

# Medically Unexplained Symptoms

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## KEYWORDS

• Medically unexplained symptoms • Somatization • Somatoform • Depression • Pain

## KEY POINTS

- Medically unexplained symptoms (MUS) are a significant cause of morbidity for patients and of resource use for the health care system.
- Multiple diagnostic categories exist for patients with MUS.
- Risk factors for MUS include female gender, low socioeconomic status, and a history of trauma (specifically childhood sexual abuse).
- A careful history and physical examination is required for all patients with MUS, with additional diagnostic testing dictated by the patient's symptom severity and chronicity.
- Treatments for MUS include cognitive behavior therapy, antidepressant treatment, and empathic, patient-centered care.

## CASE 1: MS D

*Ms D is a 71-year-old woman with a history of peptic ulcer disease, metabolic syndrome, major depressive disorder, and osteoarthritis who presents for clinical follow-up with pain all over her body. She states that she cannot remember a time when her entire body did not hurt. She is also concerned about chronic abdominal pain.*

*On examination, her vital signs are within normal limits. She is tender to light palpation in every major muscle group. She is diffusely tender to light palpation on abdominal examination, but without palpable masses, organomegaly, rebound, or guarding.*

*Her evaluation so far has included a basic metabolic panel, liver function tests, and a lipase, all of which were within normal limits, and a complete blood count that revealed a mild normocytic anemia (hematocrit, 34%), hand radiographs that showed advanced osteoarthritis at the first carpometacarpal joint bilaterally, lumbar spine radiographs that showed mild spondylosis, and an abdominal computed tomography (CT) scan significant for diverticulosis without evidence of diverticulitis. She has also undergone upper and lower endoscopy, which revealed no masses or ulcers, and mild diverticulosis as noted earlier.*

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*She is here to establish care with you after having seen multiple other physicians in your practice. She is concerned that she might have cancer in her abdomen or in her bones and expresses concern that her prior physicians have not taken her concerns seriously. What do you think is going on?*

## INTRODUCTION

Medically unexplained symptoms (MUS) are common in the outpatient and primary care settings. Although prevalence data vary, most studies suggest that more than 50% of patients presenting to primary care clinics with physical symptoms have no diagnosable organic disease.<sup>1,2</sup> Patients with a somatization disorder use twice as many outpatient and inpatient resources and have double the average health care costs per year, independent of psychiatric and medical comorbidity.<sup>3</sup> MUS are challenging to treat and can be frustrating for primary care physicians to address and manage. Risk factors for the development of multiple somatic symptoms include, but are not limited to, female gender,<sup>4</sup> low education,<sup>5</sup> abuse in childhood, and comorbid medical and psychiatric disease.<sup>6</sup> Having a specific and intentional diagnostic and therapeutic approach to patients with MUS can help providers build strong and effective therapeutic relationships with patients, manage limited health care resources wisely, and focus on improving long-term quality of life in the subset of MUS patients with chronic symptoms.

## DEFINITIONS

The terms MUS and somatization refer to symptoms that have minimal or no apparent basis in physical disease. These terms can also apply to patients with underlying disease explaining the presence of physical symptoms, but with a symptom burden out of proportion to what is expected. Some investigators criticize the use of the term MUS because of the ambiguity inherent in declaring a symptom to be unexplained, or unexplainable, and the importance of including diseases that may have psychological underpinnings under the broad heading of medical illness.<sup>7</sup> Other disease classifications exist for patients with specific symptom constellations within MUS, including fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and irritable bowel syndrome. There may also be significant overlap with idiopathic environmental intolerance (IEI; also known as multiple chemical sensitivity), a poorly understood and subjective syndrome characterized by nonspecific, ambiguous, and recurrent symptoms attributed to low levels of chemical, biologic, or physical agents. Somatoform disorders are found in more than one-fourth of patients with IEI symptoms and some investigators think that IEI may be a variant of MUS/somatoform disorders.<sup>8</sup> Gulf War illness, which refers to a constellation of somatic symptoms in veterans of the Gulf War, is generally one of 2 types: chronic fatigue syndrome or multiple chemical sensitivity pattern,<sup>9,10</sup> and can be included additionally under the general heading of MUS.

The prior diagnostic criteria for somatization disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were so specific and detailed as to exclude most patients with MUS. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), published in 2013, incorporates significant changes to these diagnostic criteria. Multiple prior diagnostic categories have now been subsumed into the classification somatic symptom and related disorders. The diagnostic criteria for somatic symptom disorder include:

- A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.

- B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
1. Disproportionate and persistent thoughts about the seriousness of one's symptoms
  2. Persistently high level of anxiety about health or symptoms
  3. Excessive time and energy devoted to these symptoms or health concerns
- C. Although any somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).

The diagnostic criteria require further specification if the patient has predominant pain and if the symptoms are persistent (>6 months), and also require specification of illness severity (mild, moderate, or severe).<sup>11</sup> The focus in this diagnosis is not the presence of somatic symptoms per se, but the psychological impact of symptoms on the patient. Other related disorders described in DSM-V include illness anxiety disorder, conversion disorder (functional neurologic symptom disorder), and psychological factors affecting other medical conditions.

### **PATHOPHYSIOLOGY**

The pathophysiology of MUS is poorly understood. Controversy exists as to whether the syndrome is predominantly physical or psychiatric, or a combination of the two, and whether the various named syndromes within the broader category of MUS or functional somatic syndromes are physiologically distinct, valid, and meaningful.<sup>12,13</sup> In one small study, 1 in 3 physicians thought that the cause of MUS was likely spiritual.<sup>14</sup> Some evidence suggests a familial risk for somatization, although it remains unclear whether this link is genetic, epigenetic, or environmental.<sup>15</sup> MUS has also been linked to alexithymia, or an inability to verbally express emotions,<sup>16,17</sup> although causality has not been clearly established. Multiple studies suggest an association between MUS and a history of traumatic events, including abuse in childhood.<sup>18–20</sup> Other formative childhood experiences such as unexplained symptoms, parental illness (particularly poor paternal health), and increased parental illness behavior in response to children's symptoms are additional risk factors for development of MUS later in life.<sup>21,22</sup> A history of rape victimization is also strongly associated with the development of MUS.<sup>20</sup>

Somatization occurs across cultures, and no significant differences between cultural groups with regard to prevalence have been found.<sup>23–25</sup> However, there can be differences in specific symptoms between cultural groups.<sup>26</sup>

### **SYMPTOMS**

The most common symptom attributed to MUS is pain,<sup>1</sup> including diffuse myalgias, arthralgias, low back pain, headache, and dysuria. Other possible symptoms include:

- Systemic symptoms: fatigue and insomnia
- Head and neck symptoms: tinnitus, pseudo-eustachian tube dysfunction, atypical facial pain, globus sensation<sup>27</sup>
- Cardiac symptoms: chest pain, palpitations, and dyspnea
- Gastrointestinal symptoms: bloating, nausea, abdominal discomfort, constipation, and diarrhea
- Genitourinary symptoms: chronic pelvic pain, dyspareunia, vulvodynia, and dysmenorrhea
- Neurologic symptoms: pseudoseizures, dizziness, weakness

The absolute number of physical symptoms is correlated with risk for depression and anxiety, and somatoform disorders additionally are strongly associated with mood disorders.<sup>28</sup>

## CASE 2: MS L

*Ms L is a 47-year-old woman with a history of hepatitis C and generalized anxiety disorder who presents with hemifacial pain and seizures. She states that she experiences episodes of throbbing pain that are migratory, occurring all over her scalp, lasting hours to days. It seems to occur more frequently when she has to leave the house to take her children to school or to come to medical appointments. No photophobia or phonophobia. No fevers, chills, or night sweats. No weight loss or nausea. Her seizurelike episodes usually consist of diffuse tremors followed by loss of consciousness, and she has had some mild trauma from falls related to this.*

*Her neurologic examination is normal. Routine laboratory tests were also within normal limits. A noncontrast head CT scan was performed and showed no masses or intracranial disorder. She has undergone multiple electroencephalograms, none of which show any epileptiform discharges.*

*Would you perform any further diagnostic evaluation?*

## DIAGNOSTIC TESTING/IMAGING STUDIES

A diagnosis of MUS can be made only after organic disease has been ruled out. It is therefore critical for clinicians to take a careful history and perform a thorough physical examination before making a diagnosis of MUS. History taking should be broad and comprehensive, with a specific focus on other symptoms that may suggest organic disease, and on patient attribution (to what does the patient attribute the symptoms?). The social history can be particularly useful in this setting as well, providing information on childhood factors that may predispose a patient to MUS, and on situational stressors that may be exacerbating mental and physical symptoms. However, in the absence of red flags in the history or abnormal physical examination findings, laboratory and radiographic testing should be used judiciously. Many physicians find themselves ordering tests they do not think are medically indicated in an effort to alleviate a patient's fears about underlying organic disease. However, extensive testing has not been shown to alleviate concerns about serious illness in patients with a low pretest probability of organic disease.<sup>29</sup> Some investigators recommend using MUS severity to dictate the intensity of further testing,<sup>30</sup> as follows:

- Normal to mild MUS: normal behavior, in which patients seek reassurance for infrequent and mild symptoms. Organic disease can be excluded through careful history taking, physical examination, and watchful waiting/observation over time.
- Moderate MUS: patients in this group may have either chronic or intermittent symptoms with significant physical and psychological distress and high health care use behaviors during symptomatic periods. Although these patients can be managed in a similar fashion to those with normal to mild MUS, increasing frequency of symptoms, ongoing chronic symptoms, and high use of health care resources may require clinicians to pursue further diagnostic evaluation.
- Severe MUS: patients with severe MUS have persistent symptoms, a high degree of physical and psychological distress, and high use of health care resources. In addition to a careful history and physical examination, these patients require additional diagnostic evaluation through consultation, laboratory

testing, or radiologic testing, if these tests have not already been performed at the time of evaluation.

Physicians frequently initiate further testing that is not medically indicated; failing to recognize clues offered by patients that the cause may not be organic. This failure can be detrimental to patient care, keeping the focus on making a diagnosis of an organic disorder that may not exist and overlooking the need to focus on treatment interventions that may lead to symptomatic and functional improvement.<sup>31</sup>

## DIFFERENTIAL DIAGNOSIS

Somatization and major depressive disorder commonly coexist: 50% of patients with major depression present with MUS and between 45% and 95% of patients with major depression present with only somatic symptoms at the time of diagnosis.<sup>32</sup> Depressed patients who lack a consistent primary care relationship are more likely to present with exclusively somatic symptoms.<sup>32</sup> In addition, the severity of depression symptoms and decreased quality of life ratings are correlated with the presence of painful somatic symptoms.<sup>33</sup> The psychiatric differential diagnosis includes diseases such as malingering and factitious disorder. In factitious disorder, such as Munchausen syndrome, patients intentionally cause symptoms and disease (eg, injecting insulin to cause hypoglycemia). Malingering patients do not have organic disease, but intentionally feign or exaggerate somatic symptoms for secondary gain.

Panic disorder is another important consideration in the differential diagnosis of patients who present with multiple symptoms. Panic disorder is frequently undiagnosed: 70% of patients in one study with a diagnosis of panic disorder had seen an average of 10 physicians for symptoms before the diagnosis was made.<sup>34</sup> The most commonly seen symptoms in panic disorder involve cardiac, gastrointestinal, and neurologic systems, overlapping significantly with typical MUS presentations. Both patients with panic disorder and MUS present most frequently to primary care physicians and tend to be higher users of the medical system.

Many organic diseases can also present with multiple and vague symptoms. These organic diseases include, but are not limited to, multiple sclerosis, sarcoidosis, acute intermittent porphyria, hemochromatosis, Wilson disease, and connective tissue diseases such as systemic lupus erythematosus. Patients with these conditions may have symptoms involving multiple organ systems in the absence of specific abnormal findings on physical examination.

In addition, many patients with MUS also have significant organic disease. Their somatic symptoms may be unrelated to their chronic medical illnesses, or they may have symptoms out of proportion to or unexplained by their underlying disorder,<sup>30</sup> which can present a challenge in diagnosis.

## CASE 3: MR C

*Mr C is a 55-year-old man with a history of tobacco use, physical and sexual abuse in childhood, and Reinke edema. He presents to clinic for routine follow-up of postnasal drip, hoarseness, and a sensation that he needs to keep clearing his throat. He has had these symptoms for 2 years but only recently obtained health insurance, so presents to you for primary care follow-up. Five years before today's visit, he underwent direct laryngoscopy, which showed polypoid degeneration of the true vocal cords (Reinke edema), as discussed earlier, and a CT scan of his neck, which was unremarkable.*

*What would you do next to manage Mr C?*

## MANAGEMENT

Patients with MUS are highly variable with regard to their level of insight, focus of attention, and needs from medical providers<sup>35</sup> and may provide cues to their providers regarding their need for emotional support or explanation for their symptoms.<sup>36</sup> It can be particularly challenging for providers to discuss a diagnosis such as MUS, or one of its specific variants, with patients. The patient's experience is subjective, and the lack of objective evidence of organic disorder should not minimize providers' empathy for the patient's experience of discomfort or pain.

Multiple studies show the efficacy of cognitive behavior therapy for treating patients with MUS. There are some data to support the use of antidepressants for treating somatoform disorders<sup>37</sup> generally, and chronic fatigue syndrome<sup>38</sup> and fibromyalgia<sup>39,40</sup> specifically, with the bulk of evidence supporting their use for fibromyalgia. In addition, studies suggest that primary care providers can be trained by psychiatric colleagues to effectively treat MUS.<sup>41</sup> A multidimensional treatment program that included antidepressants, elimination of ineffective controlled substance medications, exercise, physical therapy, relaxation training, and medical management of comorbid conditions has shown promise in treating both mental and physical symptoms<sup>42</sup> in this setting.

In primary care practice, several principles can help guide providers in their treatment of patients with MUS (**Box 1** provides a summary)<sup>43,44</sup>:

1. Explain to the patient about the condition with care. Most patients have little understanding of terms such as somatization, and phrases such as MUS may or may not be useful, particularly in the setting of low health literacy. Specific labels for named MUS syndromes, such as fibromyalgia and chronic fatigue syndrome, can sometimes be useful to patients<sup>45,46</sup> as a mechanism to legitimize a patient's symptoms and to move on from diagnosis into the treatment phase of management. However, labeling a patient with a disease can also be detrimental, changing how patients view themselves, how they are viewed by family and close friends,<sup>47</sup> and even how they are treated by physicians.<sup>48</sup> Thus, the use of diagnostic labels is controversial<sup>49</sup> and clinicians are best advised to use their professional judgment and consider the needs of their individual patients before deciding on the type of language that will serve them best.

Specific phrasing that may be useful includes "The good news is that with all the testing we've done so far, it does not seem that you have a life-threatening or dangerous diagnosis. Unfortunately, you do have an illness that is clearly affecting your life in a serious way. As doctors, we care for many patients with similar problems and unfortunately, at this point in time, we do not have a very good understanding of what causes these symptoms. I wish that I could provide you

### Box 1

#### Therapeutic strategies for treating patients with MUS

1. Explain to the patient about their condition with care
2. Be explicit in expressing empathy for the patient's condition
3. Spend time each visit focusing not just on specific symptoms but on the impact that this illness has on the life of the patient
4. Include at least a brief physical examination as part of regularly scheduled follow-up visits
5. Establish frequent follow-up visits
6. Engage colleagues as a source of support

with a clearer explanation and understanding of what is causing your pain. Fortunately, there are things we can do as a team to start to work on getting you feeling better.”

2. Be explicit in expressing empathy for the patient’s suffering. Suffering, as a subjective experience, is always real even in the absence of an identifiable organic disorder.
3. Spend time each visit focusing not just on specific symptoms but also on the impact that this illness has on the life of the patient. In addition, time spent on the social history to better understand sources of stress can be helpful both in strengthening the therapeutic relationship and in better understanding external events and forces that may have an impact on the patient’s symptoms.
4. Include at least a brief physical examination as part of regularly scheduled follow-up visits. In addition to being a useful diagnostic tool, the physical examination has profound significance as a therapeutic and healing ritual.<sup>50</sup> Examining a patient communicates sincere interest, concern, and care.
5. Establish frequent scheduled visits to provide stable, consistent care and to minimize the potential development of new symptoms (conscious or unconscious) to warrant frequent follow-up. Be confident in the diagnosis of MUS when it is present. Once an appropriate work-up has been done, testing or retesting of further symptoms should be approached cautiously.
6. Engage colleagues as a source of support. Treating patients with chronic disease is challenging, and it is common for providers to feel frustrated if a patient’s symptoms do not seem to be improving. Negative patient affect is a strong predictor of symptom persistence in MUS,<sup>51</sup> and personality disorders are common in patients with moderate and severe MUS,<sup>52,53</sup> suggesting that many of the patients most affected by chronic symptoms may also be the most challenging for providers.<sup>54</sup> Physician frustration is correlated with the presence of somatization disorder in patients,<sup>55</sup> which again suggests the need for physician reflection, support, and self-care.

## FUTURE CONSIDERATIONS/SUMMARY

In summary, caring for patients with MUS is challenging for health care providers. Even defining somatization syndromes is complex and controversial, reflecting the medical community’s limited understanding of the pathophysiology for this group of disorders. Although risk factors for MUS have been described and are well understood, little is known about how MUS can be prevented. Uncertainty in medicine, as in any human enterprise, is a given, but the difficulties in identification and treatment of patients with MUS highlight the limitations in understanding the intersection between physical and mental health. Patients come to their physician looking for clarity, understanding, and relief of debilitating symptoms. The understanding of MUS will evolve, and perhaps an organic cause not yet understood or described may emerge to lend clarity and therapeutic opportunities to some patients with somatic disorders. In the meantime, the most powerful tools available are the ability to communicate the limits of current understanding, acknowledge the difficulties faced by patients with this disorder, and reinforce the willingness and desire of clinicians to partner with patients as the focus shifts from diagnosis to symptom management. Thus, the physician-patient relationship, still in its rightful place at the heart of the practice of medicine, lies at the center of effective treatment of patients with MUS.

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