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HIGH UTILIZING PRIMARY CARE PATIENTS WITH MEDICALLY UNEXPLAINED SYMPTOMS

By

Francesca Colecraft Dwamena

A THESIS

Submitted to Michigan State University In partial fulfillment of the requirements for the degree of

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ABSTRACT

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By

Francesca Colecraft Dwamena

Some patients with symptoms have diseases but for 50% or more of ambulatory patients, and 7-9% of hospitalized patients, either no organic disease exists, or their diseases do not explain their symptoms. Many of these patients with medically unexplained symptoms (MUS) become high utilizers of healthcare resources without getting any relief. Both they and their physicians become progressively frustrated because until recently, there had been little treatment for them. This thesis summarizes advances in the field over the last 10 years.

In the first chapter, I provide a critical review of the epidemiology, diagnosis, and treatment of MUS. In chapter 2, I explore potential mechanisms of MUS with a systematic review of neuroradiological studies. The final chapter is a qualitative study of typical high utilizing primary care patients with MUS. This unique study of the experiences, perceptions, and behaviors of MUS patients has uncovered important questions for future quantitative studies.

To My Parents, Emmanuel and Victoria, and to my soul mate, Ben, who have always been my unmovable rock

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LIST OF ABBREVIATIONS

MUS
DSM Disorders Somatoform Disorders
SD Somatization Disorder
IBSIrritable Bowel Syndrome
SSRIsSelective Serotonin Reuptake Inhibitors
TCAsTricyclic antidepressants
SCL-90-R revised Symptom Checklist 90
DIS Diagnostic Interview Schedule
NURSNaming, Understanding, Respecting, and Supporting
RCT Randomized Controlled Trial
MAIMinor Acute Illness
MCS Mental Component Summary
CBTCognitive Behavioral Treatment
OROdds ratio

CHAPTER ONE

Epidemiology, Diagnosis, and Treatment of Medically Unexplained Symptoms – A Critical Review

Francesca C. Dwamena, MD

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1. Introduction

In spite of costly diagnostic testing each year, about 33% of the 400-million physical complaints in ambulatory patients can be classified as medically unexplained symptoms (MUS) [1-4]. Patients with medically unexplained symptoms (MUS) account for at least 50% of outpatient visits, and almost 10% of inpatient admissions. Either these unfortunate patients have no organic disease or, when they do have organic disease, the disease does not explain the presence or severity of their symptoms [5, 6]. Most patients with MUS have primary psychological problems that are overlooked by physicians' unending but futile attempts to find an organic disease explanation [7-11]. Attended by worry, these patients become high utilizers of healthcare resources. Unnecessary diagnostic tests [12-15], hospitalizations [15-17], and surgery [15, 18-21] in these patients lead to high iatrogenic complication rates and excessive utilization [14, 17, 21]. The physician becomes progressively more frustrated with his/her failure to find organic disease [12, 22-24] and often conveys wittingly or unwittingly that the problem is "all in the head" of the patient. The unhappy patient then leaves the physician, finds a new one, and the process begins again [12, 22-24].

Although primary care physicians are familiar with MUS patients, the spectrum of MUS in primary care had not been elucidated as most studies of MUS have focused on a small subset of patients.

2. Definition and classification of MUS in the Literature

2.1 Literature review

According to the Diagnostic and Statistical Manual of Mental Disorders, medically unexplained symptoms (MUS) are physical symptoms that suggest, but are not

fully explained by, a general medical condition; or the direct effects of a substance or by another mental disorder. This definition requires the exclusion of organic and mental disease, yet studies show a higher prevalence of symptoms without pathology in patients with chronic medical conditions independent of the severity of their medical disease [25]. Thus this definition may hinder the study of unexplained symptoms in patients with chronic organic disease. Lipowski defines somatization as "a tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness and to seek medical help for them." This definition does not exclude comorbid organic disease and highlights the importance of the patient's health seeking behavior. Many patients with MUS never or seldom seek care for it [26-28]. The problem for healthcare arises, when MUS leads to excessive utilization, or when it complicates the presentation and management of patients with organic or mental disease.

Classification of MUS has been difficult. Medical specialties have described several functional somatic syndromes such as fibromyalgia, irritable bowel syndrome (IBS) and the chronic fatigue syndrome [26]. Although controlled studies have suggested the presence of biochemical and physiological abnormalities in many patients with these disorders [29, 30], none of the disorders can be defined with specific tissue pathological changes [31]. Each of the syndromes is seen in a heterogeneous group of patients, has a higher than expected association with psychological disorders like anxiety and depression and is often refractory to standard medical treatment [32, 33]. Furthermore, the high overlap and co-occurrence [34-36] seen in this disorder has called the notion that they are distinct entities into question and many believe that they should instead be conceptualized

as different manifestations of the same problem [32, 33, 37]. The Diagnostic and Statistical Manual of mental Disorders Somatoform Disorders (DSM) provides the only comprehensive classification of medically unexplained symptoms to date. Of the seven disorders identified (somatization disorder, undifferentiated somatoform disorder, somatoform disorder not otherwise specified, conversion disorder, pain disorder, body dysmorphic disorder, and hypochondriasis.), only somatization disorder has been validated [38]. The fourth edition of DSM (DSM-IV) defines somatization disorder based on the patient's age at onset (before 30 years), chronicity (more than 6 months), number of symptoms (8 of 35 specified symptoms), and absence of organic disease. Somatization disorder is very rare with an estimated prevalence of 0.06 - 1.4% in primary care, presumably due to its stringent criteria [39, 40]. However, even the residual category, "somatoform disorder not otherwise specified", which requires at least one physical complaint, lasting more than 6 months and causing significant distress, ignores all chronic symptoms not included in the pre-specified list of 41 symptoms as well as recurrent or transient symptoms.

In a chart review of 883 patients with 6 or more visits in the previous year, Smith et al.. found that 51% of patients had multiple visits for different, minor transient symptoms, typically with little or no investigation [41]. This high utilization for multiple minor problems persisted over 2 years. A more recent study that used a reliable chart rating method as the gold standard [42] demonstrated that all four DSM-IV specific somatoform categories (somatization disorder [SD], hypochondriasis, conversion, and pain disorder) combined with the less restrictive 'abridged SD' [43] comprised less than 75% of all high utilizing primary care patients with MUS [44]. Thus, the majority of

primary care patients with MUS may not fit any DSM category. Yet these patients may have significant functional and psychological disability because of excessive worry. Conelly et al. [45] found that 21% of primary care patients had poorer health perception scores than expected for their level of physical health as rated by their physicians. These patients felt to be physically healthy by their physicians had more health worry, acute pain and depression than those with higher health perception scores.

2.2 An Alternative Classification System for Medically Unexplained Symptoms

We have proposed an alternative classification system that conceptualizes patients with MUS as a heterogeneous group with a spectrum of presentations ranging from mild to severe [46, 47] based on the number and duration of symptoms they experience and amount of healthcare they utilize [47]. The individual symptoms can be of any intensity and comorbid organic and psychiatric diseases are common across the entire severity spectrum of MUS. Psychological dysfunction, functional disability, and prescription and non-prescription substance misuse [48, 49] increase with increasing severity of MUS. Patients with severe MUS are also more likely to have a history of physical and sexual abuse [50, 51].

2.2.1 Mild MUS (about 80% of all MUS patients in clinical settings [47]

Patients with mild MUS experience unexplained symptoms, usually one or two in number, which last from days to weeks and do not lead to high healthcare utilization [2, 52]. Although these patients often undergo unfruitful diagnostic tests [2], their condition is usually not recognized as MUS because the symptoms are self-limited and usually

present little difficulty for clinicians. Nevertheless, making mild MUS explicit as a diagnosis may help resolve the problem of excessive laboratory testing, unnecessary treatments, and iatrogenic complications. These patients have not been studied [53] and are often considered "noise in the system" that is difficult to differentiate from normality [46, 47]. Psychosocial factors in patients with mild MUS are assumed (e.g., "stress" and worry) [54], but have not been specifically studied.

2.2.2 Moderate MUS (about 15% of all MUS patients in clinical settings [47])

Patients with moderate MUS have unexplained symptoms that last from one to six months and high rates of healthcare utilization (e.g., they have an average of 8 or more clinic visits a year) because of multiple recurrences of the same or different sets of symptoms (i.e., those with minor acute illness) [41]. These "worried" [45] patients often present a significant challenge for clinicians presumably because of psychological dysfunction which is difficult to diagnose and treat as they often do not meet criteria for any defined psychiatric MUS entities [42]. Prevalence of psychiatric disorders including depression, anxiety, dysthymia and other psychiatric problems is estimated at 20% in patients with moderate MUS [47].

2.2.3 Severe MUS (about 5% of all MUS patients in clinical settings [47])

Patients with severe MUS have chronic, persistent and multiple unexplained physical symptoms of at least 6 months duration that result in significant functional impairment and excessive utilization of healthcare resources [55]. These patients are well recognized and perceived as "difficult" by primary care clinicians, who lack confidence

in their ability to care for them [22, 56]. Subsets of severe MUS have been studied extensively under entities whose validities have been questioned because of significant overlap in symptom criteria [6, 32, 46]. These entities include Somatoform Disorders [5] in the psychiatric literature and Functional Somatic Syndromes [32, 46] in the medical literature. Studies suggest that at least 67% of patients with severe MUS meet criteria for some psychiatric disorder [43] and that 61 to 72% have a personality disorder [57, 58].

2.2.3.1 Severe MUS: Somatoform Disorders

DSM-IV classification of MUS includes somatization disorder, undifferentiated somatoform disorder, conversion disorder, pain disorder, hypochondriasis, and body dysmorphic disorder [5]. The most validated of these entities, somatization disorder, comprises less than 1% of all MUS patients in primary care [6, 39, 42]. In an attempt to increase detection of severe MUS, investigators have defined and studied 2 derivative entities, abridged somatization disorder [[43, 59-61] and multisomatoform disorder [62, 63].

2.2.3.2 Severe MUS: Functional Somatic Syndromes

This includes medical syndromes that are characterized more by symptoms, suffering, and disability than by disease-specific, demonstrable abnormalities [32, 46, 64]. Examples of these syndromes are multiple chemical sensitivities, sick building syndrome, and the Gulf War syndrome. More established syndromes are fibromyalgia [65], chronic fatigue syndrome [66] and IBS [67].

3. Frequency and Cost of MUS

The prevalence of all MUS in the outpatient setting ranges from 25 - 75% depending on the definition used [68, 69]. One study of ambulatory patients could identify organic disease in only 16% of ambulatory patients with new symptoms, even though diagnostic tests were performed in 70% of them [2]. A follow-up prospective study revealed that the majority of patients (~70%) improve after 2 weeks and that this improvement was sustained after 3 months [70], suggesting that the majority (~80%) of these MUS patients had mild MUS [47]. One study found that 51% of primary care patients with an average of 5 or more visits per year had moderate MUS and 14% had severe MUS [41]. The prevalence of severe MUS ranges from 4.4 - 22% in the community to 33% in the outpatient setting [41].

The cost of healthcare for MUS is estimated at more than \$256 billion /year [68]. This does not account for excessive utilization in mild MUS or the costs of loss wages and early retirement.

4. Etiology of Medically Unexplained Symptoms

The notion that one can have genuine physical symptoms that are unexplainable [71] is problematic for both clinicians and patients. Patients require specific mechanisms to help them understand their illnesses, to achieve legitimate sick roles, to access support and resources, and to take actions on their illnesses. Similarly, clinicians need to explain and treat distress, make appropriate referrals, and to recognize and process the threat of MUS to their sense of competence. Understanding the following proposed mechanisms of MUS has therefore been helpful to many clinicians.

4.1 Psychological explanations

In his comprehensive review, Brown [72] identified three groups of psychological explanations of the pathogenesis of MUS based on dissociation, conversion and somatization. <u>Dissociation</u> is a mental process that produces a lack of connection in a person's thoughts, memories, feelings and actions by reducing attention to certain sensory channels, usually in response to traumatic experiences. Supported by cognitive, electrophysiological and neuroimaging studies, modern dissociation theories assert that MUS arise when normally adaptive dissociative process becomes overgeneralized [72]. Furthermore, children who were exposed to models of illness behavior, like an ill parent, or those who were exposed to physical or sexual trauma are more susceptible MUS than those who did not have similar exposures [73].

4.1.1 Conversion theories [72]

Conversion theories extend dissociation model by describing the way in which emotional and motivational factors contribute to MUS generation. Unconscious suppression or repression of traumatic memory purportedly protects the individual from potentially overwhelming negative affect. To preserve energy balance, the brain "converts" the repressed, negative affect into a somatic symptom that either was present at the time of the initial trauma or is some symbolic representation of it. Thus the primary motivation for MUS is to reduce anxiety by allowing individuals to express underlying psychological conflicts without consciously acknowledging them. Secondary motivation arises from all other advantages associated with being ill, such as sympathy, attention and

avoidance of work. Conversion theories are supported by studies that associate alexithymia [74] and reinforcement (secondary gain) [75] with MUS, although such associations are not consistent across all studies [76, 77].

4.1.2 Somatization models [72]

These focus more on the process and less on the specific mechanisms of MUS as demonstrated by Lipowski's [78] definition of somatization, "a tendency to experience and communicate psychological distress in the form of somatic symptoms and to seek medical help for them." Best articulated by Kirmayer and Taillefer [79], somatization models postulate that MUS develop when emotional arousal or normal bodily sensations produced by everyday physiological processes are misinterpreted as indicators of disease leading to illness worry, catastrophizing and demoralization and adoption of the "sick role." This exposes MUS patients to social forces that reinforce their illness behaviors. The somatization process is moderated by several factors including patients' personality structures, previous illness experiences, response of significant others and healthcare providers, work conditions, disability, insurance and compensation systems.

4.1.3 Integrative model

Brown proposes an integrative approach [72] in which symptoms are purportedly caused by stored information in the cognitive system that disrupts the interaction between conscious and preconscious aspects of information processing. The development of the stored information often is driven by defensive reactions that mitigate traumatic effects. Central to the creation and maintenance of MUS is excessive focus on symptoms,

amplified by abnormal illness belief and behavior, worry, negative affect, secondary gain and abnormal personality features.

While psychological theories, especially integrative models like that of Brown [72], may provide a useful scheme for organizing existing and future research, cultural biases against the notion of embodied emotions and mental illness limit the acceptability of psychological explanations to patients [31, 80, 81]. Qualitative studies suggest that MUS patients instead prefer tangible (physical) explanations that they can understand and that free them from blame [82]. Consistent with this, Sharpe and others [31] have proposed a paradigm shift in which MUS is "remedicalized" around psychophysiologic explanations. These theories simultaneously acknowledge psychological and neurobiological correlates of physical symptoms by highlighting reversible functional disturbance, rather than fixed psychological pathology.

4.2 Psychophysiologic explanations

Psychophysiologic theories provide plausible explanations for most common physical symptoms [31, 71]. Bi-directional fibers make emotional and cognitive input from the brain possible in the perception of symptoms. Disturbed regulation of physiological systems caused or aggravated by psychosocial stress or limitation causes MUS. These perturbations do not require structural lesions detectible by current clinical examinations or diagnostic tests. A classic example is provided by the Gate Control Theory of pain, the basic premise of which is active CNS modulation of pain from peripheral nerves through a network of bidirectional pathways. This 'gating system' can be affected by many psychological factors known to affect the brain, like current emotion

and prior experiences with pain and anxiety [83, 84]. Pain disorders purportedly result from disruption of normal CNS response to sensory stimulation that alters patients' perceptions and interpretations of normal bodily sensations [85]. Functional and structural brain imaging as well as other preliminary physiological studies support mechanisms in other MUS syndromes like chronic fatigue syndrome and fibromyalgia [86], and IBS[67].

In all the mechanisms discussed thus far, the etiology of MUS is thought to originate in the individual. This may be problematic in some patients such as those who belong to groups where social values are elevated above individual autonomy. For these patients, sociosomatic theories which are supported by ethnocultural studies provide an alternative framework for explaining MUS [71].

4.3 Sociosomatic explanations

Sociosomatic explanations locate the etiology of symptoms in societies rather than individuals [71, 87, 88]. Many social groups have developed culturally acceptable language that embody combinations of physical, emotional and social meanings and offer clues to accepted meanings of certain symptoms [87]. For example well-described culture-bound syndromes like "ataque de nervios" among Hispanics and "hwa-byung" in Koreans are understood as resulting from cumulative anger repressed to maintain social harmony and relationships [89-92]. Other symptoms serve as a form of social protest or challenge that helps to mobilize appropriate resources while protecting individuals from the consequences of complaining about one's psychological or social plight. For example, illness narratives of Vietnamese immigrants attributed the etiology of their

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MUS "uat u'c" to indignation over a social injustice that had to be endured in order to maintain social order and harmony [71]. The study provided the first opportunity for many of these participants to discuss their interpretations [71]. Mindful clinicians can offer patients with MUS similar opportunities to create meanings for their symptoms by exploring their characteristics,

5. Risk factors for MUS

Several studies have shown a high association of MUS with anxiety and depression. In a large multinational cross-sectional survey of primary care patients, Gureje et al. [93] showed that patients with somatization disorder were more likely to have depression in 13 out of 14 countries (OR 2.54 - 7.07, p<0.001). Similarly, anxiety was more prevalent among patients with SD in 13 out of 14 countries (OR 2.20 - 7.34). These findings are consistent with data from the Epidemilogical Catchment Area trial [4], which showed that most symptoms in community patients were associated with at least a twofold increased lifetime risk of depression and anxiety. Katon et al. [55] enhanced the documentation of this association by demonstrating a "dose-response" relationship. In an attempt to test their hypothesis that MUS represents a spectrum rather than a dichotomy, they divided distressed high utilizers who were randomized to receive psychiatric intervention into four categories according to the number of medically unexplained somatic symptoms. Their results, which are summarized in Table 1, show that the burden of psychiatric illness and disability increases with increasing number of unexplained symptoms. A major limitation of all these studies is their cross-sectional design, which

precludes conclusions about the directionality of the association between MUS and anxiety or depression. Does one cause the other, or is one a subset of the other?

If one causes the other, which is the cause and which is the effect? None of the studies reporting associations can answer these questions.

Inconsistent results of trials of treatment of MUS syndromes with antidepressant medication also highlight the lack of clarity about the nature of the relationship [94, 95].

Table 1: Prevalence of Lifetime Anxiety andDepression in High Utilizing Patients with MUS			
Group (Number of symptoms; n)	Panic Disorder N (%)	Major Depression N (%)	Dysthymic Disorder N (%)
1 (women < 6, men <4; 31)	1 (3.2)	14 (45.2)	7 (22.6)
2 (women: 6- 8, men 4-8; 40)	8 (20.0)	30 (75)	9 (22.5)
3 (9 – 12; 21)	4 (19.0)	15 (71.4)	5 (23.8)
4 (≥ 13; (N=27)	13 (48.1)	22 (81.5)	17 (63.0)

In addition to depression and anxiety, childhood and adult violence are emerging as important risk factors for MUS [96-102]. A cross-sectional survey [100] of 1931 women who sought care in 4 community-based internal medicine clinics revealed more physical symptoms (mean \pm SD 6.2 \pm 0.2 vs 4 \pm 0.9, p<0.001) and higher mean MUS score (p<0.001) in patients with previous childhood sexual or physical abuse. The prevalence ratio of previous childhood abuse was 3.5 (CI = 2.3 – 5.1) in women with the highest scores (upper third) for MUS compared with those the lowest (lower third) scores. Although this study had several limitations such as possible selection as well as recall bias, it has important strengths that help to validate its results. Firstly, the study was designed specifically to assess the relationship between physical / sexual abuse and subsequent MUS and psychological illness. Their a priori hypothesis formulation provided some protection against chance findings. Secondly, study participants were

demographically and socio-economically diverse, thus increasing generalizability. Thirdly, the strength of the association was relatively large, thus diminishing the likelihood of important confounders. Finally the association is consistent with other studies [96, 97, 99, 101], whose results are summarized in Table 2. Lessons learned from these studies may prove useful in the design of MUS prevention and treatment studies.

Table 2: Summary of Studies on Sexual and Physical Abuse			
Study (reference)	Study setting and design	Main findings	
I [101]	Case-Control: somatization disorder compared with primary affective disorders	Higher childhood molestation in SD	
II [96]	Case series; 7 patients with history of sexual abuse	Mean of 18 medical visits, 8 operations, 66-70% normal findings with visits and operations	
III [97]	Cross-sectional: functional vs. organic disorders, consecutive women in specialty clinic.	Functional disorders associated with: sexual abuse (OR 2.08. CI = 1.03 - 4.21) and physical abuse (OR 11.39, $CI = 2.22 - 58.48$)	

6. Diagnosis MUS in primary care

Effective treatment for MUS in primary care exists [103], but often is not utilized as both healthcare providers and patients are caught in a cycle of fruitless diagnostic testing and unsatisfactory symptomatic treatments. Diagnosis of MUS is essential to limit excessive diagnostic testing and to initiate treatment of MUS.

6.1 Clinical Diagnosis

6.1.1 Mild MUS

Mild MUS is diagnosed primarily by obtaining an appropriately detailed history and physical exam and observing the patient over time for resolution [47]. Most symptoms in primary care resolve spontaneously without being medically explained. For example, review of the charts of 1000 ambulatory care patients revealed an organic cause in only 16% of patients even though diagnostic tests were performed in 70% of them [2]. Similarly, a prospective study of 500 ambulatory clinic patients showed that 70% of patients improved after two weeks and that this improvement was sustained after 3 months [70].Ordering unnecessary tests that come back negative can heighten patients' concerns that a serious disease is being missed. False positive tests can lead to further, sometimes harmful testing and can increase anxiety. Therefore, for low-utilizing patients with acute or new symptoms in whom organic disease is unlikely following an appropriately detailed history and physical exam, a diagnosis of mild MUS can be made. The psychosocial context of the patient's symptoms must be determined to ascertain stress or to help diagnose those patients whose symptoms may be due to their psychosocial circumstances. Rather than tests and consultations, clinicians rely upon observation over time for prompt resolution.

6.1.2 Moderate to severe MUS

In contrast to mild MUS, moderate to severe MUS must be evaluated by appropriate testing and consultation to exclude organic disease. There is a high prevalence of organic disease in patients with chronic, disabling symptoms, initially felt to be due to MUS because there were no objective findings on history and physical exams. For example, Laparoscopic studies in 100 women with pelvic pain for at least 6 months revealed organic pathology including endometriosis, adhesions, and others, in 83% [104]. Similarly, ten (11.8%) of 85 patients referred to a psychiatric hospital with a diagnosis of conversion disorder were found to have a neurological disorder after median

follow-up period of 2.4 years [105]. False positive rates for conversion disorder have been found to be as high as 15% in a comparable study with 10 years of follow-up [106] and as low as 4.7 % in a 6-year follow-up study conducted at secondary and tertiary neurological centers [107]. Clinicians must maintain a high level of suspicion for conditions like multiple sclerosis, Lyme disease, systemic lupus erythematosus, porphyria, celiac sprue) can elude diagnosis if the physician has a low index of suspicion. In addition, many functional somatic syndromes (e.g., IBS) cannot be distinguished from organic disease (e.g., inflammatory bowel disease), based on symptom criteria alone. For instance, in a study of 602 new referrals to a gastroenterology clinic, the Rome criteria yielded a sensitivity of 85% and a specificity of 71% for diagnosing IBS [108]. In another study that used both retrospective and prospective designs, adding the absence of red flags to the Rome criteria yielded a sensitivity of 63% and a specificity of 100% in the retrospective study, and a positive predictive value of 98% in the prospective study. However, the study used gastroenterologists' evaluation as the 'gold standard' and only 45% of patients 45 years or younger had their colon investigated [109].

Complicating matters further, MUS can occur with co-morbid physical and/or psychological disease. Patients with co-morbid MUS are more severely ill than expected from their physical disease. A medically unexplained symptom often may co-exist with an organic disease (e.g., IBS with Crohn's disease) that will respond to different treatments; therefore, it is important to diagnose both co-morbid conditions.

However, one must guard against making a diagnosis of moderate to severe MUS because prominent psychological features are present. In a prospective study of 97 referred patients that sought to determine the utility of six psychosocial factors for

diagnosing IBS, Smith et al.. [110] found that the psychosocial factors did not distinguish between IBS and organic disease. Instead, psychosocial factors were related to high utilization in both IBS and organic disease. The authors concluded that psychosocial criteria were of limited value in differentiating IBS from organic disease.

Once definitive work-up has been completed, however, it is not necessary to repeat them. Most excessive diagnostic testing is instigated by the doctor rather than, as commonly believed, by the patient. This appears to satisfy the doctor's diagnostic need "to be sure" but, at the same time, it inadvertently avoids the patients' expressed and hidden psychosocial and emotional needs [111].

6.2 Identification of MUS patients for research

Our group has developed and published a reliable chart rating procedure to identify high utilizing patients with MUS for research [44]. We clarified symptom categories from the charts of ambulatory patients with eight or more visits per year and developed decision rules so that all symptoms could fall into a category and all categories were mutually exclusive. We trained three senior internal medicine residents and two primary care faculty members to rate charts to determine whether an organic disease was identified for all recorded symptoms in the year before a randomized controlled trial of treatment for patients with MUS. The raters classified each physical symptom as 'documented organic disease' if definitive tests such as laboratory, radiographic or other diagnostic testing, classic or definitive physical findings and/or consultants' opinions based on objective testing provided an organic disease explanation; if tests were negative, symptoms were rated 'documented non-organic disease". Symptoms that had either

insufficient or no testing were rated 'undocumented disease." Raters then summarized each visit based on the number of categories represented and added all categories in the 12 month-period. Percent MUS/visit was defined as the sum of documented organic and undocumented categories divided by the total number of categories over 12 months. Inter-rater reliability was high – percent agreement for documented organic, documented non-organic and undocumented were 92%, 96% and 92% respectively. We used this method to identify patients with MUS, and to quantify the proportion of MUS/visit over 12 months and their medical co-morbidities.

Because of difficulties previously mentioned, an alternative method of MUS case identification, like this validated chart review method, may be more effective than the DSM-IV-oriented structured interview [44] or widely used screening instruments like the Symptom Checklist 90, Revised (SCL-90-R) in patients with multiple outpatient visits. The SCL-90-R is limited in the diagnosis of MUS in patients with chronic medical diseases because it contains many items that reflect symptoms possibly attributable to the medical disease [112]. The method is able to determine whether an organic disease was identified for any recorded symptom and to classify MUS as documented non-organic (appropriate tests, no organic disease) or undocumented (no documented test) MUS. Because it does not rely on patient recall, it may be more accurate than a structured interview like the diagnostic interview schedule (DIS) that requires patient recall of lifetime prevalence of symptoms[44, 113].

7. Treatment of Medically Unexplained Symptoms in Primary Care

Patients with moderate to severe MUS are likely to be very concerned, angry, or sad about their symptoms and are potentially mistrustful of the clinician because of previous experiences or because of worry about serious organic disease. Thus, empathic interactions with clinicians enhance the patient's participation in the treatment plan and improve outcomes. A systematic review of 23 analytical and/or randomized controlled studies found that patient-centered communication interventions reduced patients' symptoms, increased satisfaction, and improved functional status and adherence to medical recommendations [114]. However, most of the studies included in the review involved patients with organic disease rather than MUS. In a RCT [115], resident physicians trained in a 5-step, 25-substep patient-centered method that used an empathic method called NURS (naming, understanding, respecting and supporting emotions), were more likely to report increased confidence in their psychological sensitivity and management of MUS than resident controls. The study also showed a trend toward improved patient satisfaction and health in the patients of trained residents compared with those of resident controls. A review of the literature indicated that most trials of interventions for MUS rarely attended to the provider-patient relationship systematically [116].

Recently, primary care providers used the 5-step, 25-substep method to motivate patients with moderate to severe MUS to engage in individualized treatment plans. This RCT [103] demonstrated statistically and clinically significant improvements in patients' satisfaction with the providers' communication and relationship building skills. Satisfaction was in turn associated with adherence to the treatment plan (i.e., more

intervention patients decreased use of controlled substances (p=0.043) and more increased use of full dose antidepressants (p = 0.037) compared with controls).

In addition to an effective relationship, the treatment employed proven cognitive behavioral techniques. A systematic review [117] of 31 controlled trials (29 randomized, 2 nonrandomized), revealed that specialty conducted CBT significantly improved physical symptoms in 20 (71%) of the 28 studies that assessed them, and showed a trend toward improvement in another 3 (11%). Similarly, CBT definitely (n=9, 47%) or possibly (n=5, 26%) improved functional status in 17 studies. In contrast only 38% and 8% of 26 studies showed definite or possible improvement respectively in psychological distress with CBT. Benefits obtained at the end of treatment persisted at follow-up (range: 1 month – 24 months) in 29 of 30 studies that studied durability of outcome. Smith et al. [103] demonstrated that primary care providers could use similar cognitive behavioral techniques of education, commitment, goal-setting and negotiation to treat MUS. In their study [103], 48(49%) intervention patients compared with 34(33%) usual care patients achieved the primary endpoint of a 4-point improvement in the mental component summary (MCS) of the SF-36 (OR = 1.92, CI = 1.08 - 3.40). According to the authors, a 4-point improvement in MCS corresponded with the improvement observed following combined mitral and aortic valve replacement.

An important part of MUS treatment is to motivate patients to adopt healthy lifestyle behaviors. Healthy behaviors enhance the effectiveness of other aspects of the patient's specific treatment plan, and improve the MUS patient's function and quality of life. Many of the recommended activities have some, though not optimum, supporting evidence. For example, a non-randomized controlled trial [118] of a convenience sample

of 16 patients showed that 15 minutes of relaxation response meditation twice a day for six weeks reduced symptoms recorded in symptom diary, especially pain and bloating, in patients with IBS. The effects of the program persisted after 1 year of follow-up [119]. Similarly, a prospective, randomized trial [120]of 58 patients revealed that swimming pool exercises matched to patient's threshold of fatigue and pain significantly improved Fibromyalgia Impact Questionnaire score and 6-minute walk test compared with usual care controls. Follow-up was after 6 months. In addition to better improvement in the primary end-point, the RCT trial by Smith et al..[103] demonstrated significant improvement in disability scores of intervention patients (p = 0.001), but not in the scores of control patients (p = 0.26).

In addition to this non-drug therapy, research also supports some pharmacologic agents, but not others. Narcotics and other addicting medications may cause depression and exacerbate the patient's symptom, while non-narcotic analgesics and other benign symptomatic medications are often effective and inexpensive. Antidepressants are useful for both symptom reduction and treatment of co-morbid depression and anxiety. In a systematic review [121], 64 out of 94 trials (69%) demonstrated some benefit of antidepressants in patients with MUS. Patients receiving antidepressants were more than 3 times as likely to experience symptomatic improvement than patients receiving placebo. Meta-regression did not differentiate effect across different classes of antidepressants, however studies of tricyclic antidepressants (TCAs) were more likely than studies of selective serotonin re-uptake inhibitors (SSRIs) or antiserotonin agents to have a beneficial outcome (p=0.02). Depression was assessed in only 49 (52%) of studies and association between depression and response to treatment was performed in only 24

studies (25% of all studies). Of the 24 studies, only 8 (33%) demonstrated a correlation between physical symptom response and depressive response. Moreover, the study was plagued with significant publication bias. In Smith et al.'s study [103], 65 (68.4%) intervention patients, compared with 20 (19.8%) usual care controls increased use of antidepressants to full doses (p<0.001). Similarly among patients who were previously using controlled substances, 26 (70.3% of using intervention patients) compared with 6 (14.3% of using control patients) reduced usage (p < 0.001). Increase in use of full antidepressant (p = 0.001), but not reduction in use of controlled substances (p=0.26), was associated with improvement in the primary endpoint of the trial [103]. Thirty-seven (80%) of patients who improved took full dose antidepressants, suggesting that full dose antidepressant use was a significant, but not the only contributor to improved patient outcome. There is consensus that TCAs may have more analgesic efficacy in chronic pain than SSRIs mainly because more studies involve TCAs and studies involving TCAs more consistently demonstrate efficacy against pain [122].

Physicians commonly experience negative emotional reactions to patients with MUS. These negative emotions can be harmful to patients and lead to physician 'burnout' if not recognized and addressed. Moreover, physicians' personal characteristics, past experiences, and biases can have important effects on communication with patients, especially those with MUS. A qualitative study [123] revealed that maladaptive behaviors like being overly controlling, avoiding psychological material and being passive or detached were common during medical residents' and fellows' interactions with patients. These behaviors were usually associated with previously unrecognized emotions like anxiety about losing control, anxiety about addressing psychological material, or anxiety

about harming the patient. Infrequently, discussions with these trainees uncovered feelings of sexual attraction, anger, disdain, feelings of inadequacy or intimidation that may have been rooted in personal issues and previous experiences. Another qualitative study showed that 6/53 resident learners had personality patterns that inhibited self-awareness work [124]. These learners showed little learning and little clinical use of the patient-centered methods being taught. It may be occasionally necessary for clinicians with similar personality patterns and attitudes to transfer care of MUS patients to other colleagues.

8. Summary

MUS is a difficult and common problem in primary care. We have made significant progress over the last ten years. We have recently published a proposed classification scheme that may be more useful to clinicians. It is awaiting empirical testing. We have also developed an effective treatment that can be deployed by primary care clinicians. The field needs descriptive data on MUS in primary care.

CHAPTER TWO

Structural and Functional Neuroradiological Changes in Patients with Medically

Unexplained Symptoms (MUS) Syndromes: A Systematic Review

Francesca C. Dwamena, MD

1. Introduction

Medically unexplained Symptoms (MUS) refer to physical symptoms that suggest, but are not fully explained by, a general medical condition; or the direct effects of a substance or by another mental disorder. [5] In the psychiatric literature, these "functional somatic symptoms" [125]and "somatization symptoms" [126] are incorporated into the nomenclature as "somatoform disorders." Some medical specialties have also developed "functional syndromes" such as IBS, chronic fatigue syndrome, and fibromyalgia. These conditions share common features including symptoms like fatigue, pain, disability out of proportion with physical examination findings and an association with stress and psychosocial factors. Indeed, the overlap between these syndromes [32, 127] has led some authors to suggest that they are different manifestations of the same basic problem, [34, 35, 37, 64] whose cause and pathophysiology remains enigmatic. Because many of these patients complain of headaches and show some cognitive dysfunction, the brain is believed to be a good candidate for abnormality.

In addition to laboratory studies, investigators have pursued brain defects in some of these syndromes by conducting structural and functional neuroradiological studies. Although both computer assisted tomography (CT), and magnetic resonance imaging (MRI) permit reliable in vivo structural imaging of the brain, MRI appears to be more sensitive in detecting abnormalities in at least one MUS syndrome [128] and is chosen for evaluation in this paper. More recently, more sensitive functional imaging techniques including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI have been developed and are being employed in the study of MUS syndromes [129, 130]
The purpose of this paper is to summarize studies of structural and functional neuroimaging using MRI, functional MRI, PET and SPECT in patients with MUS. We also sought to examine whether there were common patterns of neuroradiological findings among studies of MUS syndromes, and suggest directions for future research.

2. Methods

2.1 Literature retrieval

English-language articles were identified through a search of the SilverPlatter Medline database from 1966 to June 2002. Search terms and strategy included (magneticresonant-imaging/all subheadings, PET scan or positron emission and tomographyemission-computed/all subheadings) and ("Somatoform-Disorders"/all subheadings or "hypochondriasis"/all subheadings or "hysteria"/all subheadings or "fibromyalgia"/all subheadings or "Fatigue-Syndrome-Chronic"/all subheadings or "Food-Hypersensitivity"/all subheadings or "Colonic-Diseases-Functional"/all subheadings). Variants of these terms were also included by using the 'explode' function. Additional keywords included functional somatic symptom(s) and functional somatic syndrome(s). Finally, the bibliographies of retrieved reports were examined for other articles. This process yielded 27 articles, 11 of which are included here. A meta-analysis could not be conducted given the small number of studies and because of variations in study design, methods, and case definitions.

2.2 Inclusion Criteria

Original articles describing neuroradiological studies in patients with MUS are included in this article. Only 1) full articles published in peer review journals in the English language are included. To ensure adequate comparisons, we required that 2) radiological studies should be done in all study subjects. Other inclusion criteria are 3) adequate number of patients (\geq 10), 4) at least one control group and 5) a clearly defined patient population. One original study [131], which assessed MRI abnormalities in patients with chronic fatigue syndrome did not have radiological studies in all patients and was excluded. Another study [132], whose main goal was to assess cognitive functioning and MRI findings in chronic fatigue was also excluded because patients did not have to meet criteria for CFS, or any other MUS syndrome. Two studies [129, 133] were excluded because they evaluated patients with MUS syndromes but had no controls. All other studies were excluded either because they were not original studies or did not address this study's question.

2.3 Recorded Variables

Recorded variables from each study included the full study reference, type of MUS syndrome, type of radiological study, number of patients, number of healthy controls, type and number of other controls, central nervous system site and abnormalities reported, and the major findings. The following variables were also extracted to assess the quality of the different studies: Sampling, study design, gender distribution of subjects, mean age, and whether or not the one reading the radiological study was blinded.

3. **Results**

The qualities of the studies selected for inclusion in this report are summarized in the Table 3. Most of the studies were controlled cross-sectional studies of convenience samples. About half of the studies documented blinding of the radiologist that reviewed the neuroradiological study. There was however some variation in the quality of studies as shown in the table.

Table 4 summarizes the major findings from the studies. Seven and four of the eleven studies involved chronic fatigue syndrome (CFS) and IBS (IBS) respectively. There were no suitable studies of fibromyalgia, somatization disorder or other somatoform disorders, hypochondriasis or any of the other MUS syndromes included in our extensive literature search. Studies of CFS evaluated both structural as well as functional abnormalities while all IBS studies were investigations of functional abnormality. IBS studies all involved neural responses to rectal stimuli.

Although there was considerable variability among studies within each MUS syndrome, all but one study documented significant functional abnormality compared with normal and other controls. Because the methods employed in IBS studies were similar among each other, but completely different from CFS studies no comparisons could be made between the two groups. Thus, I have made only within group comparisons.

3.1 Chronic Fatigue Syndrome (CSF) studies

Five of the seven CFS studies used functional neuroradiological studies (mostly SPECT). Most of the abnormalities involved the frontal, temporal and parietal lobes, but one relatively large study documented brainstem hypoperfusion in all CFS patients compared with normal and depressed control patients.

There were 3 MRI studies of structural changes in CFS. All of these showed increased subcortical white matter signal intensities compared with controls. Most of the abnormalities, like the functional studies, involve the frontoparietal lobes. Other changes, which were not consistent among the studies, include increased intensities in the corona radiata, centrum ovale, frontal white matter and periventricular areas.

3.2 Irritable Bowel Syndrome (IBS) studies

Three of the four studies used functional MRI while two used PET scans. One study used both. Again, there was significant variability but all the studies showed enhanced anterior cingulate gyrus activation with rectal distension compared with normal controls. Other areas of abnormality that are not consistent among studies include the left prefrontal cortex, left somatosensory cortex, the brainstem, temporal lobes, insular cortices and the thalamus.

4. Discussion

The most important finding of this systematic review of the literature on structural and functional neural abnormalities in MUS syndromes is that very few studies have been conducted. All studies that met inclusion criteria involve either CFS or IBS. Similar

studies must be conducted in patients who meet criteria for fibromyalgia, somatoform disorders or other MUS syndrome if the possible common etiological factor of these syndromes is to be fully elucidated.

The review also shows that although the current literature precludes comparison of neuroradiologic changes between different MUS syndromes, there are some common observations from studies within groups. Patients with CFS appear to have significant abnormalities in the subcortical white matter of the frontal, parietal and temporal lobes when compared with controls. This is not surprising given the fact that there is considerable cognitive dysfunction in patients with CFS. It will be interesting to see if similar changes are documented in other MUS syndromes. It must be emphasized, however, that there was considerable variation in other areas of abnormality among the CFS studies.

Studies of IBS also showed remarkable consistency in abnormalities involving the anterior cingulate gyrus. The reported alterations may be related to altered central noradrenergic modulation and are consistent with findings of emotional lability in patients with IBS. It is quite possible that these findings are common to other MUS syndromes or psychological disorders but this has not been studied.

The findings of this review must be interpreted with consideration of its limitations. Although considerable effort was made to find all relevant articles, it is quite possible that important studies were missed. In order to improve comparability, I did not include studies with CT scans, but this may have systematically excluded important information about structural abnormalities in these patients. Furthermore, broadening the search to include studies with CT scans may yield information on other MUS syndromes

such as fibromyalgia and somatoform disorders, thereby permitting comparisons between the groups.

These limitations notwithstanding, this preliminary review is the first attempt to summarize and compare information on structural and functional abnormalities in different MUS syndromes. It provides a framework for a more complete literature search and subsequent review, whose data can inform the search for the pathophysiology of the vexing problem of MUS.

Table 3: Systematic Review - Study Demographics and Quality						
Study (Ref)	Sampling	Case Definition	Study Design	Gender	Mean age	Blinded review?
Schwartz et al.[128]	Convenience sample, healthy volunteers	CDC, British or Australian definition of chronic fatigue syndrome (CFS)	Cross- sectional	64% female	70 <u>+</u> 13.2	Not stated
Ichise et al [134]	Convenience sample	Clinically defined	Cross- sectional			Yes
Schwartz et al [135]	Convenience sample, healthy volunteers	CDC, British or Australian definition of chronic fatigue	Cross- sectional	69% female (SPECT) 62% female	42.5 ± 2.3 49.6 + 6.2	Yes
		syndrome (CFS)		(MRI)	_	
Costa et al. [136]	Convenience, healthy volunteers	Clinical diagnosis	Cross- sectional	67	40	Not stated
Lange et al. [137]	Convenience sample	1994 case definition	Cross- sectional	80% female	36 <u>+</u> 8	Yes
Tirelli et al. [138]	Convenience sample	CDC definition for CFS	Cross- sectional	65% female	34 ± 15 48 ± 7 (dep)	Not stated
Greco et al. [138]	Convenience sample	Clinical diagnosis	Cross- sectional	75% female	Range 22 - 78	Yes
Silverman et al. [139]	Cosecutive sample from referral center	Rome criteria for IBS	Cross- sectional	Not stated	Not stated	Not stated
Bernstein [140]	Convenience	Clinical diagnosis	Case series	67% F in cases 100% males in controls	40.2 ± 6.6 33.8 ± 9.4	Not stated
Naliboff et al.[141]	Convenience	Rome criteria	Cross- sectional	16% female	39 (27 - 58)	Not stated
Mertz et al [142]	Convenience sample	Rome criteria	Cross- sectional	90% female	33 (20 - 52)	Yes

	Major findings	CFS patient had similar number of defects as depression, less than AIDS and more than healthy controls. Miderethal uptake index similar to AIDS and less than	wepression on neuron controls 80% of CFS patients with at least one area of reduced cerebral blood flow. CFS with significantly lower cortical/cerebellar regional cerebral blood flow ratios than controls	2.06 foci in CFS vs. 0.80 foci in controls. MR abnormalities in 50% of CFS vs. 20% of controls (p=NS). PECT abnormalities in 81% of CFS vs. 21% of controls fo-0101	Brainstern hypoterfusion was confirmed in all CFS patients. CSF patients with no psychiatric disorders showed significantly lower brainstern perfusion than depressed patients.	Larger number of brain abnormalities in CFS patients with no psychiatric disorders compared with others. No difference between combined CFS group and normal controls
	CNS site and abnormality	Frontal and temporal lobe defects and midcerebral uptake index	Frontal, temporal, parietal and occipital lobes	Increased T2-bright signal in periventricular and subcortical white matter and centrum ovale	Brain stem perfusion	Small, punctate subcortical white matter hyperintensities in predominantly frontal lobes
ables	Other control (n)	AIDS ¹ (27) Depression (14)	None	None	Epilepsy (10) Depression (29)	None
xtracted Varia	# of healthy control	38	14	15(matched) 14(matched)	40	19
f Studies and F	# of patients	45	60	16	67	39 21- no psych 18- psych
v - Summary o	Type of radiological study	Single photon emission computed tomography (SPECT)	SPECT	Magnetic resonance Imaging (MRI) and SPECT	SPECT	MRI
matic Review	MUS syndrome	Chronic fatigue syndrome (CFS)	CFS	CFS	CFS	CF5
Table 4: Syste	Study (Ref)	Schwartzet al [135]	[134]	Schwartz et al. [128]	Costa et al.[136]	Lange et al.[137]

AIDS = Acquired Immunodeficiency Syndrome - dementia complex

	Major findings	CTS patients with significant hypometabolism in both fromat cortex and brainstein compared with exact and the particular particular showed significantly more hypometabolism of medial and hypometabolism of medial and brainstein corregions but normal brainstein corregions but normal	No difference in prevalence of white matter hyperintensities between CFS and controls.	Pain perception was positively correlated with anterior cingulated correlated with anterior cingulated but not in patients with IBS, In IBS, there was significant activation in the prefrontal cortex	therizer eighting eyrus activation was greater in IIS than normal controls but less than IBD. Left and ansuccensory teactivation was greater in IIS than either IBD or normal controls. Frontal normal controls. Frontal than either IBD or FIBS
	CNS site and abnormality	Hypometabolism in right mediofrontal cortex and brainstem	Mostly frontoparietal subcortical white matter foci but also corona radiata, centrum ovale and frontal white matter	Anterior cingulated cortex, and left prefrontal cortex	cingulated gyrus or deactivation cingulated gyrus or deactivation of left somatosensory cortex.
	Other control (n)	Depression (6)	None	None	Inflammator y bowed disease (IBD) (6)
	# of healthy control	6 (matched)	43 matched	9	9
	# of patients	18	43 15-no psych 14- depressn 14-other psych	9	9
	Type of radiological study	[18F]fluorin e- deoxyglucos e positiron emission tomography (FDG-PET)	MRI	¹⁵ O-water positron emission tomography (PET)	Functional MRI
ned	MUS syndrome	CFS	CFS	Irritable bowel syndrome (IBS)	IBS
Table 4 Contin	Study (Ref)	Tirelli et al. [138]	Greco et al. [143]	Silverman et al.[139]	Bernstein [140]

_		
	Compared with controls, IBS patients showed lateralized activation of the right prefrontal cortex; reduced activation of perigenual cortex, temporal lobe and brainstem; but enhanced activation of rostral anterior cingulate and posterior cingulate cortices	In IBS pain caused greater activation of the anterior cingulated gyrus than nonpainful stimuli. IBS activation of the anterior cingulate gyrus was stronger than response of controls to painful stimuli
	Activation of frontal and cingulate cortices, brain stem and temporal lobes in response to rectal stimuli	Anterior cingulated prefrontal cortex, insular cortices and thalamus
	None	None
	12	16
	12	18
	Functional MRI	PET and Functional MRI
nued	IBS	IBS
Table 4 Conti	Naliboff et al.[141]	Mertz et al.[142]

CHAPTER THREE

In Their Own Words: Qualitative Study of High-Utilizing Primary Care Patients with Medically Unexplained Symptoms

Francesca C. Dwamena, MD; Judith S. Lyles, PhD; Richard M. Frankel, PhD; Robert C. Smith, MD, ScM.

ABSTRACT

Objective: To describe perceptions and experiences of primary care patients with medically unexplained symptoms (MUS).

Methods: A random sample of 19 high utilizing primary care patients, for whom 69.6% of visits were medically unexplained, were encouraged to talk spontaneously about themselves and answer semi-structured questions. Verbatim transcripts of interviews were analyzed using Grounded theory.

Results: All but one participant described at least one type of negative experience. Regardless of their experiences, all except three participants recounted stories of achievement, positive action, and/or altruism. The three participants who did not report any positive behaviors projected very low levels of insight and a sense of entitlement. They talked often and vaguely about their symptoms and expected to be excused from societal roles. Regardless of their level of insight, achievement, action, and/or altruism, five participants who were worried about missed diagnosis complained about their healthcare and focused on their symptoms.

Conclusion: Different perceptions and behaviors separated patients with similar negative experiences. Lack of insight and a sense of entitlement were associated with symptoms focus. Worried participants complained and focused on symptoms.

Practice implications: Rather than negative experiences, MUS patients' levels of insight, entitlement, and worry may influence illness and functional behaviors.

1. Introduction

Patients with medically unexplained symptoms (MUS) are common in primary care [1, 144]. Caring for them can be expensive [145], and frustrating[145-147]. Descriptive studies of MUS have traditionally relied on definitions of MUS derived from the Diagnostic and Statistical Manual (DSM). However, recent studies show that 50 – 75% of all high utilizing primary care patients with MUS do not meet full or abridged DSM criteria [41, 42]. Thus, descriptive studies that use DSM may not well represent MUS patients seen in primary care. Moreover, qualitative studies with more liberal definitions have focused on referral patients [82, 148, 149]. We conducted the study reported here to better understand the perceptions and experiences of high utilizing primary care patients with MUS.

2. Methods

We used Grounded Theory methods [150-152] to test, elaborate, and refine emerging categories from verbatim transcripts of 19 interviews to provide the analysis for this study. The Institutional Review Board at Michigan State University approved the study, and all patients gave informed consent.

2.1 Subjects and Setting

We have described elsewhere how we identified patients for a randomized controlled trial (RCT) of treatment for primary care MUS patients in a large health maintenance organization in Michigan in January 2000 [103, 116]. Briefly, trained physicians used a reliable chart rating method [44] to identify high utilizing patients for

whom MUS accounted for at least 50% of visits. The study sample was a heterogeneous group of patients with frequent minor complaints and patients with chronic, persistent symptoms. We recruited a random sample of 19 control patients after they completed the RCT to participate in this qualitative study. Participants of this study were similar to other control patients in mean age (47.95 yrs vs. 46.26, P= 0.47), gender (84% female vs. 74%, P=0.55), and mean number of visits/year (12.79 vs. 13.26, p= 0.72), but had a higher percentage of MUS visits (69.6% vs. 60.4%, p= 0.04).

2.2 Interviewing and Analysis

The interviewer (FCD) was trained in qualitative interviewing and had no prior relationship with any participant. She told participants that the goal of the study was to understand the experiences and perceptions of patients with multiple clinic visits. Using a semi-structured questionnaire, (Appendix 1) she began each interview with open-ended inquiry that allowed participants to determine the content, pace, and sequencing of the interview. She noted and followed up important clues and tested, in later interviews of different patients, theories that emerged from earlier ones. For example, after the first two interviews, she tested the emerging theme of childhood distress and history of abuse in the remaining interviews, and, after analyzing the first five interviews, she asked follow-up questions whenever patients spontaneously brought up the topic of religion. Similarly, she tested the notion of gender influence on doctor-patient relationships in subsequent interviews when the narrative of one of the participants suggested it might be important. If after 30 - 45 minutes the following a priori topics had not arisen, she asked about them: participants' explanatory models [153], locus of control [154], health-seeking

behavior [155], relationships, and expectations for the future. All interviews were audiotaped and were transcribed verbatim. The transcripts, stripped of patient identifiers, were used to conduct further analysis.

We used an inductive process [150-152] to ensure that further analysis was grounded in the data rather than based on our own pre-existing groupings or framework. Three of the authors (FCD, JSL, and RCS) derived *preliminary themes* (see Table 5) by independently reading, taking notes, and verifying concepts from the first five transcripts. We reconciled differences, clarified, and refined categories by consensus and then developed *working themes* (see Table 5) by testing preliminary themes against a second set of five transcripts. With the working themes in hand we read and discussed the remaining nine transcripts to further identify, refine, and elaborate previous themes and to identify any new themes that emerged. Finally, we reread all 19 transcripts, developing and testing relationships in categories, and independently verified our final themes. We completed our analysis when we had categorized all relevant text in the 19 transcripts and could make no further modifications.

3. Results

We identified eleven final themes. In Table 6, we have defined the themes and listed participants who projected them. Appendix A shows the degree (low, moderate or high) to which each participant communicated each theme. Themes fell into three broad categories: a) "Experiences" were participants' actual descriptions of events that occurred in their lives; b) "Perceptions" captured participants' attitudes and/or insights; c) "Behaviors" were actions of participants that were observed during the interview, or were

inferred from their narratives. Certain perceptions appeared to be connected with certain behaviors. In general, negative perceptions coexisted with negative behaviors and vice versa. We did not discern similarly discriminating relationships between experiences and perceptions or behaviors.

3.1 Experiences

This category consisted of three uniformly negative themes. All except Participant 2 had endured at least one of these negative experiences. Six participants had suffered at least two of the negative experiences and four had experienced all three.

3.1.1 Negative experiences - Childhood trauma

Ten participants reported personal abuse, loss, and/or death of a loved one during their childhood. An important feature of this theme was the emotional expression that accompanied participants' stories. For example, Participant 7 who was sexually abused by her aunt's husband at 8yrs old said simply, "*I was so scared let me tell you*." Similarly, Participant 15, sobbed as she recalled the shame and isolation she felt about her childhood abuse, "*When I was 7, I was molested by my dad's best friend. They would never have believed that; and I never talked about it until I was 41... for years I thought it was my fault.*" Some stories were more notable for the absence of emotional expression. Participant 4's explanation for her calm demeanor as she talked about being inappropriately fondled by her grandfather was, "*I think I shut my feelings off quite a while ago. My dad died when I was 10.*" She went on to share about other consequences

of her father's death, "I didn't have him while I was growing up through my teenage years, I did a lot of self-destructive behavior."

3.1.2 Negative experiences - Adulthood abuse

Six participants were abused physically, sexually, and/or verbally as adults. Participant 6's story was typical, "*I got knocked around*... *I was in the hospital at least a couple of times*... *he kept me dragged down. I was nothing.*" Some experiences were associated with physical symptoms. For example, Participant 14 was raped and abused physically by her boyfriend when she was 16 years old. She subsequently developed chronic pelvic pain. Similarly, Participant 6 who suffered abuse at the hands of two consecutive husbands suffered with medically unexplained chronic musculoskeletal pain for over 12 years. Participants 6, 15, and 19 had divorced their abusive husbands by the time of the interview. Participants 12 and 17 suffered primarily from emotional or verbal abuse. The following statement by participant 12 showed the toll that even verbal abuse could have on the victim's self-esteem, "He was the very controlling type, very "I'm smart you're stupid. It took me a long time to get myself together."

3.1.3 Negative experience - Family patterns of distress and/or dysfunction

This theme captured notable familial patterns of illness behavior, or behavioral illness in 16 participants. For example, seven of Participant17's immediate family members had reversal of gastric bypass surgery, and Participant 3 regularly visited the same chiropractor with her four sisters. Similarly, according to participant 5, somatization was a common response to stress in his family, and Participant 19 was worried about

being a hypochondriac like her mother. Others described the cost of familial alcoholism (Participants 11. 14, and 15) and mental health problems (Participants 1, 8, 13, and 18). This theme also captured expressions of primarily negative feelings about families and close relationships. Participants 1's simple statement about perceived parental discord and general household chaos summed up a lot of participants' reactions – "*They would scream and throw things… That was scary.*" Participant 1 also felt pressured by family members' unreasonable expectations – "*It makes me feel as if I'm not parenting to their expectations… My friends at work said, "You are driving yourself crazy."*" Others were disappointed by parental favoritism (e.g., Participant 9 said, "*they can never give me anything materialistic that would equal what they sacrificed for [sister]"*), and/or neglect ("*they had an opportunity to take care of me… but they didn't and I have a lot of struggles from that."*)

3.2 Perceptions

There was one positive theme (insight) and two negative ones (entitlement and worry) in this category.

3.2.1 Positive perception - Insight

This theme characterized six participants' demonstrated appreciation of the relationship between symptoms and stress. Participants 5, 8, 11, and 15 stood out as being particularly insightful. Participant 5 understood the psychological basis of his medically unexplained symptoms – "*The symptoms I imagine, well, you know, is probably where I started. ...I had spent a very strenuous weekend working in the yard, that type of thing, so*

there were some physical aspects to what happened I think, but there were some psychological aspects too, because my wife that very weekend informed me that I should move out of the house." Participant 8, seemed to understand the importance of sharing her feelings, "no one [in her family] ever talked..., but I talked about everything," and suggested a key to effective coping - "at least 50% has to be your attitude." Participant 11 shared how he had learned from his brother that "most of the problems you have aren't out in the world. They're up here (pointed to head), and if some day I can control that, then I wouldn't have the problems... the aches and pains come with that."

Participant 15 had been able to process growing up with an alcoholic father, childhood sexual abuse, living with two abusive husbands, and many childrearing mistakes through 22 years of psychotherapy. The stories of these participants revealed the sources of their insight as psychotherapy (Participant 15), wise counsel (Participant 11), and personal reflection (Participants 5 and 8).

More commonly, however, participants appeared unconscious of the possible effects of psychological stress. In particular, Participants 1, 4, and 6 were noted for having very low insight. Participants 1 and 4 repeatedly coupled descriptions of their symptoms with their jobs, housework, spouses, and/or children. They seemed completely unaware of this and did not even consider the possibility of association between their symptoms and aversion to any of their roles. Similarly, Participant 6 was abused, "*he became even* ... more violent with me. He threw me on the floor and was choking me," but attributed her MUS to a concrete event from her past, "*after a lady drove me off the road, I hit the curb and I felt a real sharp pain,*" and appeared unable to imagine any possible contribution from the concurrent abuse. When asked if she felt her husband's

abuse might have contributed to her symptoms, she said, "I had no lingering pain from anything he did..."

3.2.2 Negative perception - Entitlement

Nine participants appeared to believe that their symptoms entitled them to special considerations (see Table 6). They expected their families to assume responsibility for household chores, and to be excused from their jobs. All participants labeled with very low insight (Participants 1, 4, and 6) demonstrated this sense of entitlement. Conversely, none with very high insight (Participants 5, 7, 8, 11, 12, and 15) conveyed entitlement. Participants with entitlement offered their symptoms as excuses. For example Participant 6 gave the following reason for her absenteeism, "I'm just gonna feel rotten today and not do very much. I am in pain, the more I do, the worse the pain gets, but I will just take the day off." These participants' expectations led to a lot of angst in their families. For example, according to Participant 16, "There are days when you're angry at either friends or family because they still don't get it... [My husband] will say, 'Well I don't understand why you couldn't carry those groceries'... My daughter has to help me with a lot of that stuff, garbage and groceries and things... she's mentioned to one of my friends that she hated me because I was always in pain... she will say, "I'm like your slave because you are hurt.""

3.2.3 Negative perception - Worry

Six participants were concerned about undiagnosed disease. With the exception of Participant 3, none of these worried participants was characterized with entitlement. For

Participants 5, 7, and 19, the root of this concern appeared to be a strong family history of cardiovascular disease. Similarly, Participants 3 and 12 were concerned about developing cancer because of a strong family history of the same. None had explicitly discussed their underlying concerns with their healthcare provider. Neither normal tests, nor doctors' benign assessments of their symptoms reassured worried participants. Usually, either they or someone they knew had been the victim of a medical error. For example, Participant 12 said, "I had severe chest pains last winter, and of course they did a bunch of testing and they couldn't find anything... I don't know what caused it and that kind of bothers me... it was scary; you only have one heart... I have this thing in the back of my head all the time; they missed my mom's cancer twice so medicine is not fallible."

For some of these participants, the current interview was the first time they had talked openly with anyone about their fear of unrecognized disease. Participant 7's comment hints at a possible reason for this – "No, No! They don't spend time with you; they don't. They are always in a hurry." No participant felt to have very low insight conveyed an impression of being worried. However, three highly insightful participants (Participants 5, 7, and 12) also were worried.

3.3 Behaviors

The remaining five themes fell under the behaviors category. Like perceptions, this category included both positive (achievement, action, and altruism) and negative themes (symptoms focus and complaining). There were notable relationships between these behaviors and the perceptions described above.

3.3.1 Negative behaviors - Symptoms focus

The transcripts of 13 participants showed a pervasive emphasis on symptoms (see Table 6). Narratives about symptoms were often long and vague. Participant 10's monologue demonstrated how frustrating this communication style in particular and symptoms focus in general could be for providers:

"I go in and I say, 'I can't sleep, and it kind of comes and goes... 'One thing goes out of whack and I feel a lot of things so I come in a lot of times and ... I need to get them all in, I need to tell her_everything that is going on... I think in the beginning I might have overwhelmed her; but she now knows... that I do have a lot of things coming at me."

All participants labeled with entitlement were also categorized with symptoms focus. For example, Participant 10 above blamed her symptoms for her constant tardiness at work. Indeed, she fantasized about not working because a job "falls into something where it just doesn't work with me."

Conversely, with the exception of Participant 5, none of the participants with insight emphasized symptoms. The relatively few symptoms they talked about were more concrete. Furthermore, their descriptions were concise. For example, Participant 15 said of her back pain, "*I would hurt within two hours [of bending over and underneath cars at work]*." Participant 5's idiosyncratic symptoms focus may have been related to worry – "*I was really worried, that when you are in the situation you get, you do not know when you are going to get better or not. You know, what is the rest of your life going to be like? If I was so bad, at the relatively young age that I needed a cane. Would I be able to go back to work? Would I have to go on disability? Would I be in pain all the time?*"

Worrying was associated with symptoms focus in Participants 3, 5, 9, and 19. For example, Participant 12 went to the doctor for "*lots of ongoing little things*" because she worried about cancer; and she said, "*When something happens, you know, if I get a toe injury or whatever of course the first thing you think is* "Oh my God!" She insisted on having five lumpectomies, even though her surgeon did not think they were indicated, because "If they can make a mistake once, they can make a mistake again, and it isn't gonna to be on me. I mean, I guess I feel like I have to be extra vigilant."

3.3.2 Negative behaviors - Complaining

This theme captured expressed and/or inferred dissatisfaction with healthcare systems and/or providers. Four of the eight participants that displayed this theme questioned the financial motivation of their doctors and/or insurance providers. For example, participant 9 wondered about one of her doctors, "*Do you get an extra little money in your pay check or something for finding diseases, I mean what's the scoop here, you know?*" Similarly, Participant 7 thought the only reason she was expected to see a nurse practitioner instead of a specialist for routine gynecological care was "*to save money, because that is the only thing, there is no other excuse, it is just to save money.*"

With the exception of Participant 5, all worried participants complained about some aspects of their healthcare. For example, according to Participant 7, "*The nurse sees you instead of the Gynecologist. She doesn't order any ultrasound unless you ask...*" Later she revealed that she preferred physicians and wanted tests because of concern about a missed diagnosis. She believed tests were not being ordered because her providers were "following some orientation [from insurance companies]." She continued

to share her emotional response, "I think this is bad... I feel helpless when it comes to doctors because I don't know where to go to complain... Frustration is the biggest word in my life, just about everything." With the exception of those who were also worried, no insightful participant complained about the healthcare system. Similarly, none except two entitled participants complained unless they were also worried, and no participant with very low insight complained.

3.3.3 Positive behaviors - achievement, action and altruism

Sixteen participants shared about some significant achievement of higher education, leadership, professional status, entrepreneurship, and/or creativity (theme: achievement). For example, Participant 8 wrote poetry and managed a local store while she pursued a professional degree, and Participant 7 proudly operated an award-winning website. Twelve of these participants also demonstrated ability to cope effectively and/or make appropriate lifestyle changes (theme: *action*). For instance, Participant 12 returned to school after divorce and retrained for her current job. She was also careful to seek out the best medical advice and follow it, and Participant 5 was able to quit smoking and maintain a healthy diet. Nine participants demonstrated *altruism* in addition to achievement and action. For example, Participant 8, who was a poet, actively pursued pleasurable activities to help her cope with her illness, and she provided supportive care for several family members - "I was there when [my stepfather] had his surgery... My oldest brother suffers from post-traumatic stress syndrome... I have been doing a lot to help him." Similarly, Participant 15 was able to quit a lifelong habit of drinking heavily, quit smoking, and control her diabetes with diet. She also enjoyed her work and planned

to volunteer after her imminent retirement. Unlike participants who sought excuses to not go to work, she actually felt ambivalent about retiring. Given the context of their negative experiences, the positive attributes of some participants were remarkable. For example, Participant 15 said, "I was raised in a very dysfunctional family; my dad had a bad drinking problem ... when I was seven I was molested by my dad's best friend ... But I have now dealt with it ... [I quit drinking] because I was having black outs and it was scaring me... I just quit."

Three participants (Participants 1, 4, and 6) did not demonstrate any of the three positive behaviors. These same participants were rated very low on insight, and high on entitlement. All three focused on symptoms, and instead of finding meaning in their work, they seemed to focus on getting time off, or they quit their jobs. In contrast, all participants who were worried, and or insightful demonstrated all three positive behaviors.

4 Discussion And Conclusion

4.1 Discussion

We achieved our primary objective of exploring the perceptions and experiences of these high utilizing primary care patients with MUS. None of the themes uncovered could be characterized as positive experiences. Instead, all but one, participants reported at least one negative experience of childhood trauma, family patterns of distress, and/or adulthood abuse. This is consistent with other studies [97, 156, 157] that have demonstrated an association between the psychological distress of sexual / physical abuse and MUS.

We also identified one positive (insight) and two negative (entitlement and worry) perceptions that were associated with specific behaviors. Participants who demonstrated psychological insight also shared stories of achievement, action, and altruism. Their psychological growth resulted from psychotherapy, continuing wise counsel from a relative, and or personal reflection. Unless they were also worried, these insightful participants did not complain about their healthcare. In contrast, those felt to have very low insight had no stories of achievement, action, or altruism. Instead, they perseverated on their symptoms and projected a sense of entitlement. These participants resembled the stereotypical somatization patients described by Pilowski and others [55, 78]. Consistent with observations of alexithymia in patients with somatization disorder [158], they did not complain or seem worried about undiagnosed organic disease.

The third perception identified was worry, usually resulting from a significant family history, previous knowledge of negative healthcare outcome, and/or perceived avaricious intent of doctors and third party payers. Regardless of whether they were insightful or not, participants characterized with worry complained about their healthcare and/or focused on their symptoms. This finding parallels the results of an earlier qualitative study of somatizing patients [159]. All worried participants shared stories of achievement, action, and altruism. For at least one participant, the association of worry with illness and health seeking behavior was unrecognized prior to this study. No worried participant reported explicitly discussing his or her underlying fear with a healthcare provider. At least one participant perceived a system and/or physician level barrier to such a discussion,

We must acknowledge important limitations. Our findings, like other qualitative studies with small samples, may not be applicable to other primary care patients with MUS and are subject to the biases of the investigators. Findings of associations are preliminary. Secondly, relying on patient report, rather than direct observation may have limited the content validity of some of our themes, especially those purported to describe experiences and behaviors. However, the information obtained from interviews more closely approximates the information available to clinicians from patients like those in our study and therefore may be more useful clinically.

Moreover, this study has study generated several hypotheses for later quantitative research: 1) Perceptions, like worry and entitlement, are more important than negative experiences in the well-being and behavior of patients with MUS, 2) complaining about healthcare and or a pervasive emphasis on symptoms is a marker for unrecognized on unexpressed worry in some high utilizing primary care patients with MUS, 3) systematically identifying and addressing concern about undiagnosed organic disease will improve and/or alleviate symptoms focus and/or complaining behavior in some high utilizing patients with MUS.

4.2 Conclusions

This descriptive study identified eleven themes that described the experiences, perceptions, and behaviors of these high utilizing primary care patients with MUS. Psychological insight was associated with achievement, action, and altruism. Conversely, lack of insight was associated with entitlement and symptoms focus. Previously unexpressed concern was associated with complaining and symptoms focus even in those

with insight, achievement, action, and altruism. These patterns of diverse personal features underscore the potential value of unique diagnostic and treatment approaches in similar high utilizing primary care patients with MUS.

4.3 Practice implications

Our study provides support for emphasizing effective communication in treatment of MUS [102]. Distrustful and complaining high utilizing patients are likely to benefit from empathic listening, investigation of the source of their distrust and education about its relation to their problems. Recognizing and addressing concern about undiagnosed organic disease may improve patient satisfaction and outcomes, and increase clinicians' confidence with their treatment. We also identified improved insight and patient responsibility (opposite of "entitlement") as possible worthwhile goals of treatment. Characteristics and stories of achievement, positive action, and altruism may be helpful in motivating MUS patients to live lives that are more productive.

Table 5: Qualitative Study - Preliminary and Working Themes			
Preliminary Themes	Working Themes		
1. Behavior/Action (Pleasure in life, Coping / Dysfunction, Job satisfaction)	1. Primary mechanism		
2. Primary relationships (Duration of marriage)	2. Secondary gain		
Secondary relationships	3. Insight (mind/body connection)		
3. Doctor-patient relationship	4. Emotionality		
4. Mechanism of illness Identity/invisible, Stage of development, Personality, Locus of control, Number of siblings, Location of patient, Abuse,	5. Symptoms focus		
Family History, Explanatory model	6. Fear of physical disease		
5. Physical Symptoms Fear of physical disease, Care seeking, Secondary gain	7. Quality of dominant relationships		
6. Diagnosis Medical (primary or secondary), Psychiatric diagnosis (primary or secondary), MUS diagnosis (minor acute, somatization, neither)	8. Obesity		
7. Emotionality Expression during interview, Evidence of emotionality in life, Insight / psychological savvy)			
8. Excessive testing / medicalization			
9. Reaction to interview and study			
10. Religion / spirituality			
11. Healthcare system			
12. Litigation			
13. Education/training			

Category	Theme	Participant ID	
Experiences	1. Childhood trauma	3, 4, 6, 7, 8, 9, 13,	
(All are negative)	Expressions of traumatic experiences at a young age	14, 15, 19	
	2. Adulthood abuse		
	Explicitly described physical, verbal or sexual abuse during adulthood	6, 12, 14, 15, 17, 19	
	3. Family patterns of distress and/or dysfunction		
	Expressions of illnesses, behaviors, or conditions that were repeated among different family members; also includes expressed negative emotions about the actions and intentions of family members and other personal relationships	1, 3, 4, 5, 6, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19	
Perceptions	4. Entitlement	1, 3, 4, 6, 10, 14,	
a) Negative perceptions	Inferred lack of participant's sense of accountability for his or her actions or inactions, usually from statements that offer symptoms as excuses for not being able to fulfill societal roles	16, 17, 18	
	5. Worry		
	Expressed or inferred participant concern about serious undiagnosed disease. Neither normal tests nor doctors' benign assessments of their symptoms reassured patients who expressed worry. Either they had personally experienced a medical error, or they knew someone who had.	3, 5, 7, 9, 12, 19	
b) Positive perception	6. Insight Expressed or inferred awareness of the relationship between personal psychological stress and physical symptoms	5, 7, 8, 11, 12, 15	

Table 6: Qualitative Study - Final Themes with Definitions (n = 11)

Table 6 Continued

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Category	Theme	Participant
Behaviors	7. Symptoms focus	1, 3, 4, 5, 6, 9, 10,
a) Negative behaviors	A pervasive emphasis on symptoms	13, 14, 17, 18, 16, 19
	8. Complaining	3, 7, 9, 11, 12, 13,
	Expressed and inferred dissatisfaction with healthcare system or providers.	14, 16, 19
b) Positive	9. Achievement	2, 3, 5, 7, 8, 9, 10,
behaviors	Expressions of higher education, supervisory role, professional status, entrepreneurship, and/or creative activities	11, 12, 13, 14, 15, 16, 17, 18, 19
	10. Action	
	Expressed or inferred ability to cope effectively or change behavior for the better	2, 3, 5, 7, 8, 9, 11, 12, 13, 15, 16, 19
	11. Altruism	
	Spontaneous descriptions of volunteer activity, significant care-taking or meaningful work	3, 5, 7, 8, 9, 11, 12, 15, 19

Appendix 1: Semi-structured Questionnaire for interviews

Introduction:

- 1. Myself
- 2. The study
- 3. The interview (audiotape, notes)

Pause for questions

Open-ended beginning (30 - 45 minutes):

Say: "Tell me about yourself"

Use patient-centered method (patient-directed, empathic) to expand the patient's story of the physical, personal and emotional aspects of their illness

Directive Questioning (30 – 45 minutes): (Ask these questions if the corresponding topics have not been discussed, continue to expand newly raised topics with clarifying questions and patient-centered techniques.)

Explanatory models:

- 1. What do you believe is the root cause of your problems?
- 2. What are your concerns about your problems?
- 3. How have your health problems affected your life?

Locus of control:

1. Who do you feel has the most control over your health (life)? Health-seeking behavior:

2. Whom do you turn to for information about your health? Is there anyone else?

Relationships:

- 3. How is your relationship with your healthcare provider
 - What are your expectations when you go to the doctor?
 - Do your issues get resolved to your satisfaction?

• How satisfied are you with the care you have received?

Expectations for the future:

1. What are your expectations about your future?

Added after Interview 2: (Ask these questions if not already discussed)

- 9. Describe your childhood.
 - a. Have you ever been abused?

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