PERSPECTIVES

Classification and Diagnosis of Patients with Medically Unexplained Symptoms

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Patients with medically unexplained symptoms (MUS) have little or no demonstrable disease explanation for the symptoms, and comorbid psychiatric disorders are frequent. Although common, costly, distressed, and often receiving ill-advised testing and treatments, most MUS patients go unrecognized, which precludes effective treatment. To enhance recognition, we present an emerging perspective that envisions a unitary classification for the entire spectrum of MUS where this diagnosis comprises severity, duration, and comorbidity. We then present a specific approach for making the diagnosis at each level of severity. Although our disease-based diagnosis system dictates excluding organic disease to diagnose MUS, much exclusion can occur clinically without recourse to laboratory or consultative evaluation because the majority of patients are mild. Only the less common, "difficult" patients with moderate and severe MUS require investigation to exclude organic diseases. By explicitly diagnosing and labeling all severity levels of MUS, we propose that this diagnostic approach cannot only facilitate effective treatment but also reduce the cost and morbidity from unnecessary interventions.

KEY WORDS: somatization; medically unexplained symptoms; diagnosis and classification; primary care mental health; DSM-IV.
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Patients with medically unexplained symptoms (MUS), also called somatization, represent one of the most common conditions in medicine.[1–3] We define MUS as those physical symptoms having little or no basis in underlying organic disease;[4] when organic disease exists, the symptoms are inconsistent with or out of proportion to it.[5] We caution that people with MUS are not necessarily abnormal. Many exhibit it but seldom or never seek care.[6] MUS becomes a medical issue when it leads to health care–seeking for feared but nonexistent physical illness.[7,8]

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The prevalence of all MUS in the outpatient setting is reported from 25% to 75%, and pain is the most common type, [1–3] i.e., on average, approximately one-half or more of all outpatients have little or no physical disease explanation for their symptoms. Consistent with this, Kroenke and Mangelsdorf found, among all new symptoms, that only 16% had an organic disease basis.[9]

Limited evidence suggests that treatment in primary care and specialty settings is effective, but MUS patients seldom receive it.[10,11] They *first* must be recognized and diagnosed. In addition to lack of treatment, inadequate identification occasions safety and cost problems: ill-advised lab testing and "trial treatments" can lead to iatrogenic complications and increased costs.[12–16] To facilitate diagnosis, we present an emerging consensus that proposes a unitary diagnostic classification system of MUS.[4,17–24] We also review the diagnostic approach it requires.

CURRENT WAYS TO CLASSIFY MUS

Psychiatric Nosology—DSM-IV

Table 1 summarizes the criteria for the 7 DSM-IV Somatoform Disorders.[18] The only validated entities, somatization disorder (SD) and conversion disorder, are infrequent.[18,20,25–33] The failure to validate the other DSM-IV entities stems from extensive overlap of criteria.[34] An abridged SD (ASD) construct requires fewer symptoms and is more comprehensive, but it also lacks validation.[26,35] Multi-Somatoform Disorder (MSD) [36–38] defines MUS patients of similar severity, [39] and its reliability and validity presently are under investigation.[36,38,40,41]

MUS Patients Without a DSM-IV Diagnosis

Consistent with others, [4,26,42] Smith, Gardiner, and colleagues demonstrated in 206 distressed, high-utilizing MUS patients that less than 25% had any DSM-IV Somatoform Disorders (4.4%) or ASD (18.9%). Nonetheless, 60.2% had nonsomatoform ("psychiatric") diagnoses, primarily anxiety and depression.[23] This study's gold standard definition of MUS came from a reliable, physician-conducted chart review.[23,43] The "DSM-negative" patients were less psychologically and physically distressed than those with DSM-IV Somatoform diagnoses or ASD, but they were more distressed than the normal ones. Because researchers have relied almost entirely on DSM as the gold standard for MUS, these large numbers of distressed DSM-negative patients have been

Table 1. DSM-IV Somatoform Disorders

Somatization disorder is of many years duration, begins before age 30, is more common in women, and has (over a lifetime) at least four pain symptoms, two gastrointestinal symptoms, one sexual symptom, and one pseudoneurological symptom.
Undifferentiated somatoform disorder, the vast majority of persistent somatizers, is a residual category for patients who do not meet criteria for other somatoform disorders, is of at least 6 months duration, has no gender or age limit, and has at least one symptom.
Conversion disorder usually occurs acutely and lasts about 2 weeks but may be recurring or chronic, is most frequent in women before age 35, and exhibits one or more motor, sensory, or seizure (pseudoneurological) symptoms.
Pain disorder occurs at any age, more often in women, usually is chronic and persistent, and has one or more pain symptoms that are the predominant focus of the presentation and that are not restricted to dyspareunia.
Hypochondriasis occurs at any age in males and females, may be more common in early adulthood, is at least 6 months duration and often chronic and persistent, and has one or more symptoms that provoke an unwarranted fear (which is not delusional or restricted to concerns about appearance) of organic disease even after reassurance and appropriate investigation.
Body dysmorphic disorder begins in adolescence, occurs in males and females equally, is chronic and persistent, and is suggested by preoccupation with an alleged defect in appearance that causes patients to feel ugly (anorexia nervosa is classified elsewhere); when of delusional intensity, an additional diagnosis of delusional disorder, somatic type is made.
Somatoform disorder not otherwise specified includes disorders with somatoform symptoms that do not meet the above criteria, such as pseudocyesis and symptoms of less than 6 months duration.

completely overlooked by the field.[43] An earlier study identified some of these patients as "minor acute illness" (MAI) to highlight minor, transient symptoms that differ from the 41 in DSM-IV.[44]

In low-utilizing MUS patients, most symptoms in primary care resolve spontaneously and permanently. For example, a prospective study of 500 ambulatory clinic patients showed that 70% improved after 2 weeks and that this improvement was sustained after 3 months.[45,46]

Medical MUS Syndromes

In medical settings, chronic MUS patients typically are understood as "difficult"[47] or as one of several named MUS conditions, e.g., Chronic Fatigue Syndrome, Irritable Bowel Syndrome, Fibromyalgia. These also lack validity because of overlapping criteria.[21]

PROPOSED CLASSIFICATION OF MUS

Many have favored an approach that lumps all "MUS" patients into 1 category, and other names have been suggested, e.g., "MUS Spectrum Disorder" or "Physical Symptom Disorder".[4,17–24] Table 2 provides a template and supporting data for an evolving unitary or continuum model, and it identifies where the categorical disease entities fall on the spectrum of MUS.

In summarizing this classification, we also have been guided by Klinkman, Coyne, and colleagues who identified 3 parameters for classifying depression, and we have applied them to MUS: severity, duration, and comorbidity.[48–51] In this continuum or dimensional model, SD is at the very severe end, whereas ASD and MSD also are labeled severe. Those who do not resemble DSM-IV entities (DSM-negative; Minor Acute Illness) are in the moderate range of the spectrum, merging into mild and normal MUS patients when health care–seeking and psychological distress decrease.

Extrapolating from many[9,46,52], we estimate in Table 2 that ~80% of all MUS patients in a clinical setting are "mild": acute symptoms, low utilization, respond to reassurance and resolution of stressors, and present little difficulty for providers. Although often receiving much testing, they typically are not recognized as MUS at all; they are viewed, for example, as "noise in the system." The remaining 20% of MUS patients are high utilizers, which vary from subacute to chronic, and exist on the severity spectrum from "moderate" to "severe." This group features the physical disability and severe psychological problems that command most of our clinical attention, the ones providers usually think of as somatization, MUS, or the "difficult" patient.

Comorbid organic and psychiatric diseases are common across the entire severity spectrum, but psychological dysfunction and psychiatric diagnoses increase as the MUS becomes more severe,[53] as do functional disability and joblessness,[26,54] a history of physical or sexual abuse,[55–57] and prescription and nonprescription substance misuse.[58–60] In primary care patients with SD, 10 psychiatric problems were more prevalent than in the general population, in the order of decreasing prevalence: depression, anxiety, phobia, panic, alcohol abuse, obsessive-compulsive, antisocial personality, schizophrenia, cognitive impairment, and mania.[61] Some posit that personality disorders in general are comorbid conditions.[57,62]

DIAGNOSIS OF MUS

MUS can be *diagnosed only by excluding organic diseases*.[18,63] After that, clinicians also can make DSM-IV Somatoform diagnoses or ASD—or one of the named syndromes such as IBS.

Our focus on excluding organic diseases does not preclude the possibility of underlying, explanatory psychophysiological changes,[64] nicely summarized recently for IBS,[65] nor does it preclude that improved understanding in the future could provide organic disease explanations for what we now call MUS.[28] Nevertheless, with our present universally applied, disease-based classification system, the only useful, broadly applicable way to diagnose MUS patients is to exclude organic disease. Our long-range goal, however, continues to be integrating psychosocial and biomedical aspects to produce the biopsychosocial diagnoses articulated by Engel over a quarter of a century ago.[29,66,67] Bespeaking our progress toward biopsychosocial medicine, the isolated-disease focus needed for diagnosis does not apply to treatment because psychosocial factors already are demonstrably key elements in successful medical treatment.[11,68,69]

We recommend the following clinical guidelines to exclude organic diseases.

Normal to Mild MUS. The label "normal to mild" reflects the infrequent, appropriate seeking of reassurance for worrisome symptoms, a normal illness behavior.[70] Symptoms may be of any type and intensity but usually are few and mild, and they seldom require much laboratory or other diagnostic investigation. Rather, excluding organic diseases occurs primarily by history and physical examination and by follow-

Table 2. The Clinical Spectrum of MUS*

	Normal to mild ~80% [9,46,52]	Moderate ~15%	Severe ~5%	Very severe† <1%
Common name	"Worried well"	DSM-negative; MAI	ASD; MSD	SD
Utilization‡	Low [9]	High [23,44]	High [3]	High [3,91,92]
Age of onset	Any	Any	Any	<30 years [18]
Specific physical symptoms	Any	Any	From DSM symptom list of 41 (ASD) or 15 (MSD) [18,39]	41 specific symptoms in DSM-IV from 4 areas: Pain, GI, sexual, neurological [18]
Body systems involved	Any	Any	Musculoskeletal, GI, nervous, or ill-defined systems [93,94]	Musculoskeletal, GI, nervous, or ill-defined systems [93,94]
Symptom duration [95]‡	"Acute" days to weeks	"Subacute" < 6 mos.	"Chronic" >6 mos [18,39]	"Chronic" >6 mos [18]
Number of symptoms‡	Few	Any	>3 (men) & >5 (women) for ASD [35,96]	>7 [18]
Symptoms occur and recur with external stress and clear when it abates [95]‡	Yes	Yes, but recur frequently	No, but worsen with stress	No, but worsen with stress
Depression, anxiety, dysthymia, and other psychiatric problems‡	?	20% [23,97,98]	67% [35]	88–99% [61,99]
Personality structure	"Normal"	?	Personality disorder [98,100]	61–72% Personality disorder [101,102]; rarely, psychotic
Prevalence, community	~100% [6,103]	?	4.4–22% [20,25–27,35,104]	0.03–0.7% [18,20,25–27]
Prevalence, all outpatients	?	?	33% [3]	5–7% [3,92]
Prevalence, inpatients	?	?	?	9% [91]
Prevalence, outpatients with >5 visits per year	?	51% had MAI [44]	14% (includes very severe) [44§]	

MUS = medically unexplained symptoms; MAI = minor acute illness (derived from chart rating); DSM = Diagnostic and Statistical Manual of Mental Disorders; ASD = abridged somatization disorder; MSD = Multi-Somatoform Disorder; SD = somatization disorder; GI = gastrointestinal.

**Comorbid medical disease is frequent throughout the spectrum; psychiatric disease also is prevalent, but increases with increasing severity and utilization in MUS.*

†Because there are many data on SD, a separate column ("Very severe") has been included, although SD is very rare.

‡After organic disease is excluded, these areas particularly lend themselves to the quantification needed for explicit, concrete criteria for MUS subtyping, e.g., an average of 15 visits yearly over many years with 8 MUS symptoms during the last year that are chronic in a patient with severe depression = SEVERE; an average of 8 visits/year for the last 24 months for 5 MUS symptoms that occur intermittently but are becoming regularly persistent in a depressed patient = MODERATE; an average of 2 visits yearly for many years for 2 or 3 MUS symptoms that always occur in relationship to stress and abate with its resolution in a non-depressed patient = MILD. These examples highlight the proposed need for research to provide specific criteria for each sub-category of MUS, e.g., cutoff points for number of symptoms, number of visits, and the degree of depression.

§This study did not separate severe and very severe.

?Areas where data are unavailable and where research is particularly needed.

up *observation over time.*[44] Making mild MUS explicit as a diagnosis can help resolve the problem of excessive laboratory testing, unnecessary treatments, and iatrogenic complications.[12–16] When symptoms do not follow the expected acute clinical course (prompt resolution), an organic disease or moderate MUS with incipient high utilization is considered.

Moderate MUS. Moderate MUS also can have symptoms of any type and intensity, but this newly recognized group exhibits much greater psychological and physical distress and utilization than those with normal to mild MUS.[23] Each episode of symptoms tends to be self-limited over a few weeks to months, but these patients exhibit high utilization during this symptomatic period and with recurrences of the same or a different episode, the subsequent episode often clearing completely as well; some, however, have chronic, low-grade symptoms—and merge into the next category. Initially, after a careful history and physical examination, *observation over time* suffices to exclude organic diseases. Nevertheless, with frequent recurrences or chronicity and increased utilization, diagnostic work-up to exclude organic disease usually is needed.

Severe MUS. In contrast to moderate MUS, severe MUS is characterized by more bothersome and persistent physical symptoms (more often of the type found in DSM-IV), still greater utilization, and more physical and psychological dysfunction. These patients require *definitive laboratory or consultative investigation or both* to exclude organic diseases in many instances—but only if not already performed [6,20,35,71] and if not resolved by the initial history and physical examination (H & P) where a diagnosis sometimes can be established without further investigation, e.g., a clinical

diagnosis of angina. The H & P, of course, also provides the guidance that specifies which lab tests to order.[72] Because of the frequent presence of serious current or lifetime psychiatric disorder, one also makes sure that the diagnostic process itself does not frighten an already distressed patient. Making a clear, definitive diagnosis of moderate/severe MUS is essential: it leads the provider to the next-step—treatment[11]—rather than repetition of testing and consultation in a few months for persisting symptoms.

Moderate and severe MUS patients require work-up, even with prominent psychological complaints and without classical textbook criteria for disease, because there is a high prevalence (prior probability) of underlying organic diseases.[5] Patients with chronic low back pain, even with no objective neurological signs, usually require MRI, CT, or myelography to exclude impending neurological compromise, infection, or tumor.[71,73] For example, 1 study showed clinically significant disease (beyond the common uncomplicated disc protrusion and degenerative changes) in 15%.[74] The sensitivity and specificity of clinical findings, except for sciatica, are not sufficient to exclude significant organic diseases in chronic low back pain.[75] Similarly, 35% of patients with chronic abdominal pain or altered bowel habits or both, the symptoms alone suggesting IBS, had underlying organic disease explanations. [76] Investigation (e.g., colonoscopy) is indicated before one can diagnose these patients as MUS [77], especially those over 45 years of age.[78] Chronic pelvic pain is often thought to be caused by MUS because of prominent psychological symptoms and a negative physical exam. But, from 41% to 75% of these women have organic disease explanations, such as endometriosis, adhesions, and chronic pelvic inflammatory disease,[79–81] and laparoscopy usually is recommended.[79–83]

We note that recognizing some organic diseases may still not lead to success in difficult-to-treat conditions such as endometriosis, and that severe chronic organic diseases, especially those with pain, can lead to illness behaviors similar to those found in chronic MUS patients.[68,84,85]

The following illustrate the pitfalls of relying on symptoms alone to make a diagnosis of moderate and severe MUS.

Physical symptom criteria alone (the Rome Criteria) for the diagnosis of IBS show a sensitivity of 0.85 and a specificity of only 0.71 when gastrointestinal (GI) symptoms (e.g., bloating, diarrhea) are used to distinguish IBS from organic diseases.[77,78,86] In another study, 1 of 3 of all organic diseases and one-half of patients with active peptic ulcer were missed using clinical symptom criteria alone.[87] Involving 11,366 patients, a review of 15 studies of upper GI symptoms concluded that physical symptoms did not distinguish between nonorganic (MUS) and organic diseases.[88]

Psychological symptom criteria alone did not distinguish IBS from those with subsequently proven organic diseases in a prospective study of patients with abdominal pain and altered bowel habits.[76] Both groups had similarly elevated psychological symptom scores compared to healthy population normals. Therefore, psychosocial symptoms could not be expected to differentiate them. These data can be predicted by the biopsychosocial model[66], which tells us that psychosocial factors are indeed ubiquitous among organic and nonorganic (MUS) patients.[85]

Table 3 provides several examples demonstrating how the proposed diagnostic classification might look.

Table 3. Examples of MUS

Case 1—the most common: mild MUS

A 32-year-old man with controlled hypertension presented with the new onset of fatigue and distracting headaches, and he mentioned the threat of being laid off work. Physical examination was negative, and you empathized, supported, reassured, ordered no tests, and recommended ibuprofen. He reported 2 weeks later the symptoms had cleared, and that he was back to work.

DIAGNOSIS—MUS
Severity—mild
Duration—acute
Comorbidity—essential hypertension

Case 2—less common: moderate MUS

A 44-year-old woman presented with yet another episode of low back pain without radicular symptoms. Her diabetes also was poorly controlled, and she had gained weight. The pain interfered with work, and she had been in the clinic with recurrences 7 times in the preceding 12 months. She was not enjoying her life and said that she had difficulty sleeping, but did not feel depressed. Physical exam revealed no neurologic deficits and mild paraspinal muscle spasm. You obtained an MRI of the spine that provided no explanation for the pain (small disc without neurologic compromise), and you implemented a program of treatment for her MUS and depression,[10,11] advised exercise and weight control, and increased her metformin dose.

DIAGNOSIS—MUS
Severity—moderate
Duration—subacute
Comorbidity—depression and poorly controlled diabetes mellitus

Case 3—least common: severe MUS

A 50-year-old man related a long history of severe neck pain and headaches, virtually constant over the last 5 years. He wanted a "new approach" because he was "not getting better," even though he went to 4 doctors and 2 pain clinics in the last year. His COPD was somewhat worse recently as well. He denied depression but did have anhedonia (lack of enjoyment), insomnia, difficulty concentrating, and weight gain over the preceding year. Physical exam was negative except for changes of COPD. You did not repeat the neck and brain MRI his previous doctor had obtained 3 months earlier but reviewed it with the radiologist and learned that several minor abnormalities (a few white matter changes and mild disc protrusion without neurologic compromise) were unrelated to his symptoms. You initiated treatment for his MUS and depression[10,11] and advised a short trial of antibiotics for his COPD.

DIAGNOSIS—MUS
Severity—severe
Duration—chronic
Comorbidity—depression, COPD

Differential Diagnosis

Rare organic diseases (such as Wilson's Disease), or those with vague or unusual presentations (such as multiple sclerosis, Lyme disease, and porphyria), or those that may have prominent psychological symptoms (such as some with carcinoma of the pancreas, subdural hematoma, or ulcerative colitis) may be misdiagnosed as MUS if the physician does not have an appropriate index of suspicion.

MUS also must be distinguished from 2 rare psychiatric disorders: factitious disorder (FD) and malingering. For the sole purpose of assuming the sick role (lack external incentives), patients with FD intentionally produce organic disease, the Munchausen Syndrome being an extreme example, or they feign psychological symptoms. Unlike MUS, patients with FD usually have obvious organic diseases, although the self-induction itself may not be recognized initially, e.g., bleeding secondary to surreptitious anticoagulant ingestion or fever

caused by self-injection of feces. FD patients feigning psychiatric illness, however, are much more difficult to differentiate.

Malingering patients do not induce organic diseases, but they feign or grossly exaggerate physical or psychological symptoms for some external incentive such as financial compensation or obtaining drugs. MUS patients do not intentionally produce or feign their symptoms and usually do not have obvious external incentives.

A much more common primary care differential diagnosis occurs when a patient known to have significant organic disease develops MUS around the same symptoms and thus poses a difficult diagnostic problem,[63] e.g., the patient with a recent myocardial infarction who now complains daily of chest pain. After investigation to ensure stability, the physician often is able to restrict further study.

Equally troublesome, how does one determine whether a known MUS patient develops an organic disease? It has been proposed that when a symptom represents a new organic disease, the patient will present in a clearly different way .[5,89,90] If the physician carefully listens to and briefly examines the patient for objective evidence of disease, a significant organic disease seldom is overlooked.[5]

CONCLUSIONS AND RECOMMENDATIONS

To maximize care and understanding, an emerging perspective indicates that MUS be classified according to: (1) *severity*, ranging from mild → moderate → severe; (2) *duration*, where most MUS patients will be acute (and mild), but the most difficult ones will be subacute and chronic (moderate and severe); and (3) *comorbidity*, psychiatric or medical or both.

History and physical examination and observation over time suffice to make the diagnosis, by excluding organic diseases, in ~80% of MUS patients. These "mild" patients have a few acute visits and little ongoing physical or psychological distress. Conversely, ~20% of patients, classified as "moderate" or "severe," have increased utilization for subacute/chronic symptoms and are more physically and psychologically distressed. They typically require laboratory evaluation to exclude organic diseases and make a diagnosis of MUS.

MUS is largely untreated, common and costly, and attended by considerable distress and morbidity—some iatrogenic. Because improved recognition/diagnosis can ameliorate these problems, we recommend convening a group of experts to develop research-based, consensus definitions for each subtype of the MUS spectrum. Whereas the symptom and utilization parameters cannot themselves exclude organic diseases to diagnose MUS, they can be used to subclassify its 3 dimensions. The mild, moderate, and severe categories, we propose, must be more concretely defined, analogous to DSM criteria, if we are to maximize their potential for better defining treatment and prognosis at all levels of MUS. Only with explicit, agreed-upon criteria, for all their shortcomings, can the field move ahead. Finally, we suggest that the consensus group, at some point, include patients and work jointly with them to develop a nonpejorative name for MUS.

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