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REVIEW

Approach to Adult Patients with Musculoskeletal Complaints and Normal Findings: A Guide for Clinical Practice

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Background: Musculoskeletal (MSK) complaints are among the most common reasons for visits to primary care and outpatient clinics. While many cases are attributed to identifiable pathology, a significant proportion of patients present with persistent MSK symptoms despite normal physical examinations and imaging findings. These presentations pose diagnostic and management challenges and often result in patient frustration, clinician uncertainty, and overutilization of healthcare resources.

Objective: This narrative review aims to provide a comprehensive, evidence-informed, and practical framework for clinicians to evaluate and manage patients with MSK complaints in the absence of clear diagnostic abnormalities.

Methods: A targeted narrative review was performed using PubMed, MEDLINE, and major international clinical guidelines to identify relevant literature on the evaluation and management of musculoskeletal (MSK) pain without objective abnormalities. Evidence and expert consensus were synthesized into a biopsychosocial diagnostic and management framework specifically tailored for primary care and general outpatient settings.

Key Findings: The review underscores the importance of empathetic communication, structured clinical assessment, and early exclusion of serious pathology. It presents a broad differential diagnosis encompassing mechanical, neuropathic, nociplastic, referred, and functional pain mechanisms. Management strategies are organized across key domains, including watchful follow-up, patient education, graded physical activity, stress and lifestyle management, psychosocial and occupational support, and functional goal setting. Pharmacologic therapy—such as short-term use of paracetamol or NSAIDs, and selected antidepressants for chronic nociplastic pain—should be considered cautiously and within a multidisciplinary, shared-decision framework. Opioid use is discouraged due to limited efficacy and high potential for harm.

Conclusion: Patients presenting with MSK complaints and normal diagnostic findings benefit most from a structured, individualized, and patient-centered approach that integrates clinical reasoning, effective communication, and functional rehabilitation. Applying this framework enables clinicians to address the multidimensional nature of such presentations while avoiding unnecessary investigations or interventions.

Keywords: musculoskeletal pain, normal imaging, diagnostic uncertainty, biopsychosocial model, patient-centered care, non-specific pain, primary care management

Introduction

Musculoskeletal (MSK) complaints are among the most frequent reasons for outpatient and primary care consultations worldwide, representing up to 20–30% of visits in some settings.[1,2] These complaints encompass a wide spectrum of presentations—from acute injuries to chronic degenerative conditions—and affect patients across all age groups. Beyond physical discomfort, MSK symptoms substantially impair health and well-being.[3] Chronic or recurrent MSK pain is frequently associated with functional limitations, fatigue, sleep disturbance, social withdrawal, and psychological

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distress, including anxiety and depression.[4,5] This multidimensional burden contributes to reduced quality of life, impaired work capacity, and increased dependency, with considerable personal and socioeconomic consequences.[6,7]

The prevalence and chronicity of MSK complaints place a considerable strain on healthcare systems.[8] Patients often undergo repeated consultations, imaging, and laboratory tests, yet many of these investigations yield little diagnostic value, particularly when clinical findings are normal.[9] This overutilization of resources increases healthcare costs and exposes patients to potential iatrogenic harm from over-testing and unnecessary interventions.[10] Moreover, such cases challenge the delivery of effective, patient-centered care and can lead to frustration among both patients and healthcare providers.

A particularly challenging subgroup involves patients with persistent MSK symptoms but unremarkable physical examinations, laboratory results, and imaging studies. These cases often fall into diagnostic ambiguity, where no clear structural or pathologic source of pain is identified. This uncertainty can heighten patient anxiety and dissatisfaction, especially when symptoms are minimized or dismissed.[11–13] For clinicians, the absence of objective findings complicates decision-making, increases professional frustration, and may contribute to burnout within systems that emphasize diagnosis-driven management.[14]

Clinically, this subgroup presents a dilemma where both underdiagnosis and overtreatment carry risks. Failure to recognize subtle manifestations of serious conditions—such as early inflammatory arthropathies, referred visceral pain, or neuropathic syndromes—may delay appropriate management.[15] Conversely, excessive reliance on investigations when no abnormalities are evident can lead to overmedicalization and reinforce maladaptive illness behaviors.[16] These dynamics undermine quality of care and may perpetuate chronic pain syndromes, long-term functional impairment, and psychological comorbidities.

Importantly, the absence of radiographic or laboratory abnormalities does not imply the absence of disease. Many clinically relevant conditions—such as central sensitization syndromes (eg, fibromyalgia), somatic symptom disorders, or referred pain from non-musculoskeletal sources—may present with normal initial studies.[17] Psychosocial stressors, occupational strain, and emotional distress further influence symptom persistence and require a biopsychosocial approach to assessment.[18]

Despite the high prevalence and clinical burden, adults presenting with non-specific MSK pain and normal diagnostic findings remain underrepresented in clinical guidelines and research. Most existing protocols focus on specific diseases (eg, osteoarthritis, tendinopathy, inflammatory arthritis), overlooking patients with diffuse or localized pain without identifiable pathology, particularly those seen in primary care and general outpatient settings. This review aims to address that gap by providing a structured, evidence-informed, and practical framework for clinicians managing adults with persistent or unexplained MSK complaints. By synthesizing current evidence and clinical insight, the review offers guidance on evaluation, differential diagnosis, and management strategies applicable across anatomical regions, emphasizing patient-centered and function-oriented care while minimizing unnecessary investigations and interventions.

Epidemiology and Clinical Relevance

Musculoskeletal (MSK) disorders affect over 1.7 billion people globally,[19] making them among the most prevalent and disabling health conditions, according to the Global Burden of Disease Study 2019, with low back pain alone accounting for approximately 7.5% of global disability-adjusted life years (DALYs),[20] making it the leading cause of disability across all age groups.

Despite their high prevalence, a substantial proportion of MSK complaints are classified as non-specific due to the absence of definitive physical or radiological abnormalities. For example, studies indicate that up to 90% of patients with acute low back pain have no identifiable anatomical cause on imaging.[21] Similarly, nearly 50% of patients with chronic shoulder pain demonstrate no clinically significant pathology on ultrasound or MRI.[22] In rheumatology referrals, approximately one-third of new patients are ultimately diagnosed with non-inflammatory or non-structural causes of pain, despite presenting with disabling symptoms.[23]

This diagnostic uncertainty is particularly pronounced in middle-aged adults and women, who are more likely to report diffuse or multifocal MSK symptoms without correlating objective findings.[24] Furthermore, the increasing

availability of imaging has paradoxically contributed to greater diagnostic confusion; MRI studies of asymptomatic individuals reveal degenerative changes in up to 60% of cases, leading to the potential misattribution of incidental findings as causative pathology.[25] In older adults, age-related changes in the spine, joints, and tendons further complicate interpretation, making it difficult to distinguish between clinically significant pathology and normal aging.[26]

From a healthcare delivery perspective, patients with non-specific MSK complaints often consume disproportionate resources. These individuals are more likely to receive repeated imaging, multiple specialist referrals, and trial-and-error pharmacologic treatments. A UK study found that patients with unexplained musculoskeletal pain are known to have higher rates of healthcare utilization, including more frequent general practitioner visits and increased referrals to secondary care, compared to those with clearly defined diagnoses.[27] This not only strains clinical capacity but also contributes to unnecessary healthcare expenditures and potential harm from over-medicalization.

Methods and Scope of the Review

This article is presented as a narrative review aimed at providing a comprehensive, structured, and practical framework for the evaluation and management of adult patients presenting with musculoskeletal (MSK) complaints despite normal physical examination, laboratory, or imaging findings. The review synthesizes relevant evidence and expert-based recommendations to assist frontline clinicians, particularly those in primary care, internal medicine, rehabilitation, and general outpatient settings, in addressing the diagnostic uncertainty, clinical complexity, and therapeutic challenges associated with this underrecognized patient group. The focus is on promoting a biopsychosocial, patient-centered approach that integrates accurate assessment, appropriate reassurance, and rational management while avoiding unnecessary investigations or interventions.

The review was informed by a targeted search of the medical literature using databases such as PubMed, MEDLINE, and Google Scholar. Search terms included combinations of "musculoskeletal pain", "normal imaging", "non-specific musculoskeletal complaints", "central sensitization", "nociplastic pain", "functional pain", "diagnostic uncertainty", and "biopsychosocial approach." Guidelines from major professional societies (eg, NICE, ACR, CDC) and key narrative reviews were also included to ensure clinical relevance and updated perspectives. Studies were selected based on clinical applicability, conceptual clarity, and support for multidisciplinary, patient-centered care.

Given the broad scope and heterogeneous nature of this clinical challenge, the review does not adhere to formal systematic review methodology but instead prioritizes narrative synthesis, expert-informed frameworks, and practical decision-making tools applicable in real-world practice.

Differential Diagnosis Framework

The diagnostic process begins with establishing a foundation of empathy and trust. Many patients with musculoskeletal complaints and normal findings experience frustration, fear, or a sense of being dismissed.[28] It is essential to acknowledge the difficulty of their experience, validate their concerns, and reassure them that their symptoms are real and will be thoroughly assessed. This empathic approach not only fosters a stronger therapeutic relationship but also sets the stage for a more open and informative clinical encounter.

The differential diagnoses in patients presenting with musculoskeletal (MSK) complaints and normal findings are broad and often complex.[29] In such diagnostically ambiguous scenarios, clinicians should begin with a thorough and structured clinical assessment. A detailed history is paramount and should extend beyond the presenting complaint to include occupational exposures, psychological factors, family history, and social context. Utilizing open-ended questions allows patients to share perspectives that may uncover overlooked contributing factors or early indicators of systemic or functional conditions.[8] This approach not only facilitates diagnostic clarity but also reinforces a patient-centered model of care, enhancing the therapeutic alliance.

A comprehensive physical examination should follow, incorporating both focused and general assessments. The focused examination is designed to identify signs of local pathology, such as regional musculoskeletal or neurologic findings, while the general examination aims to detect systemic abnormalities that may suggest an underlying inflammatory, infectious, or metabolic process. This dual-layered approach aids in narrowing the differential diagnosis while signaling to the patient that their symptoms are being taken seriously. Reviewing prior investigations—imaging and

laboratory studies—is also essential to avoid redundant testing and to reframe past findings within the context of the current clinical picture. If a new diagnosis is suspected, additional investigations may be warranted, but these should be selected thoughtfully—balancing the risk of overtesting against the need to avoid dismissing potentially significant pathology.

Before progressing to broader differential considerations, it is essential to first exclude serious or potentially life-threatening conditions that may initially present with subtle or non-specific musculoskeletal symptoms. These include malignancies, infections (such as osteomyelitis or septic arthritis), and inflammatory rheumatologic diseases, as well as referred pain from visceral or vascular sources. Although rare, missing these diagnoses can have significant consequences.[30] Therefore, clinicians should remain alert for red flags such as unexplained weight loss, nocturnal pain, neurological deficits, systemic symptoms (eg, fever, fatigue), or a history of cancer, immunosuppression, or trauma. Early identification and timely referral or investigation in the presence of such features are critical to avoid delays in appropriate management.

Building on this foundation, clinicians should adopt a broad and integrative differential diagnosis framework that extends beyond conventional structural causes. Mechanical and soft tissue conditions—such as myofascial pain, muscle strain, or early degenerative changes—may not manifest clearly on imaging or examination.[31] Referred pain from visceral sources (eg, cardiac, renal, or gastrointestinal) or from spinal structures may mimic primary MSK disorders in the absence of localized findings.[32] Neuropathic pain syndromes, including small fiber neuropathy and post-traumatic nerve sensitization, often present with severe symptoms despite normal imaging and neurological exams.[33] Increasingly, nociplastic pain mechanisms—seen in conditions like fibromyalgia or central sensitization syndromes—are recognized as significant contributors to persistent, diffuse MSK pain. These syndromes are frequently associated with sleep disturbances, fatigue, and mood symptoms, and lack identifiable peripheral pathology[34] (Table 1).

Clinicians must also remain vigilant for inflammatory or systemic diseases in their early phases—such as rheumatoid arthritis, spondyloarthropathies, or autoimmune myopathies—which may initially present with vague MSK symptoms and minimal clinical or radiologic changes. Finally, functional and somatic symptom disorders—often driven by psychological distress or maladaptive coping—must be considered as legitimate contributors to MSK complaints, requiring sensitive, multidisciplinary assessment.

A comprehensive and empathetic diagnostic approach enables clinicians to balance clinical uncertainty with diagnostic rigor. It helps avoid both premature reassurance and unnecessary interventions, ensuring that potentially serious conditions are not missed while fostering a validating and supportive environment for the patient.

Table 1 Summary of Key Diagnostic Categories and Clinical Features in Patients with Musculoskeletal Complaints and Normal Findings

Category	Key Clinical Features	Diagnostic Clues
Mechanical / Myofascial	Localized, worsens with movement	Tender points, posture/activity related pain
Referred Pain	From visceral or spine	Poor localization, non-MSK source history
Neuropathic	Burning, shooting, paresthesia	Dermatomal patterns, sensory abnormalities
Nociplastic	Diffuse, chronic, fatigue, poor sleep	Fibromyalgia, central sensitization signs
Inflammatory (early)	Morning stiffness, systemic signs	Family history, subtle joint swelling
Functional / Somatic	No objective findings, worsened by stress	Associated psychological distress

Notes: Mechanical pain arises from musculoskeletal strain or mechanical overload of joints and soft tissues. Referred pain originates from non-musculoskeletal sources, typically visceral or spinal, perceived at a distant site. Neuropathic pain results from injury or dysfunction of the peripheral or central nervous system. Nociplastic pain refers to pain arising from altered central pain processing without clear peripheral damage, as seen in fibromyalgia and central sensitization syndromes. Inflammatory pain is driven by immune-mediated processes affecting joints or periarticular structures. Functional or somatic pain describes symptoms without structural pathology, often influenced by psychological or behavioral factors.
Abbreviation: MSK, Musculoskeletal.

Psychosocial Context

An often underrecognized yet essential component of the diagnostic work-up in patients with unexplained musculoskeletal (MSK) complaints is the psychosocial context. Psychiatric disorders—particularly depression, generalized anxiety disorder, somatization, and post-traumatic stress disorder—are well-documented to produce somatic manifestations, including persistent, diffuse, or vague MSK symptoms in the absence of identifiable pathology.[35] These presentations may either mimic or exacerbate physical complaints, making it imperative for clinicians to assess mental health as part of the diagnostic process.

Routine screening for mood and anxiety disorders using validated tools, such as the Patient Health Questionnaire-4 (PHQ-4)—a brief, reliable screening instrument combining depression (PHQ-2) and anxiety (GAD-2) scales—can aid in early identification of psychiatric comorbidities that may otherwise go undetected.[36,37]

Beyond formal screening, a detailed psychosocial history should be elicited to explore potential contributing factors, including recent life stressors, occupational pressures, home environment dynamics, interpersonal relationships, unresolved conflicts, sleep disturbances, financial instability, and signs of emotional exhaustion or burnout. The presence of chronic stress or adverse social circumstances can alter pain perception, amplify somatic symptoms, and impede recovery.

Recognizing and addressing these psychosocial influences not only facilitates more accurate diagnosis but also allows for more holistic, patient-centered management that acknowledges the interplay between mind, body, and environment. Figure 1 is a flowchart of our proposed approach.

Management Strategies (Proposed Clinical Algorithm)

Watchful Follow-Up

In cases where musculoskeletal (MSK) complaints persist despite normal clinical and radiological findings, and a definitive diagnosis cannot be established—even after a thorough biopsychosocial assessment and exclusion of serious pathology—physicians are advised to adopt a strategy of watchful follow-up. This approach is neither dismissive nor passive; rather, it reflects a structured and compassionate model of continued care.

During this phase, the patient's symptoms should be acknowledged and validated. Physicians should openly recognize the frustration and uncertainty experienced by the patient, reinforcing that the absence of a diagnosis does not diminish the legitimacy of their complaints. Importantly, follow-up should be arranged regularly and with the same physician who conducted the initial evaluation whenever possible, to maintain continuity of care and preserve the therapeutic rapport that has been established.

The goal of watchful follow-up is to monitor for any evolution in the clinical presentation—whether that be the emergence of new symptoms or signs, the development of more localized findings, or spontaneous resolution. This approach provides a safety net, allowing for timely re-evaluation if new diagnostic clues arise, while also avoiding unnecessary investigations or treatments in the absence of clear indications. It reflects a balanced strategy that respects both the patient's experience and the limits of current diagnostic capabilities.

Patient Education and Reframing

A cornerstone of effective management in patients with musculoskeletal (MSK) complaints and normal diagnostic findings is patient education and cognitive reframing.[38] Many patients associate pain with structural damage or serious disease, and the absence of identifiable pathology can paradoxically increase anxiety, leading to fear-avoidance behaviors and chronicity.[39]

Clinicians should proactively explain that pain does not always indicate tissue damage, and that in many cases, symptoms are related to temporary dysfunction in how the body processes pain signals. Introducing the concept of "harmless pain"—pain that is real but not dangerous—can help patients shift their understanding and reduce fear. Education should emphasize that such pain often improves with movement, reassurance, and self-care, and that remaining active is both safe and beneficial.

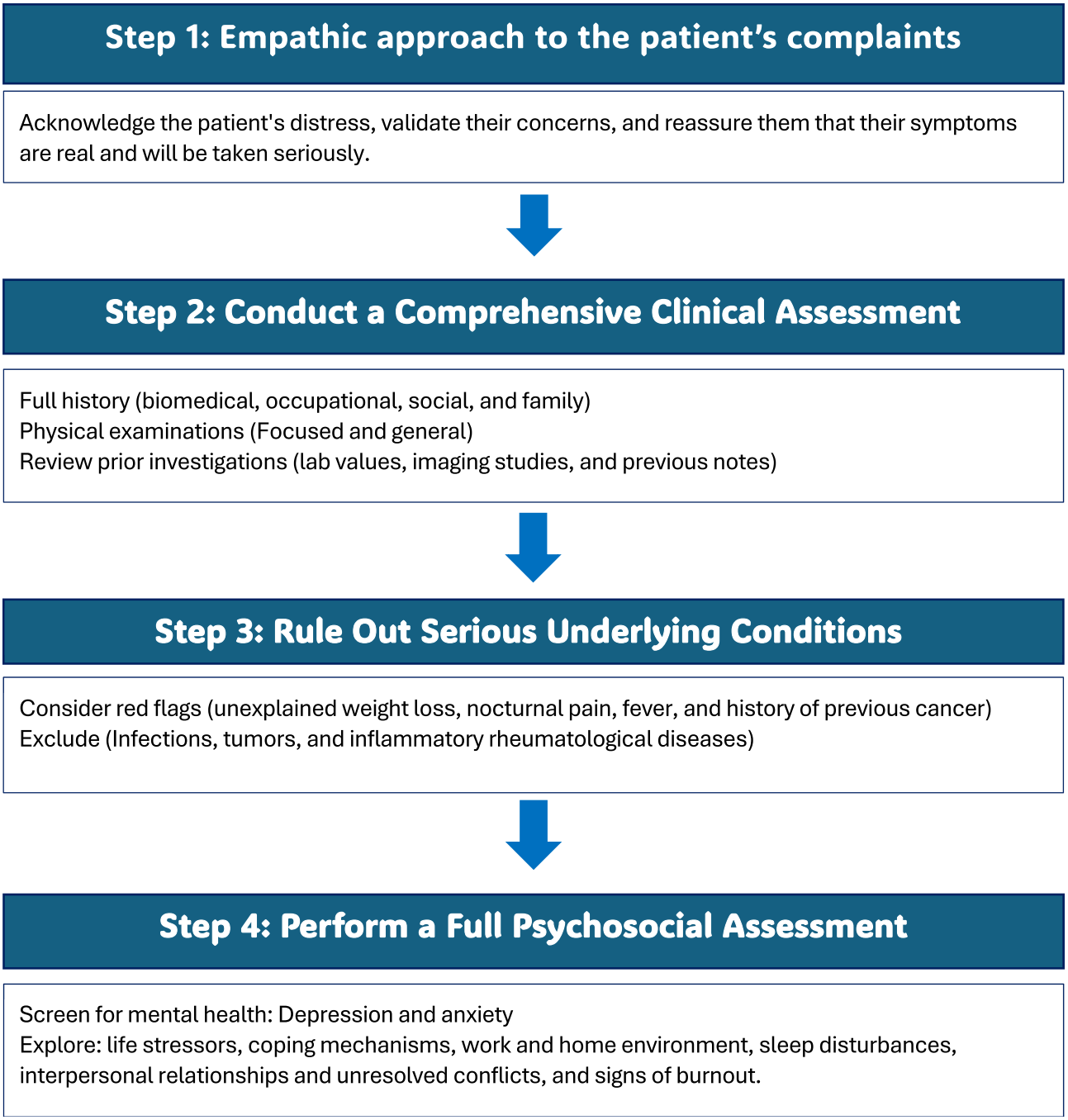

Figure 1 Flowchart illustrating the proposed diagnostic approach for patients with musculoskeletal (MSK) complaints and normal diagnostic findings.

Using simple analogies, diagrams, or validated pain education materials can further reinforce these messages.[40] This approach not only empowers patients to take an active role in their recovery but also helps dismantle unhelpful beliefs that may perpetuate distress and disability in the absence of pathology.

Graded Physical Activity and Exercise Therapy

Graded physical activity is a cornerstone of managing musculoskeletal (MSK) complaints, particularly in cases where structural abnormalities are absent.[41] Many patients with unexplained or non-specific MSK pain develop fear-avoidance behaviors—limiting movement due to the belief that activity will worsen their condition.[42] This inactivity can contribute

to deconditioning, increased pain sensitivity, and further functional decline.[43] Clinicians should address these beliefs early and encourage patients to re-engage in movement safely. Graded activity involves a structured, stepwise reintroduction of physical tasks, tailored to the individual's baseline function and tolerance. Unlike traditional exercise programs aimed at fitness, the goal here is to rebuild confidence in movement, restore daily function, and prevent long-term disability.[44]

Referral to a physiotherapist trained in chronic pain or functional rehabilitation can greatly support this process. Programs may begin with low-intensity activities, such as walking, stretching, or water-based exercises, and gradually increase in duration or complexity over time. Education should accompany exercise therapy to reinforce that movement is safe and beneficial, even when mild discomfort is present. Importantly, progress should be guided by function rather than pain elimination, with a focus on sustainable improvements. This approach not only counters the effects of inactivity but also empowers patients to take an active role in their recovery, improving physical resilience and psychological well-being alike.

Stress Management and Lifestyle Modifications

General life stress—distinct from stress related formal psychiatric disorders—can play a significant role in the persistence and amplification of musculoskeletal (MSK) symptoms.[45] Even in the absence of a diagnosable mental health condition, stress can contribute to muscle tension, sleep disturbance, and increased pain sensitivity.[46] Recognizing stress as a modifiable factor, clinicians should explore patients' everyday stressors, coping mechanisms, and routines. Simple interventions such as breathing exercises, progressive muscle relaxation, and mindfulness can be effective tools for symptom relief.[47]

Lifestyle modifications should be encouraged alongside stress management. Optimizing sleep hygiene, increasing light physical activity, and addressing unhelpful habits such as prolonged inactivity or poor ergonomics can support recovery. These adjustments, though small, help patients regain a sense of control, improve resilience to pain, and contribute meaningfully to long-term wellbeing.

Occupational and Social Support

Occupational factors can significantly influence the persistence of musculoskeletal (MSK) symptoms, even in the absence of identifiable pathology. Work-related stress, poor ergonomics, repetitive strain, and low job satisfaction may exacerbate pain or hinder recovery.[48] It is important for clinicians to explore the patient's occupational demands, functional limitations, and potential barriers to return-to-work. In some cases, referral to occupational health services may be warranted to assess workplace conditions and recommend adjustments that facilitate recovery and prevent further strain.[49]

Social context is equally important. Limited social support, strained family dynamics, caregiving responsibilities, or isolation can negatively impact coping and contribute to the chronicity of symptoms.[50] Discussing these factors with patients and connecting them to social workers, community support programs, or peer networks can help reduce psychological burden and enhance resilience. Recognizing and addressing occupational and social stressors as part of a holistic management plan ensures more sustainable and meaningful recovery outcomes.[51]

Functional Goal Setting and Shared Decision-Making

In patients with musculoskeletal (MSK) complaints and normal findings, the absence of a clear diagnosis can shift the clinical focus from cure to management and function. Functional goal setting becomes essential in helping patients regain control and direction in their recovery. Instead of aiming for complete symptom elimination—which may be unrealistic in many cases—clinicians should guide patients to set achievable, personalized goals such as improving mobility, returning to work, resuming daily activities, or increasing exercise tolerance. These goals help redefine success in measurable, practical terms and foster a sense of progress, even if pain persists to some degree.

Shared decision-making is critical in this process, ensuring that treatment plans align with the patient's values, expectations, and lifestyle. Engaging the patient in discussions about available options—including their benefits, limitations, and potential risks—can improve treatment adherence and satisfaction. It also helps shift the dynamic

Table 2 Summary of Recommended Non-Pharmacologic Strategies for the Management of Unexplained Musculoskeletal Symptoms

Strategy	Indication	Key Benefit
Watchful Follow-Up	Diagnosis unclear, no red flags	Maintains continuity, prevents harm
Patient Education & Reframing	All patients	Reduces fear, promotes engagement
Graded Physical Activity	Deconditioning, fear-avoidance	Improves mobility and function
Stress Management & Lifestyle	Chronic stress, poor routines	Reduces pain amplification
Psychosocial / Occupational Support	Job strain, isolation	Improves coping, reduces burden
Functional Goal Setting	All cases	Shifts focus to meaningful recovery
Adjunct Non-Pharmacologic Therapies	Persistent or complex pain despite initial conservative care	Enhances pain modulation and function through manual therapy, CBT/CFT, graded motor imagery, mirror therapy, and acupuncture

Abbreviations: CBT, cognitive behavioral therapy; CFT, cognitive functional therapy.

from a passive care model to an active partnership, where both clinician and patient contribute to the management plan. This collaborative approach not only supports informed choices but also empowers patients to take ownership of their recovery journey, enhancing motivation and long-term outcomes. Table 2 summarizes these interventions.

Adjunct Non-Pharmacologic Therapies

Adjunctive therapies such as manual therapy, cognitive-behavioral therapy (CBT), cognitive functional therapy (CFT), graded motor imagery, mirror therapy, and acupuncture have shown benefit in select cases of non-specific MSK pain, particularly when central sensitization or maladaptive pain processing is suspected.[52–54] These modalities can help improve movement confidence, reduce fear-avoidance behaviors, and facilitate functional recovery, especially when integrated within a multidisciplinary biopsychosocial framework.

Pharmacologic Interventions

Pharmacologic therapy should be considered only after non-pharmacologic strategies have been thoroughly explored and when symptoms continue to significantly impair function or quality of life. These interventions are not first-line treatments and should never be initiated in isolation. Instead, the decision to introduce medications should emerge from a multidisciplinary discussion and be part of a shared decision-making process with the patient. Caution is warranted to avoid reinforcing passive coping or dependence on pharmacologic solutions, particularly in patients with undiagnosed or functional musculoskeletal (MSK) pain syndromes.

Acetaminophen (Paracetamol) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

First-line pharmacologic management may include the short-term use of paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) to alleviate pain and facilitate engagement in physical activity and rehabilitation.[55] Paracetamol may be considered for mild symptoms or in patients with contraindications to NSAIDs, though its analgesic effect in non-specific musculoskeletal pain is often modest.[56] NSAIDs remain the mainstay for acute or subacute episodes of pain when tolerated, offering both analgesic and anti-inflammatory benefits.[57] However, their use should be time-limited and closely monitored, particularly in individuals with chronic pain, due to the potential for gastrointestinal, renal, and cardiovascular adverse effects. Long-term or indiscriminate use is discouraged, and treatment should always be tailored to symptom severity, patient comorbidities, and overall functional goals.[58]

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs may be helpful in patients with chronic MSK pain who exhibit significant comorbid symptoms of anxiety, depression, or emotional distress—even in the absence of a formal psychiatric diagnosis.[59] Duloxetine, in particular, has shown benefit in chronic low back pain and fibromyalgia, helping reduce central sensitization and improve overall pain

perception.[60,61] These medications should be introduced cautiously, with attention to side effects such as nausea, insomnia, or sexual dysfunction. Their use is best supported by concurrent psychological interventions such as cognitive behavioral therapy (CBT) to optimize outcomes.[62]

Tricyclic Antidepressants (TCAs)

Low-dose TCAs, such as amitriptyline or nortriptyline, are another option for patients with persistent, widespread MSK pain, particularly when sleep disturbance or fatigue are prominent features.[63] They may provide benefit in modulating nociplastic or neuropathic pain by enhancing descending pain inhibition pathways.[64] However, due to their anticholinergic side effects—dry mouth, sedation, dizziness, and potential cardiac conduction abnormalities—TCAs should be used cautiously, especially in older adults or those with cardiovascular risk factors.[65] Dose titration should be slow, and regular monitoring is advised. Their role is best suited for select patients as part of a broader, individualized plan.

Gabapentinoids

Gabapentin and pregabalin may be considered in patients presenting with clear neuropathic features such as burning, shooting pain, or paresthesia, particularly when pain is unresponsive to non-pharmacologic modalities.[66] However, evidence for their efficacy in non-neuropathic, non-specific MSK pain is limited. Moreover, these medications carry risks of sedation, cognitive slowing, and dependence, and their use should be closely monitored—especially in those with a history of substance misuse.[67] Their prescription should follow clear clinical indications and be regularly reassessed for effectiveness and side effects.

Vitamins and Supplements

While the routine use of vitamins and supplements in patients with unexplained musculoskeletal (MSK) complaints is not strongly supported by high-quality evidence, certain deficiencies or imbalances may contribute to symptom persistence and should be considered on a case-by-case basis. For example, vitamin D deficiency, which is common in many populations, has been associated with diffuse musculoskeletal pain and fatigue, and correction may offer symptom relief in deficient individuals.[68] Magnesium, an essential mineral involved in muscle and nerve function, has also gained attention for its potential role in alleviating muscle tension, cramps, and stress-related somatic symptoms; supplementation may be reasonable in patients with borderline or low serum magnesium levels.[69,70] However, clinicians should be cautious of over-reliance on supplements and emphasize that they should complement—not replace—a broader management strategy focused on activity, stress management, and psychosocial support.

Avoidance of Opioids

Opioids should not be used in the management of musculoskeletal (MSK) complaints when no clear structural pathology is identified.[71] Current clinical guidelines strongly discourage their use in cases of non-specific or unexplained MSK pain due to the lack of sustained benefit and the high potential for harm.[72] While opioids may offer short-term relief, they do not address the underlying mechanisms of functional or nociplastic pain and may actually exacerbate long-term outcomes by reinforcing passive coping behaviors and disrupting the body's natural pain regulation systems.[73] Their use also risks undermining patient education efforts that emphasize recovery through activity, self-management, and psychological resilience.

The initiation of opioid therapy in these patients carries significant risks. Even at low doses, opioids are associated with adverse effects such as sedation, constipation, hormonal changes, and increased risk of falls—particularly in older populations.[74] Long-term use may lead to tolerance, dependence, and opioid use disorder, and there is growing concern about opioid-induced hyperalgesia, where patients develop heightened sensitivity to pain.[75] Given these hazards, opioid prescribing in this context should be considered only in exceptional, well-justified circumstances and within a multidisciplinary framework. Safer and more effective non-opioid strategies, both pharmacologic and non-pharmacologic, should remain the foundation of care. Figure 2 is a flowchart of the treatment strategy for these patients. Table 3 summarizes these pharmacological interventions.

Figure 2 Flowchart outlining the management strategy for patients with musculoskeletal (MSK) complaints and normal diagnostic findings.

If Still Not Improving?

In cases where patients continue to experience persistent musculoskeletal (MSK) symptoms despite comprehensive non-pharmacologic interventions, pharmacologic options, and a multidisciplinary approach, further evaluation is warranted.

This should not be viewed as treatment failure but rather as an indication for re-examination of the diagnostic framework, therapeutic alignment, and patient context. A second look at earlier assumptions—such as early-stage

Table 3 Summary of Pharmacologic Options, Indications, and Precautions for Selected Cases of Persistent Musculoskeletal Complaints. SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; TCA, Tricyclic Antidepressant

Drug Class	Indication	Precautions
Acetaminophen (Paracetamol)	Mild pain or intolerance to NSAIDs	Limited analgesic effect; monitor for hepatotoxicity at high doses
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Acute or subacute pain; inflammatory component suspected	Avoid prolonged use; monitor for gastrointestinal, renal, and cardiovascular adverse effects
SNRIs	Comorbid anxiety, depression, chronic pain	Monitor mood, GI effects
TCAs	Poor sleep, diffuse pain	Caution in elderly, cardiac monitoring
Gabapentinoids	Neuropathic symptoms	Risk of sedation, misuse
Opioids	*Not recommended*	Dependence, tolerance, hyperalgesia

rheumatologic or neurological conditions, overlooked psychosocial stressors, or subtle functional disorders—may reveal missed or evolving diagnoses.

Referral to a multidisciplinary pain management team or tertiary specialty clinic should be considered at this stage. These centers can provide access to advanced diagnostics (eg, nerve conduction studies, specialist imaging), comprehensive rehabilitation programs, and integrated psychological support.

In select cases, inpatient or intensive outpatient pain rehabilitation programs may be appropriate, particularly when functional impairment is significant. Importantly, continued empathy, validation, and clear communication remain essential, as these patients are often vulnerable to frustration, hopelessness, or fragmentation of care. Ongoing support from a consistent care provider helps ensure continuity, trust, and sustained engagement in the therapeutic process.

Referral and Multidisciplinary Collaboration

Referral and coordinated multidisciplinary care are essential when managing patients with musculoskeletal (MSK) complaints and normal diagnostic findings. While most cases can be managed in primary or general outpatient settings, referral should be guided by symptom persistence, clinical suspicion, and the presence of red or yellow flags.

Patients suspected of having structural or inflammatory pathology may benefit from orthopaedic or rheumatology assessment, particularly when symptoms do not improve with appropriate conservative measures. Referral to neurology is indicated for those with neuropathic features, atypical sensory changes, or central pain patterns. When emotional distress, maladaptive coping, or somatic symptom disorder contribute to symptom persistence, psychiatric or psychological input can be crucial for addressing underlying psychosocial factors.

For refractory cases with disabling or nociplastic pain, pain medicine or multidisciplinary pain clinics provide valuable expertise in advanced interventions and coordinated rehabilitation programs. These centers may consider specialized options such as ketamine infusions for selected patients with refractory neuropathic or complex regional pain syndromes (CRPS),[76] under close supervision and within controlled settings. Such collaboration ensures consistent, patient-centered care, minimizes redundant investigations, and promotes functional recovery through the integration of medical, physical, and psychological approaches.

Conclusion

Musculoskeletal complaints with normal findings are common, diagnostically complex, and frequently underrepresented in existing clinical guidelines. This review addresses that gap by proposing a structured, biopsychosocial framework that integrates empathetic communication, comprehensive assessment, and early exclusion of serious pathology, while recognizing the psychological and social factors that influence symptom persistence. Clinicians are encouraged to prioritize non-pharmacologic strategies—such as patient education, graded activity, stress reduction, and functional goal setting—while reserving pharmacologic therapy for selected cases through shared decision-making. Avoiding unnecessary interventions, particularly opioids, can enhance recovery, improve patient satisfaction, and reduce healthcare

overutilization. Ultimately, adopting this framework aims to strengthen clinical confidence and consistency in managing these diagnostically ambiguous cases. Future high-quality, large-scale studies incorporating patient-reported outcomes (PROs) are essential to validate the proposed approach and inform future guideline development.

Ethical Approval

Not applicable. This article is a narrative review and does not involve human participants or identifiable data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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