of hypermobile patients fulfilled either the 2010 ACR criteria or the FiRST criteria. Conversely, 25% of patients fulfilling the 2010 ACR criteria were hypermobile, compared to 31% for the FiRST.

Limitations

This study has several limitations. Firstly, data were missing for many variables collected later in the multimodal treatment programme history. The MMP protocol was improved over time, which explains why the first patients were not fully assessed. However, data were collected consecutively and consistently, so the partial results can be extrapolated to the entire sample.

Secondly, this cross-sectional study is subject to bias and imprecision in measurement. For instance, assessing pain

experienced during childhood relies on patients' recall and interpretation of early events in life. A huge effort was made to limit the impact of subjectivity by precisely defining each variable (table S2) and by addressing many variables through various means.

Thirdly, the population described here does not correspond to chronic musculoskeletal pain syndrome patients seen in outpatient clinics, which raises questions about how applicable our conclusions are to the majority of these patients.

Lastly, while this study acknowledges the presence of promising variables, it does not explicitly explore their impact on the efficacy of the multimodal treatment programme and pain outcomes. This limitation leaves room for future investigations.

Future research and improvements

This study is part of a larger effort to optimise multimodal programmes by prospectively identifying patients who best respond to the programme and its elements. Defining what "response" means is crucial because chronic musculoskeletal pain syndromes are complex and highly subjective. Although reducing pain intensity is important, this is not always achievable or the sole objective. Independently of pain, physical dysfunction, fatigue and mood, for instance, are important impediments to a normal life. Therefore, the characterisation of endpoints is fundamental. Additionally, the separation of patients in clusters is necessary to define the profiles prone to endpoint improvements. The definition of clusters begins with the definition of clinically significant variables, and the present study allows several insights.

Firstly, our findings highlight several key variables for future investigation, including obesity, social isolation, psychiatric comorbidities (depression, anxiety, post-traumatic stress disorder and enduring personality changes after a catastrophic experience, alexithymia), pain history, immigration, hypermobility and sleep quality. These may serve as both markers of progress and potential endpoints, alongside subjective patient evaluations. Objective measures such as mobility levels tracked via actigraphy should also be used in future research.

Secondly, subjective variables should be defined as objectively as possible and measured by more than one mean where possible. The present work shows that this is possible, if imperfect. Thirdly, the new classification of pain (nociplastic, nociceptive, neurologic) appears useful for research.

Our team acknowledges that the assessment of other important dimensions is lacking and should be developed in future analysis (e.g. intellectual and introspection capacity, autonomic nervous system status).

Conclusion

Obesity, living alone, psychiatric comorbidities, sleep deprivation and opiate misuse stood out as common characteristics. Half of the sample did not originate from Switzerland, and 12% originated from unstable conflictual regions, yet they were not more prone to post-traumatic stress disorder than Swiss patients. Additionally, many patients had experienced pain since childhood or adolescence, which suggests that chronic musculoskeletal pain syndromes are often rooted in early life experiences, with a significant effect on pain impact. Multimodal treatment programmes are recognised as an efficacious strategy to address chronic musculoskeletal pain syndromes, yet relevant endpoints still need to be defined and long-term outcomes must still be assessed. Moreover, a consensus on the optimal structure for multimodal treatment programmes is lacking.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: supplementary tables

Table S1:
Patients' socioeconomic variables.

Variable		All patients	Women	Men
Sex: n (%)		202 (100%)	148 (73%)	54 (27%)
Age		Mean = 47, SD = 10, mode = 48, range: 23–74	Mean = 48, SD = 9.1, 48, [27–73	Mean = 44.8, SD = 11.3, mode = 36, range: 22–73
Origin	Swiss (n/total, %)	89/202 (44%)	71/148 (48%)	18; 54 (33%)
	Unknown origin with Swiss nationality (n/total, %)	12/202 (6%)	7/148 (5%)	5/54 (9%)
	Other European countries (n/total, %)	80/202 (40%)	53/202 (26%)	27/202 (13%)
	Non-Europeans (n/total, %)	21/202 (10%)	17/148 (11%)	4/54 (7%)
	Conflict zones (n/total, %)	25/202 (12%)	15/148 (7%)	10/54 (18%)
Reported traumatic war experience (n/total, %)		6/27 (22%)	3/17 (18%)	3/10 (30%)
Living in couple (n/total, %)		121/202 (60%)	85/148 (57%)	36/54 (67%)
Having children (n/total, %)		137/202 (68%)	107/148 (72%)	30/54 (56%)
Disability insurance status (n = 198)	Not pursued (n/total, %)	62/198 (31%)	46/144 (32%)	16/54 (30%)
	Pursued (n/total, %)	136/198 (69%)	98/144 (68%)	38/54 (70%)
	Under consideration (n/total, %)	92/198 (45%)	64/144 (44%)	28/54 (52%)
	Received (n/total, %)	27/198 (13%)	22/144 (15%)	5/54 (9%)
	Denied (n/total, %)	17/198 (8%)	12/144 (8%)	5/54 (9%)
Time off work in years: median, mode, [range]		Median = 1.5, mode = 0, range: 0–30	Median = 1.1, mode = 0, range: 0–30	Median = 2, mode = 0, range: 0–13

Table S2:
Clinical variables studied and definitions.

Domain	Variable		Definition and measurement
Demographics	Age		Age in years at multimodal treatment programme admission.
	Sex		Only birth sex was computed (women and men).
	Relationship status		Choice between “in couple” or “not in couple”.
	Parenthood status		Choice between “having children“ or “not having children”.
	Disability status (DI) insurance		Choice between DI “received“, “denied“ or “under consideration“. “Received“ DI being rediscussed was considered “under consideration“.
	Time off work		Time in years from the moment patient lost or quit their job to the date of multimodal treatment programme admission. No distinction was made between whether the patient lost the job because of pain or not (impossible to differentiate in most cases).
Physical characteristics	BMI		This was tested as a continuous variable and as a categorical variable according to the World Health Organization (<18.5 = underweight, 18.5 to <25 = healthy, 25.0 to <30 = overweight, 30.0 or higher = obesity).
	Menopausal status		Women >55 years old were automatically considered menopaused, and those <40 years old were considered non-menopaused. FSH and oestrogen levels were tested between 40 and 55 years of age.
	Hypermobility		The Beighton score was tested as a continuous variable. However, the Beighton score highly disagreed with past diagnoses of hypermobility. Thus, patients were considered hypermobile if this diagnosis was previously made by a medical doctor or if they had a history of sprains and subluxations in childhood or adolescence and referred to themselves as more flexible than their peers then.
	Biomechanical disorders		Musculoskeletal disorders due to persistent biomechanical overload. This variable was considered present when the final diagnosis appointed this mechanism.
Comorbidities	Autoimmune rheumatism		Any previous diagnosis of autoimmune rheumatic condition, regardless of potential effect on pain. This included rheumatoid arthritis, Sjögren’s syndrome, lupus, undifferentiated connective tissue disease, and axial and peripheric spondylarthritis. At the entry, these conditions were considered “suspected“ and reclassified as “confirmed“ or “not confirmed“ after clinical investigation during hospitalisation.
	Peripheral significant osteoarthritis (OA)		Patients were considered to have significant peripheral OA when complaints of pain or physical limitation were attributed to non-spinal OA.
	Airway comorbidities		This included any previous diagnosis of COPD, asthma or emphysema (other diseases were absent in our sample).
	Metabolic disease		Including previous diagnosis of diabetes, asymptomatic high uric acid levels, gout, calcium pyrophosphate deposition disease, dyslipidaemia.
	Depression or anxiety		Hospital Anxiety Scale and Hospital Depression Scale were tested as a continuous or categorical variable (according to the official cutoff of 10 for these scales). The diagnosis for both conditions was determined by the MMP’s psychiatrists according to the DSM-5 definitions.
	Post-traumatic stress disorder and enduring personality changes after a catastrophic experience		The diagnosis for post-traumatic stress disorder and enduring personality changes after a catastrophic experience was determined by the MMP’s psychiatrists according to the DSM-5 and ICD-10 definitions (respectively).
	Other psychiatric conditions		Relevant disorders in this category included bipolar and personality disorders (DSM-5 definitions) and alexithymia. The diagnosis of these conditions was determined by the MMP’s psychiatrists. Alexithymia was also tested by the Toronto Alexithymia Scale-20 (TAS-20), which was tested as a continuous and categorical variable (according to the author’s guidelines). Whenever discordance existed between the TAS-20 diagnosis and the psychiatric diagnosis, the latter was considered correct.
Pain characterisation	Localisation	Back pain	Back pain corresponded to dorsal pain or lumbar pain. Cervical pain alone was not considered back pain.
		Peripheral pain	Pain was called “peripheral“ when it was not spinal, visceral or in the head. An attempt was made to pinpoint the source of pain (e.g. neuropathies, arthrosis, enthesopathies, bursitis, tendinopathies, arthritis).
	Types of pain		An effort was made to classify each referred pain into three categories: neuropathic (either radicular or peripheral), nociceptive and nociplastic pain. The latter was diagnosed when the pain itself, its characteristics or its intensity could not be attributed to a neuropathic or nociceptive process. “Functional“ pain was considered equal to nociplastic pain. These categories were not mutually exclusive.
	Pain in childhood and adolescence		Patients were questioned about recurrent or persistent pain in childhood and adolescence. All answers were noted, but only pain with significant functional impact (from the patient’s viewpoint) was counted for statistical analysis.
Medications	Opiates		Opiates were initially classified as “weak“ (tramadol, codeine and tapentadol) and “strong“ (all others) for future testing in outcome association studies. However, this subdivision is polemic and led to small N sizes in each group so all opioids were analysed together in this study.
	Antidepressants		Antidepressants were further classified as tricyclics, tetracyclics, duals, selective serotonin reuptake inhibitors, atypical and vilazodone. Mirtazapine was classified among the tetracyclic antidepressants. Trazodone is rarely used as an antidepressant and thus was analysed separately. Due to their similar profiles and the scarcity of data, tricyclics and tetracyclics were analysed together.
	Anticonvulsants and gabapentinoids		No patient used anticonvulsants for seizure control. In all cases, they were being used to control neuropathic pain. Gabapentinoids were also used in the control of nociplastic pain. Because of the small sample size, both were analysed together.
	Z-drugs and benzodiazepines (BZD)		Despite their action on benzodiazepine receptors, the “Z-drugs“ (zopiclone, eszopiclone, zaleplon and zolpidem) have different profiles and often different uses so the two were first analysed separately. Due to the small sample, these medications were also tested together.
	Non-opioid analgesics		This class included paracetamol and metamizole.
	Immunosuppressants		Included classical and selective synthetic disease-modifying antirheumatic drugs and biologics of any kind. Prednisone was considered separate.
	Myorelaxants		Tizanidine and tolperisone were the only specimens of this class present in our sample.
	Others		The use of non-steroidal anti-inflammatory drugs (NSAIDs) and neuroleptics was also analysed.

Laboratory work	Acute phase reactants	C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were systematically analysed and helped clinical judgment on whether an active inflammatory condition was directly ("inflammatory pain") or indirectly ("secondary fibromyalgia") causing pain.
	Markers of metabolic diseases	Markers of metabolic diseases such as cholesterol, triglycerides, glycosylated haemoglobin, thyroid-stimulating hormone and uric acid levels were not systematically performed but were used when available. In practice, these results never led to a new musculoskeletal disorder diagnosis in our sample.
	Rheumatic disease markers	All rheumatic disease markers were tested when clinically appropriated to define or refine the diagnosis.
Virtual reality (VR) response		Response to VR (Visual Analogue Scale of pain and anxiety before and after VR treatment) was analysed.

DI: Disability insurance status; BMI: Body mass index; FSH: Follicle-stimulating hormone; COPD: Chronic obstructive pulmonary disease; DSM-5: Psychiatry.org – About DSM-5-TR: The Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition; MMP: multimodal treatment programme; TAS-20 ≥52: possible alexithymia; TAS-20 >60: probable alexithymia.

Table S3:
Laboratory results.

Laboratory marker		**All patients**	**Women**	**Men**
C-reactive protein	Total tested	n/total = 187/202 (93%), median = 1, mode = 0, range: 0–37	n/total = 139/148 (94%), median = 2, mode = 0, range: 0–37	n/total = 48/54 (89%), median = 1, mode = 0, range: 0–8
	Abnormal (n/total, %)	129/187 (69%)	96/139 (69%)	33/8 (69%)
	>5 mmol/l (n/total, %)	27/187 (14%)	22/139 (23%)	5/48 (10%)
	>10 mmol/l (n/total, %)	11/187 (6%)	11/139 (11%)	0/48 (0%)
Sedimentation rate		n/total = 177/202 (88%), median = 7, mode = 6, range: 1–63	n/total = 132/148 (89%), median = 11, mode = 6, range: 1–63	n/total = 45/54 (83%), median = 4, mode = 1, range: 1–33
Anti-nuclear antibodies: n/total (%)	Total tested	136/202 (67%)	107, 148 (72%)	29, 54 (54%)
	Present	34/136 (25%)	28, 107 (26%)	6, 29 (21%)
Rheumatoid factor: n/total (%)	Total tested	134/202 (66%)	104/148 (70%)	30/54 (56%)
	Present	1/134 (1%)	1/104 (1%)	0/30 (0%)
Anti-cyclic citrullinated peptide: n/total (%)	Total tested	103/202 (51%)	77/148 (52%)	26/54 (48%)
	Present	2/103 (2%)	1/77 (1%)	1/26 (4%)
Human leucocyte antigen B27 n/total (%)	Total tested	71/202 (35%)	45/148 (30%)	26/54 (48%)
	Present	10/71 (14%)	8/45 (18%)	2/26 (8%)

Table S4:
Sleep analysis according to actigraphy.

Sleep analysis		**All patients**	**Women**	**Men**
Sleep time (hours)	n/total, median, mode, [range]	173/202, 08h10", 07h27" [04:40–12:04]	134/148, 08h16", 08h09", [04:41–12:04]	39, 07h44", 07h27", [04:40–11:11]
	<6 h: n/total (%)	6/173 (3%)	2/134 (1%)	4/39 (10%)
Efficacy <85%: n/total (%)		82/173 (47%)	63/134 (47%)	19/39 (49%)
Fragmentation index >20: n/total (%)		135/173 (78%)	103/134 (77%)	32/39 (82%)
Delayed sleep phase: n/total (%)		35, 173 (20%)	24, 134 (18%)	11, 39 (28%)