University of Insubria

Department of Medicine and Surgery

Doctoral Research in Clinical and Experimental Medicine and *Medical Humanities* – XXXIII Cycle

Coordinator: Professor Marco Cosentino

Doctoral Thesis

Somatic symptom disorders in hospitalized patients: clinical features and health care costs

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ANALYTIC JUDGEMENT:

Originality of the research

The focus of the thesis of PhD student is on the "medically unexplained physical symptoms" (MUPS) and concerns the reconceptualization and definition of the diagnostic criteria of that disorder that is indicated in DSM5 as Somatic Symptoms Disorder (SSD).

Starting from a careful analysis of the current literature and from the theoretical and psychopathological reconceptualization of the characteristics of these patients, the PhD student intends to investigate possible predictors and psychopathological correlates of SSD, evaluating also the cost-effectiveness of the proposed interventions for the management of somatic symptoms in hospitalized patients.

In fact, the existing literature reports that patients with MUPS represent 15-30% of those in primary care services and about half of those in secondary care services, that the presence of MUPS represents a criterion for the diagnosis of somatoform disorders and SSD and that MUPS can cause persistent disability for at least one year in more than 30% of patients, affecting individual functioning and leading to a massive use of healthcare resources.

Based on these reflections, it can therefore be concluded that in his thesis the PhD student faces a relevant scientific issue by conducting a study that presents elements of originality and important clinical implications, in terms of scientific evidence that directs towards the need for an adequate approach to the patient with Somatic Symptoms Disorder.

Background: exhaustive and up-to-date

The PhD student made a thorough search in the scientific literature on the issue, summarizing the data reported by the reviews and analyzing the results obtained through the main clinical studies conducted at national and international level, from the farthest to the most recent. He has so provided an exhaustive and up-to-date description of the topic.

Goals

The main purposes of the study, described in a specific paragraph of the thesis, were clearly listed. They also appear to be characterized by appropriateness and congruity with respect to updates in terms of scientific knowledge reported in the first part of the thesis.

Appropriateness of methodology

The scientific methodology used in the conducted study is appropriate.

Indeed, the PhD student has:

- defined in a clearly and appropriately way the aims of the research based on the review of the literature and the identification of the variables involved;
- designed a research project that resulted feasible;
- identified the study population;
- identified clinical data sources that were accessible and reliable;
- followed correct procedures for organizing and analyzing the data;
- described in a clearly and exhaustive way the results obtained through the statistical analysis;
- interpreted adequately the results based on a comparison with the existing literature evidences.

From the methodological point of view, the study has some limitations and strengths, moreover described by the PhD student within and at the end of the thesis.

In particular, the strengths of the present study consist in the investigation of a large number of patients with MUPS; to study clinical, sociodemographic variables and psychopathological correlations involved in the development of Somatic Symptom Disorder; to provide a financial economic estimate of hospitalization costs of patients with MUPS.

Among the limitations, the PhD student mentions the fact that the data were retrospectively observed and the small sample size from non-medical specialties, limiting the possibility to extend the statistical analyses to the whole sample due to the lack of patients' personal information.

Overall, however, the methodology used is satisfactory in terms of scientific appropriateness.

Istantanea Schermo

Clarity of outcomes presentation

The PhD student describes the results with clarity and appropriateness of language. He analyzes the obtained results comparing them with the main scientific evidences, confirming a knowledge and an in-depth understanding of what emerged from the literature research and from the studies conducted on the topic.
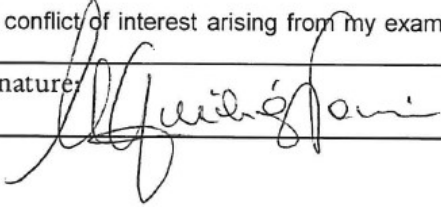
Significance of the findings

Study results confirm a significant correlation between MUPS and the clinical, psychosocial and economic variables explored, contributing and supporting scientific research in this area. Furthermore, these results are significant in terms of possible applicative impact. In line with the results of other authors, they in fact suggest the need for patients with MUPS of an early psychiatric evaluation, in order to reach important goals: to support and implement the diag-

nostic process, avoiding also unnecessary repetition of procedures associated with huge health-care costs and to facilitate the referral of patients to specific treatments when necessary, thus improving the quality of care, as well as the quality of life, of the patients themselves.

FINAL RECOMMENDATION	
The thesis does not require modifications and the candidate can defend it	X
The thesis needs minor amendments before discussion	
The thesis needs major revision and must be reconsidered	
The thesis is extremely flawed and cannot be reconsidered	

X	I confirm that there is no actual or perceived conflict of interest arising from my examination of this thesis.	
Date: 23/12/2020	Signature	

Prof. Pietro Barbetta

To Prof. Marco Cosentino
Coordinator of the Ph.D. Course in Experimental and Clinical Medicine and Medical Humanities

Review of PhD Final Dissertation by Ivano Castelli (MD):

Somatic symptom disorders in hospitalized patients: clinical features and health care costs

Ivano Castelli's work consists in an exhaustive dissertation concerning SSD (Somatic Symptom Disorder). In particular on Medically Unexplained Physical Symptoms (MUPS), intended as physical symptoms without medical explanation that can imply a psychological cause. I would divide Doctor Castelli's thesis in 3 main parts.
In my view the most relevant aspects of the first part of Castelli's essay are: 1. the definition of the MUPS and SSD phenomena, and previous categorization, by different editions of DSM and ICD (OMS) diagnostic handbooks criteria;
2. the partial overlapping of different diagnostic categories during historical times;
3. the epidemiological data on frequency of different types of MUPS, in different contexts and medical settings.

4. the difficulties of GP in facing the MUPS phenomena and more in general the costs of such phenomena for health care system.
In what I call the second part of the thesis the Author analyzes different kind of treatments, and particularly BCT and Psychoanalysis. Catelli's shows the EBM results by BTC treatment and Psychoanalytical analysis of the widely called somatoform phenomenon, implying the so called Briquet Syndrome or Hysteria.
The third part consist in an empirical epidemiological research with local data analyzed with SPSS quantitative methodology.

Further question to be explored.
Thanks to Castelli's PhD dissertation, there is something to explore from my point of observation:
In my Disciplinary Sector (M-PSI-07, Dynamic Psychology) there is some perplexity concerning the only use of randomized quantitative research concerning clinical psychology, someone of us, including myself, think that EBM criteria tend to hyper-evaluate BCT approaches, neglecting the due complexity of clinical cases analysis and humanistic approach to therapy. BCT are quantitative data under a process of EBM – what about follow ups after one or more years in cases of MUPS, is there any literature around this issue? This issue should be explored in future in detailed way for exploring if the issue is "get rid of symptoms", or focusing on therapeutic relationship (translation), which probably needs more time and patience, more connected to cure vs care.
Psychoanalysis is just a theoretical frame? The Author mentions brief psychoanalytic therapies, nonetheless with less "cure efficacy" than BCT. This is probably due to the minor impact factor of Psychoanalytical Journals, or to the simple facts that psychoanalytical research needs more space to be conceptualized and is mainly published on books or humanistic journals that do not need Standardized Impact Factor.

General assessment of the Final Thesis

Ivano Castelli's dissertation is very accurate, well written. It opens issues and hopes in different directions about both sides of costs of MUPS and other possible treatments, reminding us that, after

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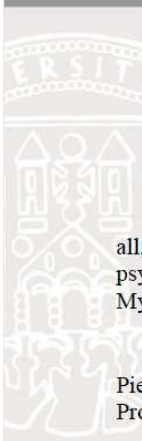
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Dipartimento di Scienze umane e sociali

all, psychoanalysis is still an important instrument within the fields of clinical psychology and psychiatry.
My General assessment is: excellence and fully admissible on the PhD discussion.

Pietro Barbetta
Prof. of Dynamic Psychology – Department of Human and Social Sciences -University of Bergamo

To my mother

III

Abstract

Background and objectives. Somatic Symptoms Disorder (SSD), formerly known as somatoform disorder, is a mental disorder which manifests as physical symptoms that cannot be explained fully by a general medical condition. In current literature, Medically Unexplained Physical Symptoms (MUPS) are intended as physical symptoms without a medical explanation. The research provides for the collection of data from hospitalized patients presenting MUPS, aiming to draw a clinical and socio-demographic profile of these patients, to estimate economic costs related to hospital management, and to explore psychopathological correlates of SSD. *Materials and methods.* The cross-sectional study consists in the evaluation of data referring to all hospitalized patients admitted between 2008 and 2018 in the wards of a teaching hospital in Northern Italy. *Results.* Data referring to 273 hospitalized patients presenting MUPS have been detected. The sample shows a prevalence of female, married, and worker patients. The most frequent ward involved are Neurology, Internal Medicine and Short Unit Stay. The most common symptoms found are headache, pain, syncope and vertigo. The overall estimated cost of hospitalization for patients with MUPS is 475'409.73 €. No evidence that a history of medical disease is associated with a diagnosis of SSD. A personality disorder diagnosis in patients with MUPS is associated with increased probability of having a diagnosis of SSD. A marginally significant positive association also emerges with anxiety disorders, but not with depressive disorder. *Conclusions.* The research provides the investigation of a large number of patients with MUPS and a financial estimate of related hospitalization costs. Moreover, it allows to study clinical, socio-demographic and psychopathological correlates involved in SSD.

Preface

Patients presenting to their doctors with bodily symptoms which cannot be explained by an identified physical disease are very common. All medical specialists and general practitioners see large numbers of such patients and these symptoms represent one of the most common reason for patients visiting doctors in Europe and in the USA. Some doctors and many patients express despair about our lack of knowledge regarding the origin of the symptoms presented and how best to treat them.

This PhD thesis is aimed to addresses several aspects of this problem. One of the problems is the prolonged suffering experienced by patients who have persistent medically unexplained symptoms without receiving adequate treatment. Another problem is the high financial cost associated with these symptoms because of frequent specialist visits, expensive investigations and the associated disability, which leads to time missed from work.

The thesis includes a section on classification and nomenclature, in light of the revision of the major diagnostic system in psychiatry (the American 'Diagnostic and Statistical Manual' and the World Health Organization's 'International Classification of Diseases') aimed to provide up-to date information about diagnosis and classification, and a review of the epidemiology of medically unexplained symptoms and somatoform disorders.

The thesis also aims to contribute to review the major evidence-based recommendations for the management and the treatment for patients presenting medically unexplained symptoms and somatoform disorders.

Despite of the methodological limitations in research in outcome of psychoanalysis treatments, a brief paragraph has been included with the objective to present in its representatives of the major currents initiated by the pioneers in the field of psychosomatics from a psychoanalytic perspective to come to the current theoretical and clinical contributions in the field of psychoanalytical therapies research.

Chapters 2, 3, 4 and 5 are dedicate to the research, which provides for the collection of data from hospitalized patients presenting medically unexplained physical symptoms, aiming to draw a clinical and socio-demographic profile of these patients, to estimate economic costs related to hospital management, and to explore psychopathological correlates of Somatic Symptom Disorder.

Chapter 1

Introduction

1.1 Definition, classification and conceptualization of Medically Unexplained Physical Symptoms

The term 'medically unexplained physical symptoms' (sometimes also called 'medically unexplained symptoms'), has gained some popularity during recent years among general practitioners and specialists to call the bodily complaints of their patients when the aetiology is unclear. The term implies that currently there is no 'organic cause' for the problem but it leaves open the potential aetiology of the question (Creed et al. 2010).

From a clinical point of view, the phrase 'medically unexplained' is a negative statement, restraining from the patient that which he or she usually seeks most – a positive explanation for their symptom(s) and support (Ring et al. 2005; Salmon et al. 2005).

A crucial problem with the concept underlying 'medically unexplained symptoms' is the dualism it fosters. In fact, a patient's symptom is seen either as an organic one ('medically explained') or 'medically unexplained', which may be taken to imply a psychological cause. This dualism is still preserved in our classifications of disease (The International Classification of Diseases, *Diagnostic and Statistical Manual of Mental Disorders*), despite the fact that it is known now that human illness is determined by a mixture of biological, psychological and social factors.

Patients who suffer from persistent bodily complaints without obvious explanation of this suffering through structural pathology of bodily organs or body systems, are challenging because of the difficulties they pose for classifications and terminology, which can be seen as major barriers to improved care for these patients.

A list of other terms that are currently used to describe the group of symptoms frequently referred to as 'medically unexplained' includes: somatoform disorder, functional disorder or functional somatic syndrome, bodily distress syndrome/disorder or bodily stress syndrome/disorder, somatic symptom disorder, psychophysical/psychophysiological disorder, psychosomatic disorder and symptom-defined illness/syndrome. The tendency to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it is referred to as 'somatisation' in a dimensional way.

The current classification of patients with persistent bodily complaints without clear organic pathology to explain them is to be found in the fourth edition of the *Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-IV) and in the tenth edition of the International Classification of Diseases of the World Health Organization (ICD-10).

The 'somatisation disorder' diagnosis has its origin in the concept of hysteria. It was introduced in DSM-III in 1980 as a diagnosis in the new somatoform disorder group; it arose from an exploratory study by Perley and Guze in the early 1960s (Perley et al. 1962). On the basis of symptoms reported by 39 female patients admitted to a psychiatric ward and diagnosis with 'Hysteria', they set up diagnostic criteria for hysteria later named 'Briquet's syndrome' (Perley et al. 1962).

From a factor analysis of all symptoms, they listed 59 physical and psychological symptoms distributed in 10 groups: 25 of the symptoms from nine groups were required to qualify for the diagnosis of Briquet's syndrome. This was a pioneer study as it was one of the first to use factor analyses to identify symptom clustering. However, as the criteria were developed in highly unrepresentative samples, the study severely violates representativeness, and the symptoms structure may more reflect the setting, the gender of the patients and what was believed to be hysteria at that time, rather than a characteristic of the illness. 'Briquet's syndrome' was modified when introduced in the DSM-III to the 'somatisation disorder' diagnosis in the way that all psychological symptoms were eliminated to avoid overlapping with other psychiatric diagnosis.

The diagnostic criteria underwent a major revision in the DSM-IV, and according to these criteria, symptoms from three of four symptom groups (pain, gastrointestinal, sexual and pseudo-neurological) are required. It is unclear on what basis this diagnostic was founded. The somatoform diagnosis category was included in ICD-10 in 1992, but the ICD-10 criteria list different symptoms and require a different number of symptoms compared with the corresponding DSM criteria, and the diagnoses are different. Although the diagnostic criteria have been modified in later modifications of the DSM classifications, its heritage is obvious. The basis of the other somatoform diagnoses in the DSM and the ICD is obscure.

To increase the sensitivity of the 'somatisation disorder' diagnosis, Escobar et al. (1989) introduced a somatization index. This required four symptoms for males and six symptoms for female out of the 37 somatic symptoms listed in the DSM-III, compared with 12 and 14 symptoms, respectively, for the full DSM-III somatization disorder diagnosis. Kroenke and colleagues have suggested a diagnosis of 'multisomatoform disorder', defined as three or

more MUPS from a 15-symptom checklist along with at least a two-year history of somatization (Kroenke et al. 1997).

These versions are characterized by the fact that the chosen number of symptoms to qualify for the individual diagnosis is arbitrary and not empirically based. Furthermore, many studies have relied on predefined symptom lists derived from DSM-III symptom list, and widely used the diagnostic instruments such as the Composite International Diagnostic Interview (CIDI) and the layperson version of the CIDI, the Diagnostic Interview Schedule (DIS), only explore symptoms included in the DSM-III symptom checklist. This means that criteria that go beyond the original ones are not explored. Few studies have used instruments such as the Present State Examination (PSE)/Schedule of Clinical Assessment in Neuropsychiatry (SCAN) or tailored instruments that are not diagnosis bound.

Because of the manifold problems inherent to the current terminology and classification of MUS, it has been suggested to include positive psycho-behavioural criteria:

a. Self-focused attention

Barsky and others have described the process of 'somatosensory amplification' (Barsky et al. 1990). They theorize that people with these syndromes focus their attention on somatic perceptions. This process of focused attention increases the perceptual intensity. Moreover, many patients reduce their social activities and other sources of external stimulation, which further increase the intensity of internal stimuli (e.g. somatic symptoms) and supports the process of persistence of these complaints (Rief et al. 2010). Neuroimaging studies support the assumption that focusing attention facilitates the perception of somatic symptoms, while distraction reduces the perceptual intensity (Bantick et al. 2002). The authors were able to show that the brain activation of the pain matrix is lower if people try to distract their attention in contrast to focusing the attention to pain stimuli. However, the continuous focusing of attention on somatic symptoms can lead to neural sensitization process that amplify process of chronicity (Smith et al. 2008).

b. Overinterpretation of bodily symptoms

The overinterpretation (catastrophizing) of bodily symptoms is another psycho-behavioural feature that is partially included in Barsky's somatosensory

amplification model. This model postulates that patients with somatization symptoms are characterized by a tendency to overinterpret everyday bodily sensations.

c. Somatic illness beliefs

It has been frequently suggested that patients with 'medically unexplained', 'somatoform' or 'functional' symptoms are characterized by rigid somatic illness beliefs. However, several studies have shown that they report several different illness explanations including psychological ones (Rief et al. 2004; Groben et al. 2011). Moreover, the more psychological illness explanations patients report, the more disabled they are. Therefore, it is not the overemphasis of single somatic explanations for their symptoms, but perhaps a kind of inflexibility of using different explanations for somatic complaints.

d. Self-concept of bodily weakness

It has been shown that patients with chronic 'unexplained' symptoms report a negative self-concept of being weak, not tolerating stress and not tolerating any physical challenges (Rief et al. 1998; Hausteiner et al. 2009). Authors have observed that a negative self-concept is a variable trait which persist over time, even in the absence of somatic perception.

e. Expectation and memory

The expectation of symptoms provokes a state of facilitated perception of bodily complaints – both lead to an activation of highly similar brain structures (Witthoft et al. 2010; Keltner et al. 2006). Brown's model of rogue perception of symptoms postulates that existing memory traces for symptoms perception can be triggered by other external and internal stimuli (Koyama et al. 2005; Brown et al. 2004). This provocation of rogue perception is more pronounced in patients with 'medically unexplained' symptoms.

f. Health anxiety

Health anxiety is the central feature of hypochondriasis. However, even in 'medically unexplained', 'somatoform' or 'functional' symptoms without hypochondriasis, many patients describe increased scores for health anxiety (Voigt et al., Hausteiner et al. 2009; Rief et al. 2007). Although, health anxiety itself is not a necessary, yet a frequent condition in these patients.

g. Abnormal illness behavior

Pilowsky introduced the concept of abnormal illness behavior, and postulates that is a characteristic feature of patients with somatization and hypochondriasis (Pilowsky et al. 1993). Illness behavior is highly depending on the healthcare system, interaction pattern of doctors, time and personal skills of healthcare professionals, etc. Nevertheless, several studies have shown the healthcare utilization is closely related to the number of somatic symptoms described by the patient (Al-Windi et al. 2005). Increased healthcare utilization by patients with somatoform symptoms is note explained by comorbid depression (Barsky et al. 2005; Rief et al. 2005). Increased healthcare use is not specific for 'medically unexplained', 'somatoform disorder' or 'functional' symptoms, since it also occurs in hypochondriasis, depression and anxiety disorders as well as physical disease (Rief et al. 2007). There appears to be a relationship between MUS and abnormal or dysfunctional illness behavior, but it is complex and not sufficiently understood (Duddu et al. 2006).

h. Avoidance of physical activity and stimuli seen as symptom-provoking

Avoidance of physical activities was the most powerful discriminator between patients with somatic complaints needing medical help and felling disabled, and those with somatic complaints but without healthcare needs or disability (Rief et al. 2010). The 'pain avoidance model' outlines how avoidance of physical activities transforms to aspects of physical deconditioning and facilitates the perception of somatic complaints (Vlaeyen et al. 2000). Patients with somatization and/or hypochondriasis avoid not only activities, but locations, information or social contacts that are supposed to elicit symptoms.

11

i. Interpersonal problems

Many patient-doctor relationships are described as problematic, in fact by both the doctors and the patients. Somatising patients tend to be less satisfied with their medical care than subject with severe organic illness or affective disorders, even when length, type and intensity of care are taken into consideration (Hausteiner et al. 2009; Noyes et al. 1999; Hahn et al. 2001). This dissatisfaction also leads to dysfunctional healthcare utilization. It is interesting to highlight that somatising patients tend to have a more insecure attachment style that contributes to a tendency to experience attempts by others to help them as unsatisfactory. These observations argue for more profound disturbances of personality development and not just reactive interpersonal problems (Waller et al. 2006). There appear to be a set of defining psychobehavioural features that help characterize these patient group. This can be of big help with regard to earlier identification and also to planning personalized treatment that focuses on the modification of these cognitive and behaviours. Nevertheless, psychobehavioural characteristics should not be confused with causality factors. Their aetiology role in the process of symptom development and persistence is far from clear: many of the psychobehavioural features mentioned can not only be conditions preceding symptom onset, but also consequences of the symptoms or predictors of poor outcome.

In the official classifications Diagnostic and Statistical Manual of Mental Disorder IV-text revision (DSM IV-TR) and International Classification of Diseases 10th revision (ICD-10), the presence of medically unexplained symptoms was a criterion to fulfill the diagnosis of somatoform disorder. This diagnosis was introduced for the first time in DSM-III (APA, 1980) and in ICD-10 (WHO, 1991), to try to create a new group useful to collect all those physical symptoms in which no organic cause was demonstrable.

In DSM-5 (APA, 2013), the nature of the physical symptoms is no longer a criterion for somatoform disorders. The latest edition of DSM 5 has moved away from the need to have no medical explanation in order to make the diagnosis of 'medically unexplained symptoms' and gain access to appropriate treatment. The emphasis now is on symptoms that are substantially more severe than expected in association with distress and impairment. The diagnosis includes conditions with no medical explanation and conditions where there is

some underlying pathology but an exaggerated response. In fact, DSM-5 focuses on the way a patient emotionally, cognitively and behaviorally copes with the physical symptoms.

According to the Somatic Symptoms Disorder (SSD) classification, even if a patient is suffering from chronic medical conditions can also be diagnosed with SSD and receive treatment (van der Feltz-Cornelis et al. 2018).

The major diagnosis in this diagnostic class, Somatic Symptom Disorder, emphasizes diagnosis made on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviours in response to these symptoms) rather than the absence of a medical explanation for somatic symptoms. A distinctive characteristic of many individuals with somatic symptom disorders is not the somatic symptoms per se, but instead the way they present and interpret them (APA, 2013)

The previous classifications were considered difficult to use in the clinical practice, especially among general practitioners and non-specialists, because of their rigid categories (Caselli et al. 2017). On the other hand, in DSM-5, somatic symptom and related disorder chapter has a limited clinical utility and presents some ambiguity (Callegari et al. 2006; Callegari et al. 2016; Poloni et al. 2018). This diagnostic classification reduces the importance of medically unexplained symptoms and emphasizes the psychological criteria and the functional impairment experimented by the patient.

A new category has therefore been created under the heading 'Somatic Symptom and Related Disorders'. This includes diagnoses of Somatic Symptom Disorder, Illness Anxiety Disorder, Conversion Disorder, Factitious Disorder, and a variety of other related conditions. The term 'Hypochondriasis' is no longer included. In two of the conditions the absence of any medical pathophysiology is a criterion for diagnosis; these are Conversion Disorder and Other Specified Somatic Symptom and Related Disorder (which includes Pseudocyesis, a false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy).

All of the disorders in this chapter share a common feature: the prominence of somatic symptoms associated with significant distress and impairment. Individuals with disorders with prominent somatic symptoms are commonly encountered in primary care and other medical settings but are less commonly encountered in psychiatric and other mental health settings. These reconceptualized diagnoses, based on a reorganization of DSM-IV somatoform disorder diagnoses, are more useful for primary care and other medical (non-psychiatric) clinicians.

The major diagnosis in this diagnostic class, somatic symptom disorder, empathizes diagnosis made on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation for somatic symptoms.

The principles behind the changes in the somatic symptom and related diagnoses from DSM-IV are crucial in understanding the DSM-5 diagnoses. The DSM-IV term *somatoform disorders* was confusing and is replaced by *somatic symptom and related disorders*. In DSM-IV there was a great deal of overlap across the somatoform disorder and a lack of clarity about the boundaries of diagnoses. Although the individuals with these disorders primarily present in medical rather than mental health settings, non-psychiatric physicians found the DSM-IV somatoform diagnoses difficult to understand and use. The current DSM-5 classification recognizes this overlap by reducing the total number of disorders as well as their subcategories.

The previous criteria overemphasized the centrality of medically unexplained symptoms. Such symptoms are present to various degrees, particularly in conversion disorder, but somatic symptom disorders can also accompany diagnosed medical disorders. The reliability of determining that a somatic symptom is medically unexplained is limited, and grounding a diagnosis on the absence of an explanation is problematic and reinforces mind-body dualism. It is not appropriate to give an individual a mental disorder diagnosis solely because a medical cause cannot be demonstrated. Furthermore, the presence of a medical diagnosis does not exclude the possibility of a comorbid mental disorder, including a somatic symptom and related disorder. Perhaps because of the predominant focus on lack of medical explanations, individuals regarded these diagnoses as pejorative and de-meaning, implying that their physical symptoms were not "real". The new classification defines the major diagnosis, somatic symptom disorder, on the basis of positive symptoms (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms). However, medically unexplained symptoms remain a key feature in conversion disorder and pseudocyesis (other specified somatic symptom and related disorder) because it is possible to demonstrate definitively in such disorders that the symptoms are not consistent with medical pathophysiology.

It is important to note that some other mental disorders may initially manifest with primarily somatic symptoms (e.g., major depressive disorder, panic disorder). Such diagnoses may account for the somatic symptoms, or they may occur alongside one of the somatic symptoms and related disorder. There is also considerable medical comorbidity among

somatizing individuals (Petersen et al. 2018). Although somatic symptoms are frequently associated with psychological distress and psychopathology, some somatic symptom and related disorders can arise spontaneously, and their causes remain obscure. Anxiety disorder and depressive disorders may accompany somatic symptom and related disorders. The somatic component adds severity and complexity to depressive and anxiety disorders and results in higher severity, functional impairment, and even refractoriness to traditional treatments (Claassen-van Dessel et al. 2018). In rare instances, the degree of preoccupation may be so severe as to warrant consideration of a delusional disorder diagnosis.

A number of factors may contribute to somatic symptom and related disorder. These include genetic and biological vulnerability (e.g., increased sensitivity to pain), early traumatic experiences (e.g. violence, abuse, deprivation), and learning (e.g., attention obtained from illness, lack of reinforcement of non-somatic expression of distress), as well as cultural/social norms that devalue and stigmatize psychological suffering as compared with physical suffering. Differences in medical care across cultures affect the presentation, recognition, and management of these somatic presentations. Variations in symptom presentation are likely the result of the interaction of multiple factors within cultural contexts that affect how individuals identify and classify bodily sensations, perceive illness, and seek medical attention for them. Thus, somatic presentations can be viewed as expressions of personal suffering inserted in a cultural and social context.

All of these disorders are characterized by the prominent focus on somatic concerns and their initial presentation mainly in medical rather than mental health care settings. Somatic symptom disorder offers a more clinically useful method of characterizing individuals who may have been considered in the past for a diagnosis of somatization disorder. Furthermore, approximately 75% of individuals previously diagnosed with hypochondriasis are subsumed under the diagnosis of somatic symptom disorder. However, about 25% of individuals with hypochondriasis have high health anxiety in the absence of somatic symptoms, and many such individuals' symptoms would not qualify for an anxiety disorder diagnosis. The DSM-5 diagnosis of illness anxiety disorder is for this latter group of individuals. Illness anxiety disorder can be considered either in this diagnostic section or as an anxiety disorder. Because of the strong focus on somatic concerns, and because illness anxiety disorder is most often encountered in medical settings, for utility it is listed with the somatic symptom and related disorders. In conversion disorders, the essential feature is neurological symptoms that are found, after appropriate neurological assessment, to be incompatible with neurological pathophysiology. Psychological factors affecting other medical conditions is also included

in this section. The essential feature of this category is the presence of one or more clinically significant psychological or behavioral factors that adversely affect a medical condition by increasing the risk of suffering, death, or disability. Like the other somatic symptom and related disorders, factitious disorder embodies persistent problems related to illness perception and identity. In the great majority of reported cases of factitious disorder, both imposed on self and imposed to another, individuals present with somatic symptoms and medical disease conviction. Consequently, DSM-5 factitious disorder is included among the somatic symptom and related disorder. Other specified somatic symptom and related disorder and unspecified somatic symptom and related disorder include conditions for which some, but not all, of the criteria for somatic symptom disorder or illness anxiety disorder are met, as well as pseudocyesis.

Individuals with somatic symptom disorder typically have multiple, current, somatic symptoms that are distressing or result in significant disruption of daily life (Criterion A), although sometimes only severe symptom, most commonly pain, is present. Symptoms may be specific (e.g., localized pain) or relatively nonspecific (e.g., fatigue). The symptoms sometimes represent normal bodily sensations or discomfort that does not generally signify serious disease. Somatic symptoms without an evident medical explanation are sufficient to make this diagnosis. The individual's suffering is authentic, whether or not it is medically explained.

The symptoms may or may not be associated with another medical condition. The diagnoses of somatic symptom disorder and a concurrent medical illness are not mutually exclusive, and these frequently occur together. For example, an individual may become seriously disables by symptoms of somatic symptom disorder after an uncomplicated myocardial infarction even if the myocardial infarction itself did not result in any disability. If another medical condition or high risk for developing one is present (e.g., strong family history), the thoughts, feelings, and behaviors associated with this condition are excessive (Criterion B). Individuals with somatic symptom disorder tend to have very high levels of worry about illness (Criterion B). They appraise their bodily symptoms as unduly threating, harmful, or troublesome and often think the worst about their health. Even when the is evidence to the contrary, some patients still fear the medical seriousness of their symptoms. In severe somatic symptom disorder, health concerns may assume a central role in the individual's life, becoming a feature of his or her identity and dominating interpersonal relationships (Limburg et al. 2016).

In the table below, differences between diagnostic criteria for Somatization Disorder in DSM-IV and Somatic Symptom Disorder in DSM-5 are shown.

Table 1. DSM-IV to DSM-5 Somatic Symptom Disorder comparison

DSM-IV	DSM-5
Name: Somatization Disorder	Name: Somatic Symptom Disorder
Disorder Class: Somatoform Disorders	Disorder Class: Somatic Symptom and Related Disorder
A. A history of many physical complaints beginning before age 30 years that occur over a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning.	B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following: 1. Disproportionate and persistent thoughts about the seriousness of one's symptoms. 2. Persistently high level of anxiety about health or symptoms. Excessive time and energy devoted to these symptoms or health concerns.
	C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).
B. Each of the following criteria must have been met, with individual symptoms occurring at any time during the course of the disturbance: 1. four pain symptoms: a history of pain related to at least four different sites or functions (e.g., head, abdomen, back,	A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.

joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination)	
2. two gastrointestinal symptoms: a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods)	
3. one sexual symptom: a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy)	
one pseudoneurological symptom: a history of at least one symptom or deficit suggesting a neurological condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis, or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative	

symptoms such as amnesia; or loss of consciousness other than fainting)	
C. Either (1) or (2): 1. after appropriate investigation, each of the symptoms in Criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication) when there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings	DROPPED
D. The symptoms are not intentionally feigned or produced (as in factitious disorder or malingering).	DROPPED
	Specify if: • With predominant pain (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain. Specify if: • Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months). Specify current severity:

	• Mild: Only one of the symptoms specified in Criterion B is fulfilled.
	• Moderate: Two or more of the symptoms specified in Criterion B are fulfilled.
	Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom)

1.2 Epidemiology

1.2.1   Prevalence of medically unexplained symptoms

Secondary care studies in the Netherlands, UK and Germany have shown that medically unexplained symptoms are the presenting problem for 35-53% of new outpatients at specialist medical clinics. Based on research, the most common detected symptoms are: headache; back, joint, abdominal, chest and limb pains; fatigue; dizziness; bloating; palpitations; hot or cold sweats; nausea; trembling or shaking; and numbness or tingling sensations (Kroenke et al. 1989; Fink et al. 2007). In seven clinics in one UK hospital, the proportion of patients with medically unexplained symptoms differed between 24% in the chest clinic to 64% in the neurology clinic (mean 52%) (Nimnuan et al. 2001).

The high prevalence of medically unexplained symptoms in neurology clinics has led to numerous studies and a summary of data from seven neurology clinics showed prevalence rates between 26% and 45% (median 30%) (Stone et al. 2009). In the largest survey, the most common categories of diagnosis were: headache disorder (26%), neurological disorders without explanations (26%), and conversion symptoms (motor, sensory or non-epileptic attacks) (18%) (Sharpe et al. 2010). The second category indicates that medically unexplained symptoms commonly occur in people who have physically illness but the presenting symptoms cannot be explained by that illness.

In primary care, symptoms judged not explained by organic disease form between 10% and 33% of presenting complaints in primary care (Haller et al. 2015). A systematic review concluded that medically unexplained symptoms constitute the primary reason for

consulting the general practitioner (GP) in 15-19% of patients (Burton et al. 2003; Rosendal et al. 2017).

The proportion of all patients with symptoms classified as 'medically unexplained' alters greatly between GPs and this variation cannot be attributed to variation in the GP's patient populations; instead it reflects GP's tendency to use this categorization (Rosendal et al. 2003).

Surveys in the general population show that pain is the most common medically unexplained symptom – headache and back, joint, abdominal and limb pain being the most common; fatigue, dizziness, bloating, food intolerance and sexual difficulties are also common (Kroenke et al. 1993; Hiller et al. 2006). These symptoms are reported by over a fifth of the population but only a small proportion report that they are severe (Hiller et al. 2006).

In a German one-year follow up study, five out of 284 patients classified as having medically unexplained physical symptoms later turned out to have a physical illness that could explain their symptoms (Kooiman et al. 2004). In the largest neurology survey, only four out 1030 patients (0.4%) had acquired an organic disease diagnosis (Stone et al. 2009).

Population-based studies suggest that most medically unexplained symptoms wane over time; fewer than half persist over one year (Hiller et al. 2006; Simon et al. 1999; Gureje et al. 1999; olde Hartman et al. 2009) and two-thirds recede over a long period (Leiknes et al. 2007). Some Norwegians study reported that painful medically unexplained symptoms may persist over many years in approximately 8% of the general population, mostly women (Leiknes et al. 2007).

Although up to a fifth of new symptoms presented to GPs are medically unexplained (Peveler et al. 1997; Escobar et al. 2010), only 10% of these had persistent symptoms that led to repeated consultations – the rest consulted for a single episode only (Verhaak et al. 2006).

In secondary care clinics symptoms tend to be more severe and persistent than those seen in primary care. Over a one-year follow up period, approximately two-thirds of patients report improvement in medically unexplained symptoms but about 40% report some continued symptoms causing problems of health (Kooiman et al. 2004; Jackson et al. 2006). The proportion may be higher in neurology clinics (Stone et al. 2009).

Therefore, medically unexplained symptoms are very common both in the general population and in primary and secondary care, but at least in the first two settings most are transient. These may not require medical intervention other than reassurance about their frequency in healthy people and a check that they do not indicate physical disease (Osugo et

21

al. 2017). In secondary care the symptoms tend to be more persistent and may have more severe consequences. In both primary and secondary care, doctors need to use proper strategies in managing patients with these symptoms.

1.2.2 Prevalence of somatoform disorders

The term 'somatoform disorder' includes several disorders where a high number of medically unexplained symptoms is the main feature. It is a diagnostic category in both the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and ICD-10 classification system (APA, 1994; WHO, 1992); where it also includes several other diagnoses. This diagnostic category includes also the diagnoses od pain disorder and conversion disorder, which refers to sensory or motor symptoms for which no medical explanation can be found, but which are disabling and lead to medical help-seeking (APA, 1994; WHO, 1992).

Most of the study on prevalence of somatoform disorders in primary care have foreseen a standardized research interview to assess diagnosis. The most commonly used interviews are the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (WHO,1994), the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al. 1994), and in population-based studies, the Composite International Diagnostic Interview (CIDI) (Wittchen et al. 1994). During these interview participants are asked about each of many bodily symptoms and, for each symptom reported, whether a doctor has declared that is 'medically unexplained' and that it causes distress or impairment. A few studies have simply used a self-administered questionnaire (e.g. the Personal Health Questionnaire (PHQ-15)) to ask respondents to tick on a checklist those bodily symptoms that they have experienced recently and found bothersome. This approach counts all bodily symptoms, regardless of whether they are medically explained or unexplained. It cannot lead to a formal diagnosis but it has been found that a high score on such a questionnaire is associated with impaired functioning and high healthcare use even after adjusting for concurrent psychiatric and physical disorders (Barsky et al. 2005; Kroenke et al. 2002; Barsky et al.2001). Patients scoring in the top 10-20% on this questionnaire were given a provisional diagnosis of 'probable somatization' (Barsky et al. 2005).

The use of different measures and different samples leads to considerable variation in the prevalence rates, but most studies provide an overall prevalence in the range 8-20%. The median for abridged somatization SSI-4/6 which concurs with a systematic review (Creed et al. 2004).

One systematic review examined the prevalence of somatization and hypochondriasis in primary care using abridged forms for both diagnosis (Creed et al. 2004). It can be seen that the median prevalence figure for abridged somatization was 16% in primary care and this concurs with a further systematic review which found that between 16% and 22% of patients had abridged somatization (Burton et al. 2003). The median prevalence rate for hypochondriasis is approximately 10% of patients attending primary care.

Very few primary care studies reporting prevalence of somatoform disorders provide clear data regarding concurrent physical illness. One study reported that 42% of patients with somatoform disorders had diseases of the circulatory system, 29% of the musculoskeletal/connective, 20% respiratory, and 18% endocrine, nutritional and metabolic diseases (Hanel et al. 2009). Another showed that 58% of patients with medically unexplained symptoms had two or more chronic diseases, most commonly chronic chest and cardiovascular diseases (Kolk et al. 2004). In another study the mean number of physical disorders was approximately 1 in the patients with high somatic symptoms score (Kroenke et al. 2002). Another one reported that 41% had at least one serious concurrent medical illness (Barsky et al. 2005). This shows clearly that somatoform disorders coexist with recognized physical diseases.

There have been few studies of somatoform disorder in secondary care. In patients newly referred to a neurology clinic, the most frequent current diagnoses were somatoform disorders (Fink et al. 2007). In two-thirds of these patients the somatoform disorder occurred in addiction to a clear organic neurological disorder, underlying the frequency with which somatoform and organic disorder can co-occur. A study of medical inpatients, most of whom would have serious physical illness, found 1.5% had somatization disorder and 10% had undifferentiated somatoform disorder, using DSM-IV criteria (Fink et al. 2004). In a larger study of patients with serious physical illnesses the prevalence of somatoform disorder (15.3%) was significantly higher than in a population-based sample of healthy controls (5.7%) (Harter et al. 2007).

In seven population-based studies, with a total of 18 894 respondents, the 12-mounth prevalence ranged from 1.1% to 11% (Essau et al. 2007). The authors of this study estimate that the number of residents aged 18-65 years in the European Union (EU) (total 301 million) affected by somatoform disorder within the previous 12 months was 18.9 million.

There have been remarkably few prospective studies of somatoform disorder (olde Hartman et al. 2009; Creed et al. 2004; Rief et al. 2001). From the results of two systematic reviews it appears that half of patients with abridged somatization reported remission of the disorder

over one year and in half the symptoms persist (olde Hartman et al. 2009; Rief et al. 2001). Symptoms are more persistent in those studies which have selected patients with severe or chronic symptoms (Rief et al. 2007; Dehoust et al. 2017).

1.2.3 Correlates of medically unexplained symptoms and somatoform disorders

It is widely accepted that somatization is associated with female sex, fewer years of education, low socioeconomic status, other psychiatric disorder (especially anxiety and depressive disorders) and recent stressful life events (Creed et al. 2004; Deary et al. 2007; Mayou et al. 1995; Katon et al. 2001). It is unclear why numerous somatic symptoms occurs more often in females and the reasons suggested comprise: sex differences in prevalence of depression and anxiety, in pain threshold and awareness/reporting of bodily symptoms, in experience of childhood abuse; and the socialization of women to be less stoical than men (Barsky et al. 2001). Many of these findings relate to studies of the more severe forms of somatisation.

There is some evidence of a genetic predisposition to develop numerous somatic symptoms. It is unclear whether this is independent of a predisposition to develop psychiatric disorders in general but several studies suggest this is so (Lembo et al. 2009; Gillespie et al. 2000; Kato et al. 2009). Early childhood experiences that are associated with somatoform disorders include a parent with poor health or high neuroticism, persistent abdominal pain as a child and childhood abuse (Preveler et al. 1997; Katon et al. 2001; Hotopf et al. 1999; Hotopf et al. 2000). The personality trait of neuroticism has been identified as an independent correlate of medically unexplained symptoms (de Gucht et al. 2002; Watson et al. 1989; Rosmalen et al. 2007). Prior experience of physical illness may predispose individuals to somatoform disorders.

Correlates thought to be important in the onset of somatoform disorders include a physical or psychiatric illness and/or a stressful life event (either direct involvement in a traumatic event or serious illness or death of a close relative) (LeResche et al. 2007; VonKorff et al. 1993; Jacobi et al. 2014).

Some prospective studies have shown that the following are associated with new onsets of somatoform disorders: female sex, lower social class, prior psychiatric disorder (especially anxiety and depression), physical illness, a negative view of one's health, and reported traumatic sexual and physical threat events (Gureje et al. 1999; Lieb et al. 2002; Eek et al. 2010; Leiknes et al. 2008).

Since medically unexplained symptoms are universal, studies have tried to explain why in some people they become established and lead to doctor consultations, whereas most other people either ignore such symptoms or do not act upon them. These features are mostly cognitive and complex, and they include sensitization to pain, heightened attention to bodily sensations, increased worry about symptoms and illness (health anxiety), attributing bodily symptoms to a possible medical illness rather than recognizing them as a normal phenomenon or psychological distress (Deary et al. 2007; Rief et al. 2004; Rief et al. 2007). These characteristics are generally through to predict persistence of symptoms.

One of the few prospective studies on somatoform disorders fond that, over a 10-year period, persistent somatoform pain disorder was more likely to be reported by women; depression at the first assessment was the only other predictor (Leiknes et al. 2007). A one-year prospective study did not find that depression was a predictor; older age, poor self-evaluation of health and impaired work role were predictors (Gureje et al. 1999).

Medically unexplained symptoms are more likely to be persistent if they are numerous and there is high health anxiety and/or continued depression (Stone et al. 2009; olde Hartman et al. 2009; Jackson et al. 2005). One study suggested that chronic physical disease, negative affectivity and selective attention/somatic attribution are independently associated with number of persistent medically unexplained symptoms (Kolk et al. 2004). Among patients attending a neurology clinic with rather more severe medically unexplained symptoms, persistence over a year occurred in two-thirds and this was associated with a patient's belief that they would not improve, a failure to attribute the symptoms to a psychological cause and the receipt of illness-related financial benefits (Sharpe et al. 2010).

1.3   Consequences of persistent medically unexplained symptoms and healthcare costs

There is a spectrum of severity of medically unexplained symptoms which is correlated with a degree of impairment. An increasing number of medically unexplained symptoms is associated with increasing level of disability indicating a dose-response relationship, as well as for health anxiety (Katon et al. 1999).

In a sample of 2917 primary care patients divided into four groups according to the number of somatic symptoms rated as bothersome of a self-report questionnaire (Patient Health Questionnaire, PHQ), it can be seen that general, painful and physical dimensions of health status all show greater impairment as number of bodily symptoms increases after adjustment for age, sex, year of education and number of physical illnesses. The 10% with the greatest

number of somatic symptoms have greatly impaired health status. The same relationship of increasing disability with increasing number of somatic symptoms has been recorded in attenders at UK secondary care gastroenterology, neurology and cardiology clinics (Jackson et al. 2006). This study showed also that the correlation between number of bodily symptoms and health status was almost identical for patients whose symptoms were medically explained or unexplained. This data cited above relate to self-rated disability. The same relationship has been observed between the number of somatic symptoms and number of days 'off sick'. After adjustment for age, sex, years of education and number of physical illnesses, people who report numerous somatic symptoms have twice as many days off sick as those with moderate score (de Waal et al. 2004).

One study compared patients with medically unexplained symptoms, patients with somatoform disorders and healthy controls. On the Health Status Short Form (SF-36) physical component score, the first two groups showed marked impairment compared with the last. On the mental component summery score, only patients with somatoform disorder showed impairment. Thus, people with medically unexplained symptoms which are not sufficiently severe to fulfil criteria for somatoform disorder did not show impairment on the mental health dimension.

In primary care, one study showed that patients with medically unexplained symptoms were impaired in seven of eight dimensions of functioning compared with the general population (Koch et al. 2007). Patients with depressive disorder were impaired in five dimensions. The pattern of impairment differed. Medically unexplained symptoms were associated with impairment especially in physical functioning and role limitation physical. Depressive disorder showed greatest impairment on role limitation emotional and social functioning. Thus, the impairment associated with medically unexplained symptoms is comparable with that of depressive disorder alone although the areas of functioning affected are different.

Among patients attending specialist gastroenterology, neurology and cardiology clinics, the Short Form (SF)-36 physical component score in patients with medically unexplained symptoms were comparable with those in patients whose symptoms were explained by demonstrable organic disease (Jackson et al. 2006). For the mental component score (MCS), the patients with medically unexplained symptoms had a significantly lower score than the patients with symptoms explained by organic diseases.

It is often thought that somatoform disorder is a form of anxiety or depressive disorder. As it can be seen, the pattern of impairment is different for patients with anxiety and depressive disorders compared with somatoform disorders. It is important to recognize, the additional

impairment in patients with somatoform disorder who also have anxiety and depression. When somatoform disorder is accompanied by anxiety and depression, the impairment of physical functioning and of physical aspects of role functioning are greater than when either occurs alone (de Waal et al. 2004). When somatoform disorder is associated by both depressive and anxiety disorders, the degree of impairment is almost five times than of somatoform disorder alone (Hanel et al. 2009).

In a US-based study, Harris et al. found in multivariate analyses that a high number of somatic symptoms was independently associated with impairment of function, but that depressive disorder and several physical illnesses were also independently associated with impairment (Harris et al. 2009). In other words, the more of these disorders that a person has, the greater their disability. In a further multivariate analysis to determine the correlates of work limitations for health reasons, a high number of somatic symptoms and medical comorbidity were the only independent correlates after adjustment for demographic variables. This is rather similar to the findings in severe functional somatic syndrome (Arts et al. 2019).

Medically unexplained symptoms, somatoform disorders and functional somatic syndromes are associated with increased costs. Such costs may involve healthcare – frequent doctor visits, numerous investigations and admissions – and may involve societal costs, such as time missed from work and unemployment trough illness, and the costs associated with carers (Konnopka et al. 2012; Weerdsteiin et al. 2017; Park et al. 2017; Baitha et al. 2019). Data from the UK Department of Health indicate that the diagnosis corresponding to ICD code 780-789 ('Signs, symptom and ill-defined conditions') accounts for the most expensive diagnostic category of outpatients in UK and the fourth most expensive category in primary care. It was noted above that in USA this is the fifth most frequent reason for visiting doctor (Cherry et al. 2005). In the Netherlands, this diagnosis is the fifth most expensive diagnostic category (Meerding et al. 1998). The costs appear to be higher than those incurred by stroke and cancer. The high costs do not include time lost from work and the reduced productivity, nor time of carers.

In the UK primary care setting, the number of somatic symptoms has been shown to be an independent predictor of frequency of consultation over the subsequent year after adjustment for chronic physical illness, psychiatric disorder, illness behavior, health anxiety and demographic variables (Kapur et al. 2004). In American primary care, patients in the top 14% of somatic symptom scores incurred higher costs and concurrent medical illnesses, these patients with numerous somatic symptoms made approximately three outpatients visits

per year more than the remainder, the total outpatient costs were approximately US$300 greater per year.

An American primary care study adjusted for the effect of depressive, anxiety and panic disorders in addiction to demographic features and concurrent medical illnesses (Barsky et al. 2005). Compared with the remainders, patients in the top 20% of somatic symptom scores made more primary care and medical specialties visits, more visits to the emergency department and had more hospital admissions; they adjusted, annual total healthcare cost was US$5678 per patient, which was US$2734 higher than that for the remaining patients. This study estimated that if these findings were extrapolated to the whole of USA then US$256 billion a year in medical costs could be attributed to the effect of somatization alone. In the UK, a similar picture has been noted (Jackson et al. 2006). Medical outpatients who scored in the top 25% of somatic symptoms scores made and additional seven visits to primary and secondary care over an 18-month period compared with those with lower somatisation scores.

Another way of demonstrating the relationship between medically unexplained symptoms and healthcare use is through the correlates of frequent attendance (top 10%) at primary care. In a large Dutch study, 25% of persistent frequent attenders over a three-year period had medically unexplained symptoms, compared with 13% of frequent attenders over a one-year period only and 6.8% of non-frequent attenders (Smits et al. 2009). In secondary care, a quarter of medical outpatients who attended very frequently had consulted for medically unexplained symptoms (Reid et al. 2001). The total cost of investigations was twice as high in the frequent attenders with medically unexplained symptoms as the other frequent attenders, whose symptoms were explained by organic disease (Reid et al. 2001; Reid et al. 2002).

Shaw and Cred found the range of expenditure on investigations for possible organic disease ranged from £25 to £2300 (median £286) (Shaw & Creed, 1991). The determinants of costs included the diagnostic difficulties of the presenting symptom, the attitude of both patient and doctor towards organic disease as an explanation for symptoms and any resistance of either's part to adopting a psychopathological view of the symptoms. It was independent of the view expressed in the GP's referral letter. In a German trial, the direct costs and indirect costs were to be reduced greatly in a controlled study with somatoform patients undergoing an inpatient treatment with cognitive behavioral therapy (CBT) (Hiller et al. 2004).

In a study of 191 consecutive patients aged 18-50 years attending their family GP, it was found that 37.5% of the patients with an ICD-10 somatoform disorder received social

security, pension or disability benefit against only 10.8% (p>0.003) among other patients (Fink et al. 2004). In a study of 1785 consecutive patients aged 18-50 years consulting their GP, 4.9% received early retirement pension/disability benefit (Fink et al. 1999).

A Danish register study of data on disability benefit/early retirement pensions in the period 1 July 1998 to 31 December 2000 reported that among all individuals who were granted pension in that period in Denmark, 8.3% had a functional somatic syndrome diagnosis; 11% of the women and 5% of the men (Stenager et al. 2003).

It is likely that there is very considerable variation across European countries regarding the causes for receipt of incapacity benefits. For example, in the UK, the most common reason for sickness absence used to be musculoskeletal disorders (Waddell et al. 2006). Over recent years, there has been a shift away from musculoskeletal disorder to mental health disorders and in Glasgow, where there is a very high rate of claiming sickness benefits, 33.6% were claiming because of mental and behavioural disorders, with corresponding reduction in claims for musculoskeletal disorders (Brown et al. 2009). In Ireland, many patients reporting musculoskeletal pain presenting to Primary Care Physiotherapy with costly comorbid overlapping complaints that remain medically unexplained (Kennedy et al. 2018).

Depressive, anxiety and other neurotic disorders account for approximately 70% of the mental and behavioural disorders given as reasons for claiming sickness benefits; 'somatoform disorders' is a diagnostic is a diagnostic label that is never used (Brown et al. 2009). The importance of this lies is the lack of specific treatment.

A Cochrane systematic review of interventions to prevent workplace disability identified only interventions to prevent musculoskeletal disorders and one for adjustment disorders (van Osostrom et al. 2009). It is expected that the opportunity to intervene should be included in the repertoire of interventions to reduce disability (Kornelsen et al. 2016; Wortman et al. 2018).

1.4 Evidence-based treatment

There have been several different approaches to improving the care of patients with medically unexplained symptoms, somatization and the functional somatic syndrome. These range in intensity and are applicable to different parts of the healthcare system.

The first set of interventions involves the training of GPs to develop their confidence and competence in managing these patients. Primary care represents the main contact with healthcare systems for many patients with new or persistent symptoms and primary care

practitioners are used to dealing with symptoms relating to anybody system and ranging in severity from minor to potentially life-threatening. They also have to work in a situation where they may have limited access to diagnostic investigations and only generalist, rather than specialists, knowledge. On the other hand, primary care is also characterized by longitudinal patient-doctor relationships in which considerable effort and trust may be invested by both parties and which have a real therapeutic potential. Most studies of efficacy of this approach have involved training GPs in the reattribution model, in which doctors initiate a communication to examine the possibility that stress or emotional distress may have a role to play in the patient's symptoms (Goldberg et al. 1989; Gask et al. 1989).

Another approach based in primary care is one where a mental health professional, usually a psychiatrist, interview the patient on a single occasion with a view to making an assessment and bringing in a conversation and/or letter to the GP a diagnosis and treatment plan. This is known as the 'psychiatric consultation' or 'consultation-liaison' model and has been used both for depression and somatoform disorders (van der Feltz-Cornelis et al. 2010).

The assessment interview may involve the GP as well as the patient and the psychiatrists. As well as offering treatment suggestions, the recommendations to the GP usually suggest that investigations are kept to a minimum in an attempt to minimize the excessive costs associated with somatization or bodily distress.

The context of secondary care is usually is quite different from that of primary care. It is usual that patients will undergo investigations for possible organic disease and the results of such analyses are either discussed directly with the patient by the physician or they are conveyed to the GP. By definition, the results of these investigations indicate no evidence of organic disease so the symptoms that are, therefore, described as 'medically unexplained'. The way this is explained to the patient by the physician or the GP is an important issue and brings into question the effectiveness of reassurance. Most doctor-patient contacts in secondary care tend to be brief and many patients with medically unexplained symptoms state that they were informed the investigation 'does not indicate organic disease' but without a positive explanation of the likely cause of symptoms. Sometimes referral to another medical specialist may be suggested, in which case the search for an organic cause continues. Alternatively, the patient may be referred back to the GP, who has primary responsibility for ongoing care, and this includes the decision regarding further investigations. In some healthcare system the patient has direct access to the specialist physician so it is the patient who decides whether further investigations are sought.

Both primary and secondary care studies have been performed to evaluate the efficacy of psychological interventions, most commonly cognitive behavior therapy administered by a mental health professional, or antidepressants, prescribed by the patient's usual doctor. One systematic review compared primary and secondary care found that patients with functional somatic syndrome did better in interventions conducted in secondary care than primary care (Huibers et al. 2003). This may be because the patients in primary care have mild disorders with a high spontaneous response rate. Alternatively, more intensive treatment might have been used in secondary care compared with those used in primary care (Raine et al. 2002). Also, patients accepting referral to secondary care may be a selected group more willing to accept and adhere to psychological treatments.

Kroenke's comprehensive review of the evidence up to 2006 included 34 randomized controlled trials (Kroenke et al. 2007). Ten trials included patients with medically unexplained symptoms, four with somatization disorder and nine with 'abridged' somatization. There were five studies of hypochondriasis, and three each of body dysmorphic disorder and conversion disorder. Thirteen trials evaluated cognitive behavior therapy, five evaluated antidepressants, four the effect of a consultation letter to a general practitioner and three the training of GPs.

The review used a liberal measure of positive outcome. The mean effect sizes were 0.92 for antidepressants (five studies), 1.43 for behavioural therapy (four studies) and 1.78 for cognitive behavioural therapy (CBT) (five studies). Since effect size of 0.8 or greater are considered large therapeutic effects, there are clinically significant results (Kroenke et al. 2007). An additional important outcome measure was the reduction of healthcare costs, which was achieved in about a quarter of studies.

Kroenke's review suggested that positive results were more often obtained in trials including the more severe conditions than medically unexplained symptoms, which so often resolve spontaneously. The review included 10 randomized controlled trials; only those which involved CBT showed some improvement in symptoms, function and/or healthcare utilization. Thirteen studies included patients with some form of somatization disorder. Benefit was observed in three of four trials evaluating the use of a consultation letter to the GP. CBT was effective in five out of seven trials and antidepressants drugs in three out of four trials.

Kroenke drew attention to the limitations of the current evidence, including heterogeneity of conditions treated, definition of disorders, type of intervention, its intensity, variable duration of follow-up and variable outcome measures. In many trials the comparison group

31

was a usual care or waiting list control, with no attempt to control for attention by the therapist. Thus, the conclusion that CBT is consistently effective across a range of somatoform disorders must be regarded with some caution (Kroenke et al. 2007). The evidence is even more tentative regarding a psychiatric consultation letter or antidepressants, and evidence regarding other forms of treatment was negative or inconclusive. Nearly two-thirds of the trials included fewer than 100 participants so this is an area of research that needs more primary research, including large, high-quality trials. Cost-effectiveness trials are scarce in this field. Some of the studies showed reduction of healthcare costs. For some, this is probably a direct result of the consultation letter that ask GPs or other doctors not to order more investigations unless absolutely necessary. But in two studies this letter was also sent to the doctor in the control group, so it cannot be the only explanation (Kashner et al. 1995; Allen et al. 2006).

Two further systematic reviews included data concerning treatment in primary care (van der Feltz Cornelis et al. 2010; Huibers et al. 2003). The first was a broad systematic review of psychosocial interventions in primary care, which included two-high quality randomized controlled trials aimed at reducing somatization (Huibers et al. 2003). One of these involved modified re-attribution and the other sessions of CBT (Blankenstein et al. 2002; Lidbeck et al. 1997). Both studies showed benefits over usual care with regards to less illness behavior, less health anxiety, and less sick leave. A third trial of re-attribution showed no benefit over usual care (Larish et al. 2004). These authors concluded that there is limited evidence of the effectiveness of a re-attribution intervention by a GP in terms of consumption of medical resources, subjective health, sick leave and somatization.

The second significant systematic review focused on the effect of a psychiatric consultation in primary care, where the patient was visited by a psychiatric, who provided the GP with a diagnosis and treatment plan (van der Feltz Cornelis et al. 2010). There were four relevant studies; the meta-analysis indicated that treatment was superior to usual care.

The Kroenke review reported four studies of antidepressants. One trial used opipramol, which led to borderline significant advantage over placebo in terms of SL-90 somatisation score, but the trial of St John's wort led to considerable improvement by this outcome measure compared with placebo (Volz et al. 2000; Volz et al. 2002). Both studies lasted only six weeks and excluded patients with concurrent psychiatric disorders. Kroenke only included people with anxiety and depression as well as multisomatoform disorders and found that venlafaxine was not significantly better that placebo in reducing somatic symptoms burden (Kroenke et al. 2006). In view of the short duration of these studies, the reluctance

of so many patients to take antidepressants and their unproven efficacy, the role of antidepressants is uncertain, with the possible exception of treating pain.

Five recent studies in primary care have included larger numbers than most previous studies (Morris et al. 2007; Escobar et al 2007; Sumathipala et al. 2008; Aiarzaguena et al. 2007; Toft et al. 2010). They reported conflicting results. The first tested a modification to the reattribution model, which involved providing the patient with a credible physical explanation for their symptoms (described as a hormonal disturbance in response in response to stress) (Toft et al. 2010). This involved 20 hours of training for the general practitioners in the intervention group compared with three hours of reattribution training for the control GPs. Patients (n=156) attended five half-hour sessions. Patients in both groups made improvements in all dimensions of the Medical Outcome Survey Short Form (SF)-36, but these improvements were significantly greater after the intervention than in control arm. The intervention included many of the ingredients of brief psychodynamic psychotherapy.

By contrast, two recent large trials of the reattribution model showed no efficacy, even though both groups of researchers had reported promising results in previous smaller trials (Morriss et al. 2007; Toft et al. 2010; Morriss et al. 1999; Rosendal et al. 2003). In a Danish study, 38 GPs were randomized to a training arm or the control group; 461 patients with medically unexplained symptoms or somatization cared for by these GPs were studied (Toft et al. 2010). Three hundred and fifty patients with somatoform disorder and 111 patients with medically unexplained physical symptoms were included and analyzed separately. There was a significantly greater improvement in physical functioning at three months for patients managed by trained GPs, compared with patients managed by GPs in the control group. This difference was not maintained at follow-up. No such difference was apparent in the patients with medically unexplained symptoms. The study concluded the training GPs may increase physical function for patients with somatoform disorder but the effect is small and may not be clinically significant.

A more recent systematic review of reattribution included seven randomized controlled trials (Gask et al. 2011). The review by Gask highlighted one successful Dutch trial, in which reattribution training was combined with collaborative care including a psychiatric consultation (van der Feltz-Cornelis et al. 2006).

Some recent trials found that CBT was effective in primary care patients with medically unexplained symptoms, most commonly pain conditions (Escobar et al. 2007; Liu et al. 2019). The intervention involved 10 CBT sessions. These focused in the reduction of physical distress and somatic fixation, activity regulation, facilitation of emotional

awareness, cognitive restructuring and interpersonal communication. This intervention was more effective than treatment as usual. It led to reduced somatic symptoms in half of participants and the benefit remained over time. The intervention also led to improved depression, but this was not maintained and the authors conclude that this improvement in depression did not mediate fewer somatic symptoms (Escobar et al. 2007).

By contrast, a recent trial in Sri Lanka found no differences in outcome between CBT and a control group for primary care patients with medically unexplained symptoms (Sumathipala et al. 2008). This research used structured care for the control group to control for the effect of the doctor's time and attention in the intervention. This involved a detailed assessment by the specialist, the patient keeping a diary of symptoms and cognitions, and regular visits to the physician. The group of patients was rather similar to that included in the trial mentioned above, with numerous somatic symptoms and considerable distress. The negative result of the Sri Lanka trial is probably explained by the good response to the structured care; both the CBT and control groups recorded over 40% reduction in symptoms in spite of their prior chronicity. The structured care was so elaborate that might itself have been therapeutic.

Most of the positive trials reported above compared the intervention to unmodified usual care or even waiting list control. The Sri Lankan trial improved usual care to the point that it was beneficial to patients, thus demonstrating the benefits of a structured approach to care of patients with medically unexplained symptoms.

It has become clear from qualitative studies of medically unexplained symptoms that the doctor-patient relationship is important and patients benefit when they feel supported and empowered by the doctor to tackle their problems (Salmon et al. 1999). Medical care of unexplained symptoms is improved if there are improvements in three inter-related elements: diagnosis, specific treatment strategies and communication (Rosendal et al. 2005). Such improvements may well have occurred in the structured care used in the Sri Lanka trial. GPs often ignore the psychopathological aspects provided by many patients with medically unexplained symptoms (Salmon et al. 2004). The doctors' initial response is often to discuss potential medical problems with a view to reassuring the patients, with or without ordering an investigation (Salmon et al. 2006). On the other hand, if both the patient and the GP discuss psychosocial issues in the consultation, the likelihood of somatic intervention decreases (Salmon et al. 2007). Similarly, if the doctor shows empathy towards patients who present with medically unexplained symptoms, the patients are more likely to report higher rating of interpersonal care (Epstein et al. 2007). The findings from the Sri Lankan trial and these systematic observations made from qualitative studies suggest strongly that improving

routine clinical care along the lines recommended by Rosendal and colleagues could greatly improve the management of medically unexplained symptoms (Rosendal et al. 2005).

An example can be found in an observational study of patients with irritable bowel syndrome (IBS), who received good clinical care in gastroenterology clinic (van Dulmen et al. 1995). Such care led to an improvement of their bowel symptoms, a reduction in their anxiety about a serious disease, an appreciation that the abdominal symptoms may be stress-related and fewer catastrophic thoughts about their symptoms. All of these would be goals of a psychological intervention for IBS. These changes were not associated with the number of investigations performed, but they were associated with seeing the same doctor on each occasion. The key feature of the consultation that was associated with improvement in symptoms was the doctor's correct perception, at the first consultation, of the patient's view of the cause of the symptoms. This was probably a marker of the quality of the patient-doctor interaction, as it is certain that the doctor who ascertains that the patient attributes their symptoms to physical rather than stress-related causes will lead on to a conceivable alternative explanation. Such work emphasizes the relevance of doctors understanding patients' views of their medically unexplained symptoms compared with the importance of performing examinations for possible organic disease.

In contrast to the relative sparse primary research concerning somatoform disorders, there have been a large number of trials of interventions for specific functional somatic syndromes.

An early systematic review found evidence of the usefulness of CBT in patients with persistent somatic symptoms; this review included studies of specific functional somatic syndromes as well as a few including patients with somatization or hypochondriasis (Kroenke et al. 2000). The authors considered the outcomes of physical symptoms, psychological distress and functional status. Of these, physical symptoms appeared to be the most responsive. Improvement of physical symptoms was greater in patients treated with CBT than in control subjects in 71% of the studies, whereas a definitive advantage of CBT for reducing psychological distress was demonstrated in only 38% of studies. In half of the studies, CBT led to an improvement in functional status compared with the control condition.

The authors noted that improvement in physical symptoms often occurred independent of improvement in psychological distress. They pointed out that CBT for somatic symptoms may require additional treatment for depression, e.g. with antidepressants.

In this review, it was noted that the CBT did not conform to a specific pattern as interventions were multifaceted and flexible. Both individual and group formats were found to be effective and the number of sessions varied between studies. Most of the studies were carried out in referred populations and there was considerable variation in the nature of the symptoms, their severity and chronicity.

The authors of this review noted that acceptability of CBT to such patients is a critical issue that had not really been addressed in many of the studies as they did not include data on participation rates. Since most studies were conducted in specialist referral clinics, future studies should examine what proportion of primary care patients with persistent somatization and symptom syndromes who were offered CBT actually accepted and completed therapy.

One of the first systematic reviews of the use of antidepressants included 94 randomized controlled trials (6595 patients in all), which most frequently included headache, fibromyalgia, functional gastrointestinal disorder and unexplained pain (O'Malley et al. 1999). Overall, two-thirds of the studies found evidence of benefit for antidepressants as patients receiving these drugs were three times more likely than those receiving placebo to show improvement. This result was recorded for patients with fibromyalgia, headache, chronic fatigue, functional gastrointestinal complaints and idiopathic pain.

The overall quality of studies included in this review was described as fair. Studies were generally of short duration, whereas these symptoms are often chronic. Many studies used a crossover design, which is inappropriate for chronic conditions. Withdrawal rate were high (40% of trials had drop-out rates over 20%), suggesting that antidepressants may not be well tolerated in this population. The number of studies for some conditions was very small. They were inadequate data to decide whether the efficacy of antidepressants was mediated by reduction of depression.

The systematic review of the effectiveness of antidepressants and CBT for functional somatic syndromes has been updated (Jackson et al. 2006). The reviewers concluded that CBT was consistently demonstrate to be effective in all of the functional somatic syndrome they examined. There is evidence of efficacy of antidepressants for headaches, fibromyalgia and IBS, with weaker evidence for back pain and a lack of evidence for chronic fatigue syndrome. These authors consider that the effect size of treatment of antidepressants is not as great as that resulting from CBT. There is evidence that CBT not interact with other medication and has few if any side effects and that CBT has increasing effectiveness over time. The recent review state that some or all of the effect of antidepressants on somatic symptoms is independent of depression.

Antidepressants are more effective than placebo in reducing back pain but not in improving functional status in patients with chronic back pain. The effect size in relation to pain, however, is modest and CBT may achieve better results. With regards to headache, there is reasonable evidence for the efficacy of tricyclic antidepressants (TCAs), but a recent meta-analysis suggests that serotonin selective reuptake inhibitors (SSRIs) were no more effective than placebo for patients with migraine headaches and not as effective as TCAs for tension headaches (Moja et al. 2005). CBT, relaxation therapy and biofeedback have been shown to yield considerable improvement in migraine and tension headaches, with beneficial effects persisting over seven years (Rains et al. 2005).

A systematic review of short-time psychodynamic psychotherapies (STPP) for somatic symptom disorder found 13 RCTs and 10 case series with pre-post outcome assessments (Abbass et al. 2009). The studies included a total of 1870 subjects, of which 873 received STPP and 535 served as controls. Six studies involved patients with chronic pain. Others included patients with functional disorders such as IBS, while others focused on somatic symptoms related to more traditional medical disorders such as Crohn's disease, coronary artery disease, emphysema and Sjogren's syndrome. Of the included studies, 31/23 (91.3%), 11/12 (91.6%), 16/19 (76.2%) and 7/9 (77.8%) reported significant or possible effects on physical symptoms, psychological symptoms, social-occupational function and healthcare utilization, respectively. Meta-analysis was possible for 14 studies and revealed significant effects on physical symptoms, psychiatric symptoms and social adjustment, which were maintained in long-term follow-up. While this review suggests potential benefit for STPP, the heterogeneity among the studies and methodological shortcomings make the evidence basis for STPP more preliminary and not nearly as convincing yet as that for CBT.

Abbass and colleagues published an update of the review to evaluate the efficacy of STPP for adults with common mental disorders compared with wait-list controls, treatments as usual and minimal contact controls in RCTs, and to specify the differential effects of STPP for people with different disorders and treatment characteristics (Abbass et al. 2014). The search strategy included 33 studies of STPP involving 2173 randomised participants. Results highlighted that, except for somatic measures in the short-term, all outcome categories suggested significantly greater improvement in the treatment versus the control groups in the short- and medium-term. Authors concluded that, given the limited data, loss of significance in some measures at long-term follow-up and heterogeneity between studies should be interpreted with caution, and variability in treatment delivery and quality may limit the reliability of estimates of effect for STPP (Abbass et al. 2014).

There are very few effectiveness or cost-effectiveness trials in the functional somatic syndrome. In irritable bowel syndrome it has been shown that the provision of a booklet for self-management significantly reduced costs to health services by £72 per patient because of a reduction in prescribed drugs, and primary and secondary care visits (Robison et al. 2006). CBT in primary care for IBS costs an additional £308 per patient (McCrone et al. 2008). In this trial there were no cost savings as a result of reduced use of other services or reduced time lost from employment during the trial period or nine months' follow up. This meant that the treatment was not regarded as cost-effective during the follow-up period.

NICE found that both TCAs and SSRIs are cost-effective treatments for IBS (NICE, 2008). Psychodynamic psychotherapy was found to be a cost-effective treatment for patients with severe IBS in secondary and tertiary care with a high level of National Health Service (NHS) service use at baseline (NICE, 2008; Creed et al. 203). The trial showed that direct healthcare costs were lower in the year following treatment for three months of psychotherapy compared with three months of usual care. This benefit offset the high healthcare costs during the intervention period for psychotherapy (Creed et al. 2003). This evidence is unlikely to be applicable to primary care patients except those with refractory IBS. NICE also found hypnotherapy to be a cost-effective treatment for refractory IBS.

A cost-effectiveness study of CBT in chronic fatigue syndrome found that this treatment also led to greater reduction of medical and societal costs that guided support group or usual care (Severens et al. 2004). CBT was expensive but, in view of the better clinical outcome was cost-effective. Compared with no treatment, the baseline incremental cost-effectiveness of CBT was 20 516 Euro per chronic fatigue syndrome patient showing clinically significant improvement, and 21 375 Euro per quality-adjusted life-year (QALY).

A study in UK found similar results – the cost of providing CBT or graded exercise was £ 149 greater than that of usual GP care plus a self-booklet, but the outcome was better (McCrone et al. 2004). There was no difference between CBT and graded exercise. When NICE analyzed these results, it appeared that cost per QALY was under £20 000, but the sensitivity analysis suggested the real cost might be higher (NICE, 2007).

One major review examined treatment for the functional somatic symptoms across all syndromes and identified five types of treatment (Henningsen et al. 2007). These were: *peripheral pharmacotherapy* (such as antispasmodic drugs for IBS), *central pharmacotherapy* (such as antidepressants for analgesia), *active behavioural interventions* (such as exercise), *passive physical interventions* (such as tender point injections) and,

finally, *interventions aimed at changing the doctor's behavior* (such as reattribution training).

The review found that the benefits of peripheral pharmacotherapy are clear in certain disorders, such as IBS or functional dyspepsia, but not helpful in other disorders. On the other hand, central pharmacotherapy, such as antidepressants, are more widely beneficial across different functional somatic syndrome. With regard to non-pharmacological interventions, the review found evidence of efficacy for those treatments that require patient these types of treatment, such as GET or psychotherapy. There is a problem comparing 'benefit' across impact on functioning and overall health status, whereas pharmacological treatments show greatest benefit in particular symptoms, such as pain or bowel dysfunction. The review drew a distinction between uncomplicated, organ-specific functional disorders, where the typical pharmacological intervention is usually effective and the multiorgan type where a different approach is required. For the latter type, a cognitive interpersonal intervention is suggested from the outset but the review found that evidence for this is lacking.

Increasingly there is a tendency to adopt a stepped-care model. This has recently been tested in chronic fatigue syndrome and the results indicate the stepped care involving a period of guided self-instruction followed by CBT only if necessary, provided similar overall results to 14 sessions of CBT for all participants: 49% and 48% in each arm of the trial achieved clinically significant improvement (Tummers et al. 2010). The advantage of the guided self-instruction was that fewer people needed CBT and, when it was needed, fewer sessions were required. It has been noted above that self-management for IBS patients attending primary care leads to improvement in symptoms and a reduction in subsequent primary care consultation (Robinson et al. 2006). Thus, the use of a stepped-care approach led to less need for treatment as well as improvement of symptoms.

With regard to multiorgan type of functional somatic syndrome, some data from one study provides evidence of efficacy of treatment. Patients attending secondary or tertiary care gastroenterology clinics with severe IBS which had not responded to usual treatment were divided into those with and without numerous other somatic symptoms outside the gastrointestinal tract, most commonly headaches, faintness or dizziness, pain in the lower back, soreness of muscles, trouble with breathing, hot or cold spells, numbness, tingling, and fatigue. These would be classified as 'multiorgan' or complex functional somatic syndrome patients. The other half had few or no somatic symptoms outside the gastrointestinal tract and these would be regarded as organ-specific IBS.

As might be expected from the literature, the patients with the highest somatic symptoms score were more disabled, more likely to have a concurrent psychiatric diagnosis and incurred higher total costs before entering the trial. They improved greatly with treatment, however, whether it was antidepressant or psychotherapy. It was this group with the multiple somatic symptoms that showed greatest difference from treatment as usual in terms of improvement of health status. This group with multiple somatic symptoms also showed greatest reduction in costs over the year following the end of treatment. These mean costs, adjusted for baseline costs, were £1092 (Standard Error (SE) 487, £1394 (SE 443) and £2949 (SE 593) for the psychotherapy, antidepressant and treatment 'as usual' groups, respectively ($p = 0.050$ adjusted for age, sex, years of education, depression, panic and generalized anxiety disorder and abuse history and for baseline costs).

This study suggests that those patients with severe IBS who do not respond to usual treatment, can be still be divided into those with single-organ or multiorgan types. Both types respond to antidepressants or brief interpersonal psychotherapy but the change is greatest in the multiorgan type because they are more impaired and incur higher healthcare costs at baseline compared with single-organ type.

From a patient-centered perspective, treatment outcome measures in somatoform disorders, need to be personalized to the patient, fit core problems that are targeted in therapy, and reflect one's capacity to adapt and self-manage anticipated deterioration. A recent overview of 60 treatment outcomes concluded that the wide variety of treatment outcomes and the observation that patients attach different importance to the outcome measures supports the value of developing new personalized measures for effect studies (Klemm et al. 2018).

1.5 Management and organization care

In primary and secondary care, the proportion of patients with bodily distress is high. A Danish primary care study examined whether patients with medically unexplained symptoms received adequate treatment. The study included 38 general practitioners (GPs) and 1785 patients (Fink et al. 2008). GPs considered their own treatment as adequate for only half of the patients with medically unexplained symptoms. This compared with 95.3% of the patients who had well-defined physical disease. Of patients with medically unexplained symptoms whose treatment was assumed to be inadequate, the GPs would have referred approximately half to a specialist, if possible. For the other half, the GPs felt they could have offered better treatment if they had more time to treat them in their own practice.

Thus, to make treatment acceptable for all patients with medically unexplained symptoms, GPs would need more time to treat them in primary care and a suitable specialist to whom the more severely affected patients could be referred. This study indicates that the care of patients with bodily distress is lagging far behind the care offered to patients with physical diseases. Moreover, at least half of patients with depressive disorder seen in primary care present to their GP with numerous medically unexplained symptoms (Simon et al. 1999). Such depression often goes unrecognized and untreated, and the risk of this happening is greater when the patient presents with numerous bodily symptoms (Wittchen et al. 2002; Goldberg et al. 1979). Thus, many patients with numerous bodily symptoms caused by depression go untreated and the bodily symptoms persist.

In secondary care clinics, bodily distress disorders are common and tend to be more persistent than in primary care. It has been documented that less than 10% of patients with medically unexplained symptoms receive specific treatment with antidepressants or psychological treatment (Hamilton et al. 1996; Mangwana et al. 2009; Hansen et al. 2001). Of patients attending specialist medical clinics with medically unexplained symptoms, anxiety and depression were documented in the case notes of one-third, yet only 4% were referred to psychiatrists and only 2% started on antidepressants (Hamilton et al. 1996). In a similar more recent study, psychosocial factors were recorded in over half of patients with medically unexplained symptoms, yet only 3% referred to a psychiatrist, 7% were started on antidepressants and lifestyle advice given to 8% (Mangwana et al. 2009). In a third study the neurologist considered that psychological or psychiatric treatment was appropriate in 40% of outpatients with medically unexplained symptoms, but one year later most complaints remained unresolved suggesting that effective treatment was not given (Carson et al. 2000; Carson et al. 2003).

A case-note study of patients with irritable bowel syndrome (IBS) attending a specialist clinic in the USA found that fewer subsequent clinic visits for irritable bowel syndrome were associated with a positive patient-doctor interaction at the first consultation (Owens et al. 1995). A positive interaction was one in which the doctor had taken and recorded a brief psychosocial history, investigated the reasons for seeking medical help and held a detailed discussion of diagnosis and treatment with the patient. These indicators of a positive interaction were present in fewer than a half of the doctor-patient encounters.

A European study of unmet need in IBS identified those faced by patients and doctors (Quigley et al. 2006). From the patient's perspective the three unmet needs were: limited awareness and understanding of IBS as a medical condition; non-invasive diagnostic

procedures; readily available treatments. The suggested remedies for these unmet needs were patient education schemes, an algorithm focusing on positive diagnosis and new treatment targeting the multiple symptoms of IBS. This study recognized also the unmet needs from the doctors' perspective. These included better understanding of IBS, simple diagnostic procedures, treatment guidelines and effect-development of practice-based algorithm, pan-European treatment guidelines and new treatments targeting multiple IBS symptoms.

A further insight into unmet needs in routine patient-doctor interactions can be gained from an intervention study in which physicians receive minimal training and information on each patient's expectations of the consultation, their degree of illness concern and whether psychiatric disorder was present (Jackson et al. 1999). Consultations with patients who have bodily distress have gained a reputation for being regarded as 'difficult', but the proportion thus rated was halved after the intervention probably because the patient' unmet expectations of the consultation were reduce greatly. The doctors reported that addressing patients' symptoms-related expectations did not take extra time. This study demonstrates, firstly, that prior to this intervention, patients had unmet needs in terms of unaddressed concerns, and, secondly, that it was quite easy to meet these needs.

Although the general impression is that patients with bodily distress are rarely admitted to medical wards nowadays, Danish studies have found mental illness and somatoform disorders to be the two most common psychiatric diagnoses, among medical inpatients (Fink et al. 2003, Hansen et al. 2001; Fink et al. 2005; Fink et al. 2004; Hansen et al. 2002). Of all those with psychiatric disorder, only 2.7% were referred to a consultation-liaison service, and 5.1% were already receiving psychiatric treatment (Hansen et al. 2001). The preponderance of patients with bodily distress and other psychiatric disorders remained untreated. Even when depressive disorders are detected and treated on a medical ward, the treatment may be discontinued at discharge (Gater et al. 1998).

The European Consultation Liaison Psychiatry Workgroup (ECLW) study collected data on 34500 patients admitted to acute wards of general hospitals across Europe (de Jonge et al. 2001). Although the prevalence of somatoform disorder in this cohort was 14% only 61patients (0.002%) were referred to a consultation-liaison psychiatry service with this diagnosis. A Danish study which included 394 consecutive internal medical inpatients found a prevalence of somatoform disorder of 17.6% (Hansen et al. 2001). Psychiatric consultations were few and most patients did not receive specific treatment for this disorder. In a study on 198 new patients referred to a neurological unit as in- or outpatients, 16 cases of somatoform disorders were found by psychiatric research interview (Fink et al. 2003;

Gater et al. 1998). Of these, only three were referred to a psychologist or psychiatrist, and all three were already under treatment for a mental disorder by their GP before admission; none of the remainder was referred for psychiatric treatment. In a UK study, approximately half of the patients admitted to a neurology ward had medically unexplained symptoms (with or without concomitant organic disease) and for 60% of these, there was evidence of underlying psychiatrist, although some were prescribed antidepressants in low doses, which is likely to be ineffective for depressive disorder. It can be concluded that the vast majority of in- and outpatients with bodily distress disorders in neurology, gastroenterology and general medical units do not receive appropriate treatment. They are rarely referred to a consultation-liaison psychiatric services and, if antidepressants are commenced, they may be discontinued at discharge.

Follow-up studies have shown that left untreated, bodily distress syndromes continue to be associated with disability and high healthcare costs. In a Dutch follow-up study of patients who had been investigated at a medical clinic and were found to have medically unexplained symptoms, 63% reported some improvement of their symptoms, but only 38% considered themselves to be in good health (Kooiman et al. 2004). In a similar study of patients with medically unexplained symptoms attending hospital clinics in the UK, at 6-month follow-up 40% reported improvement in symptoms, although their health status will still impaired (Jackson et al. 2006). For the remaining 60%, their symptoms were the same or worse and their health status remained one standard deviation below the population norm. A study of neurology outpatients showed that 54% remained the same or deteriorated during the eight months following a new outpatient appointment (Carson et al. 2003).

Factors known to be associated with continued high healthcare use among patients with bodily distress include continuing psychiatric disorder, persistent high number of bodily symptoms and high levels of health anxiety (Hansen et al. 2002; Barsky et al. 1986; Hansen et al. 2004; Hansen et al. 2005; Fink et al. 2010). Some studies of single syndromes have indicated that depression may be responsible for a part of the disability associated with functional somatic syndromes (Creed et al. 2005), whereas epidemiological studies including a broader range of patients have shown that psychiatric disorders and bodily distress results in an independent increase healthcare use (Hansen et al. 2002; Hansen et al. 2004; Kapur et al. 2004; Henningsen 2018).

Follow-up studies have shown that primary-care patients with a moderate number of medically unexplained symptoms continue to have disability over a five-year period (Jackson et al. 2008). This is often associated with continuing depression. On the other hand,

a follow-up study of health anxiety (hypochondriasis) showed persistent impairment during a two-year follow-up period with healthcare costs approximately 75% higher than those of patients with well-defined medical condition. The impairment and healthcare costs were independent of the presence of a depression or anxiety disorder (Fink et al. 2010).

Unmet needs are seen most clearly when treated and untreated patients with the same disorder are compared. In the study of severe IBS previously cited, patients with numerous somatic symptoms outside the gastrointestinal tract who received either psychotherapy or antidepressants improved their health status score by 4-6 points on the Medical Outcome Survey Short Form (SF)-36 physical component summery score (equivalent to one standard deviation in this measure) (Creed et al. 2008). By contrast, similar patients who receive 'usual treatment' experienced a deterioration of their health status of approximately five points and they continued to incur extremely high healthcare costs. The latter is a very clear description of unmet needs; denied the psychotherapeutic or antidepressant treatment used by those in the other arms of the trial, these patients experienced worsening of their health-related quality of life.

There is evidence that patients seeking help with medically unexplained symptoms in secondary-care medical units are not keen to entertain the idea of psychological treatment. In the neurology outpatients study mentioned above, the neurologist identified a need for psychological treatment in over a half of patients with medically unexplained symptoms (Carson et al. 2000). Fewer than a quarter of these patients saw the need for psychological treatment.

In another study, most patients with psychiatric disorders in a neurology unit (the majority of whom would have bodily distress), had not been asked by the neurologist about their mood. The majority were content about this because they felt it was appropriate for the neurologist to ask about psychological aspects of illness. The neurologist was perceived a doctor who investigated only physical causes for their symptoms (Bridges et al. 1984). Additional reasons for patients not thinking the neurologist should have asked about their mood included the neurologist's lack of time, the lack of privacy on the ward and the neurologist's tendency to use jargon and be evasive or vague when asked specific questions. Unmet need based on patient perception is understudied in mental health (Prins et al. 2008), and rarely studied in bodily distress. One study of primary-care patients with persistent somatoform disorder found that approximately one-third did not wish for treatment so they could not be regarded as having unmet need (Arnold et al. 2006). Besides, one-half were

either in treatment or not considered to be suitable, so only one-third of the cohort required treatment and were prepared to receive it.

Two small studies have taken patient-centred approach towards patients' goals of treatment. Affleck et al. studied women with fibromyalgia and found only around 20% sought recovery, the remainder being uniformly split between seeking to live with their condition and to be accepted by others (Affleck et al. 2001). Nordin and colleagues interviewed patients with medically unexplained symptoms and their physicians (Nordin et al. 2006). The majority (62%) of patients hoped for support from the doctor and many (40%) reported that improvement in function and coping was their main goal of treatment (Nordin et al. 2006).

A peculiar set of potential unmet needs relates to patients' views of treatment; there were several themes reported in one study of patients with IBS (Harris et al. 2008). Patients disliked certain styles, such as the fear of side effects from drugs or the pain of acupuncture, although some had said they wished for 'non-medical' treatment. Some were doubtful of the efficacy or certain treatments, including homeopathy and hypnotherapy. Quite a few patients considered that their condition was not severe enough to need drugs or similar medical treatment. Many patients expressed a desire for more information but would be very allured of the clinician recommended a particular treatment. This description of patient's feelings about possible treatment suggest that many patients have an important unmet need for more information about possible treatments. This need is generally best met by the doctor explaining the treatment options clearly in an unbiased way.

Service delivery for patients with bodily distress syndromes varies greatly across Europe. Patients with this type of disorder may be seen in general medical services where the chances of getting good treatment are rather slim. There is a growing number of services that are being specifically establish to deal with patients who have bodily distress syndrome, but these are still very much in the minority. These services recognize that bodily distress syndromes, at least when severe, are a group of disorders in their own right that require specific treatment, and not as a phenomenon secondary to another mental illness.

Ideally, the management of these patients should be organized according to a stepped-care model with milder disorders treated in primary care and in a hierarchy of services that match each level of severity with an appropriate intensity of treatment up to and including the possibility of collaborative care (Henningsen et al. 2007; Fink et al. 2008; Henningsen 2018). Existing services will be described in terms of three tiers:

(a) Non-specialized general medical services

(b) Specialist services for individual functional somatic syndrome or diagnoses

45

(c) Specialist services for all type of bodily distress syndrome.

Most patients with bodily distress are seen in primary care. A few countries have developed a model of specialized treatment of bodily distress within primary care. The specialization in primary care may appear inappropriate, but it is probably a natural consequence of the huge unmet need for care for this patient group and the fact that neither secondary mental health nor general medical services offer any specialist treatment appropriate for this group of patients. Only a minority of psychiatrists and psychologists have the appropriate skills or knowledge to diagnose and treat patients with bodily distress.

Some countries have introduced generic training for GPs which includes management of patients presenting with bodily distress. However, most of these training programs focus on specifically on bodily distress syndrome. For instance, in Germany the GPs are reimbursed for 'talk' therapy if they have trained in psychosocial treatment. In Denmark, more specific programs for bodily distress have been established during recent years. However, experience has shown that such training of GPs is not sufficient to provide adequate care for patients with bodily distress.

Models of collaborative care, in which the GPs are supported in their management by specialists at different levels, may be a way of improving care in primary care (van der Feltz-Cornelis et al. 2006). However, a precondition for this model is the existence of a local specialized service for bodily distress syndromes (psychiatrists, psychologists and/or nurses) with which the GP can collaborate, and this is only available in a few places worldwide.

Patients with bodily distress syndrome are rarely seen in general psychiatric services, and only patients displaying prominent emotional symptoms or who have a concurrent mental disorder in addition to their bodily distress are seen. Patients with health anxiety (hypochondriasis) may be included in programs for anxiety, nonetheless.

Consultation-liaison psychiatry or psychosomatics is the only medical or psychiatric subspecialty having bodily distress as a target group. In the large European study of general hospital patients referred to 56 consultation-liaison psychiatric services, 19% of the patients were referred because of 'medically unexplained symptoms' (Hutse et al. 2001). Only eight of these fifty-six consultation-liaison services had a marker preponderance of patients referred with bodily distress; six of these were psychosomatic services in Germany, in which approximately 65% of referrals were for medically unexplained symptoms. The psychosomatic services of Germany are better organized than most others to meet the needs of patients with bodily distress syndromes.

An early survey of a consultation-liaison psychiatry services in the USA found that 38% of referrals were for somatization (Katon et al. 1984). A more recent large survey of patients referred to an American consultation-liaison service found that approximately 10% of referrals from the medical inpatient units had bodily distress syndromes; this compared with 15.5% of patients seen in a psychosomatic outpatient clinic and 4% of referrals to the community psychiatry service (Bass et al. 2001). By contrast, a smaller UK study reported that bodily distress disorders accounted for 28% of referrals to a consultation-liaison psychiatry service from medical inpatient wards, 45% of referrals to the consultation-liaison psychiatry outpatient clinic and 14% of referrals direct from primary care (Creed et al. 1993). Three other UK consultation-liaison psychiatry services reported the proportion of patients referred with medically unexplained symptoms was 30%, 12% and 9% in the three services, respectively (Royal College of Physicians and Royal College of Psychiatrists, 1995).

Patients with bodily distress syndromes are often seen in various medical specialties (IBS in gastroenterology clinics, fibromyalgia in rheumatology clinics, chronic fatigue in endocrine or neurology clinics, etc.). In most cases, the patients are investigated for possible organic disease and referred back to the primary care without a specific treatment having been commenced. If the patients also have emotional symptoms, a referral to psychiatry may be tried but often these patients are also neglected by general psychiatry, especially as general psychiatry services are primarily focused on psychotic, mood and personality disorders (Bass et al. 2001; Creed et al. 2006).

Some medical specialists have responded to the large number of patients attending their clinics with these disorder by developing, within their own service, a special interest facility for treating 'their own' functional somatic syndrome, such as rheumatologists treating fibromyalgia or gastroenterologist treating IBS. The care is mostly monodisciplinary and not coordinated between specialists, so patients with numerous somatic symptoms lead to a referral to the gastroenterology clinic, musculoskeletal pains in rheumatology and fatigue top neurology. In a few centers, the management occurs in collaboration with a consultation-liaison psychiatrist or a health psychologist, as in Sweden in the treatment of chronic dizziness (Staab et al. 2006).

Although this model seems to be poorly coordinated and meeting the needs only of a narrow patient group, it is the most common in most countries. For patients with a single functional somatic syndrome it may work quite well, however, especially as it is sometimes linked to a helpful patient group concerned with that particular disorder or fibromyalgia support. The

organization of care in this model is unsystematic and dependent on local initiatives and personal interests, although some of the established programs may function very well.

Many countries have developed specialist services for various functional somatic syndromes. The most common example is pain clinics, which are found in most countries. Some of these clinics focus not on functional or idiopathic pain but on pain caused by well-defined disease, such as cancer and neurogenic pain, but others are primarily treating patients with functional or idiopathic pain or a mixture of patients (Tack 2019).

Except for pain clinics, the type of specialist clinics for various functional somatic syndrome varies greatly between countries. In the UK and Netherlands, there are well-developed services for chronic fatigue syndrome. In Belgium and Norway, huge networks of clinics for chronic fatigue syndrome are being set up under the central initiative of the governments. In other countries, chronic fatigue syndrome clinics do not exist at all. In some countries there are other specialist clinics, e.g. for multiple chemical sensitivity and fibromyalgia in Denmark. These types of clinic are often not established by doctors, according to their patients' needs, but by official authorities who have been persuaded to establish a special service and/or the media, which may highlight an individual case of suffering.

The specialized clinics for individual functional somatic syndromes are often organized and run by medical specialists from the specialty of the organ in question. This may be the only way such clinics can be founded, but the monodisciplinary nature of such clinics is a drawback. Pain clinics may be headed by various medical specialists, most commonly by anesthetists, but GPs, psychiatrists, psychologists and neurologists are also involved in assessing and treating patients in these clinics. There seems to be general accord that the multidisciplinary team model is most suitable for patients with severe bodily distress syndromes and functional somatic syndromes as the same treatment seems to be effective across various functional syndrome (Henningsen et al. 2007). Establishing different clinics, one for each functional syndrome, is therefore wasteful of resources and probably limits the number of disciplines involved. As a natural consequence of this, some specialized clinics are expanding to include other functional somatic syndromes but often they remain within the domain of a single medical subspecialty and the treatment is dominated by pharmacological methods of treatment (Hauser et al. 2010). A disadvantage of these syndrome-specific clinics is than they sanction the separate, specialty-dominated view of the functional somatic syndromes and perpetuate fragmented care instead of moving towards a more generic model.

Several different types of care have evolved at a new few centres around Europe in an attempt to improve the quality of care offered to the broader group of patients with bodily distress. One new approach is based on the identification of bodily distress syndrome as a diagnosis in its own right, and which encompasses the functional somatic syndromes and somatoform disorders but with different subtypes, reflecting severity. This approach is supported by studies that have indicated a huge overlap in symptoms and illness pictures between patients who have received different diagnostic labels. Furthermore, the same treatment methods, such as cognitive behavioural therapy (CBT), antidepressants and physical activation, have proven to be effective for patients regardless of their diagnosis, whereas somatic treatment has shown no effect (Henningsen et al. 2007). As there seem to be more similarities than differences between the patients, it therefore appears rational to treat them within the same service. Larger groups of therapists with different areas of expertise can offer a wide range of therapies within the academic setting. This may also prevent simultaneous treatment by different services or sequential treatment in different clinics, and it would make referrals much easier for GPs with only one point of entry into secondary care. Additionally, it seems to be a herculean task to establish services for each functional syndromes and even single symptoms because of the high number of functional somatic syndrome that have been suggested.

These specialized units are designed for patients with the complicated functional somatic syndromes, or multiorgan bodily distress syndromes. It is unclear whether such units can meet the full demand for the intensive multidisciplinary treatment required by such patients – perhaps they should be strictly limited to the treatment of these complex patients. Some might also have the capacity for patients with single-organ functional somatic syndromes, who can also benefit from a management program such as CBT tailored to their particular problem. It would be preferable if a separate, but linked, service could cater for single-organ bodily distress syndrome, in which the effective drugs for these conditions could be used in tandem with psychological treatments. The specialized units for patients with complicated or multiorgan bodily distress syndromes do not usually use drugs as part of their treatment regimen.

1.6   A psychoanalytic perspective on somatisation

It has been often said that Sigmund Freud was not interested in psychosomatic; he rather showed some ambivalence in tacking this subject. Nevertheless, he extensively studied the

different states of the body. All his papers concerning bodily expressions are in the line of his theoretical concern relating to drives. Studying Freud's work, one can describe four kind of somatic symptoms: conversion hysteria symptoms, the somatic symptoms of the actual neurosis, hyphocondriac symptoms, and organized organic aliments.

Conversion hysteria symptoms are memory symbols converted into the body and underlying unconscious fantasies in which sexuality plays a crucial role. According to Freud, conversion implies a relatively complete Oedipal organization, a dynamic unconscious responsible for symbolization, ant the existence of repression. In contrast, the *somatic symptoms of the actual neurosis* cover the category of the functional disorders of classic medicine and do not generally have any symbolic signification. They are typically accompanied by anxiety and are viewed as the result of an erotic hypercathexis of the somatic function.

Hypochondriac symptoms are somatic complaints for which there exists no organ lesion. They originate in a status of narcissistic libido which has not found a physical use. Hypochondriac anxiety projected on to bodily organs witness an insufficient of psychic representations of these organs.

Organic aliments are the specific domain of psychosomatics. Freud was interested in the modifications in libidinal economy tied to the presence of a somatic occurrence. The return of narcissistic libido towards the sick organs constitutes, for Freud, a regular aspect of somatically ill subjects. In 1920, he had noticed some enigmatic relationships between pathological states of the body and psychopathological psychic states; he mentions the effacement of a neurotic or even psychotic state during the establishment of a somatic disease and concludes that it must related to some movements of the libido.

From the many different perspectives that aim to explain psychosomatic disorders, psychoanalysts can broadly distinguish two main approaches: one that sees the symptoms as a product of psychic conflict (with its underlying unconscious phantasies) and another that places the accent on a deficiency or deficit in the patient's psychic structure and on the lack of a capacity to function symbolically. The lack of a capacity to symbolize (even in a primitive way) has been explored by authors from the Paris School of Psychosomatics. These authors proposed that the somatic manifestations replace a conflictive situation and that psychosomatic illnesses act as a point of fixation in a move towards a more general mental and progressive disorganization. This is seen to go together with the anarchic destruction of mental functions ant the cancellation of libidinal activity, and leads to a state of "essential depression", where the organizing of mental functions disappears and the "death instinct asserts itself" (Marty 1968, Marty 1967). The relationship between patient and clinician

cannot be described as a proper relationship, and would constitute what Marty called a "relation blanche", lacking in real emotional involvement. The idea is that patients bring to analysis their "soma" rather than their libidinal body (Fine 1998).

The Kleinian school addresses the issue of psychosomatic illnesses by exploring the potential unconscious phantasies and psychic conflicts that might underlie psychosomatic symptoms, as well as the different defence mechanisms, such as splitting and projective identification, that give way to this process (Garma 1959, Klein 1958, Rosenfeld 2001). The process of splitting and projective identification can adopt very complex forms in that, in phantasies, unprocessed features of the self can be projected not only external objects but also into parts of the subject's body. This notion was developed by Rosenfeld, who saw psychosomatic symptoms as the results of projective identification that create what he called "psychotic islands" (Rosenfeld 2001).

Melanie Klein (1958) regards phantasy as a basic mental activity, rooted in the body and present in rudimentary form from birth onwards. Isaacs described it as "the primary content of unconscious mental processes", the psychic representative of instinct (Isaacs 1948).

Isaac's and Klein's definitions of phantasy is much wider than Freud's, and there is an assumption that the earliest phantasies have an omnipotent quality and are experienced as mainly visceral sensations and urges. These early phantasies are based on early sensory experiences and feelings and have attributes that Freud thought as characteristics of primary process (Bronstein 2001; Isaacs 1948; Spillius 2001). Unconscious phantasies range from those that are very primitive, of the type described by Segal as symbolic equations and akin to what Kristera called "metaphors incarnate" (Kristeva 2000), to those carrying proper symbolic significance. Via their connection to unconscious phantasies, psychosomatic disorders are seen to be anchored in the mind and, therefore, available to analytical exploration (Bronstein 2009a).

These two ways of understanding psychosomatic disorders work on different basic assumptions that stem from a different conceptualization of what constitutes the death drive, as well as to the role that affect and representation occupy in early development.

Bion's contribution to the study of early psychic organization and of the development of the capacity to think is extremely valuable and might help to bridge the gap between a theory that stresses the lack of psychic representation of the symptom and a theory that sees it as it being always linked to an unconscious representation of conflict.

Bion's notion of the role of maternal containment had a profound theoretical and clinical impact. Early unprocessed raw impressions related to emotional experience (*beta* elements)

need to be transformed into *alpha* elements in order to be able to be used to create dream-thoughts. If they cannot be processed, they will be evacuated. One of the possible routes for evacuation is via psychosomatic disorder (Bion 1962, Meltzer 1986). Bion's ideas on the role of splitting, evacuation and projective identification are complementary with Segal's ideas of symbolic equation, by which unconscious phantasies are seen not to be represent the object and are seen instead as an equation between the subject and the object to be represented (Segal 1957).

In his later works, Bion placed greater importance on the degree of quantity of excitation experienced by the archaic state of mind and the possibility that some intense elementary feelings might be experienced as physiological ("sub-thalamic") (Bion 1979). The body can thus give rise to new thoughts that have not been thought similarities with the explanations sustained by the Paris School, though, for Bion, splitting, dissociation, and disintegration are part of an active defensive stance (Bronstein 2009a, b).

Anzieu (1980) stressed the enormous importance that early skin contact between baby and mother has in the constitution of the ego. Among the functions of the skin, he counted the function of providing support, containment, protection again stimuli, support for sexual excitation, integration, and interconnection of different sensations (Anzieu 1995, Ulnik 2007). The early experiences of feeling and holding to the mother's body would be at the base of both attachment and separation. Anzieu (1995) agrees with Angelergues (1975) that the "body imagine would be a representation of a boundary that functions as a 'stabilizing image' and a protective envelope" (Anzieu 1980). The body image would fall "within the category of fantasy and secondary elaboration, a representation affecting the body". Anzieu, as well as Esther Bick, gave great importance to the early bodily experience between mothers and their infants, both in actuality than in phantasy. The physical contact would not only provide an experience of boundary between outside and inside, but also help achieve "confidence for progressive mastery of the orifices".

The early sensation-based contact between mother and infant, where mother functions like a skin, provides a necessary physical containment and support to early, unintegrated aspects of the self.

Bion's concept of "second skin formation" describes the creation of a substitute formation that would provide the indispensable sense of cohesiveness of the skin's surface. When there are difficulties that impinge on this containing process, the infant can become imprisoned in a close system of bodily sensations (Ogden 1989).

These early stages of unorganized experience that are lived through the body are sensations that also carry some primitive form of representations ("phantasies encarnated") and via the introjection (internalization) of the mother's skin/containing function provide the basis for ego functioning that will slowly enable the discrimination between internal and external.

Among the ego's first activities are the defence against anxiety via the use of process of splitting, projection, and introjection. These processes are central to the structuring of the ego and to the organization of its experience. Projective identification corresponds to an unconscious phantasy in which aspects of the self are located in other objects. Splitting and projective identification are necessary to minimize the anxieties stemming from the death drive; anxieties about fragmentation and annihilation of life (Klein 1952). Projective identification has mainly two motivations: communication and evacuation.

The role of defence mechanisms (such as early splitting) in psychosomatic disorders has been recounted by Aisenstein in her description of patients who treat their bodies like a "foreign land" (Aisenstein 2006). Rosenfeld describes how, through projective identification, the body cab be felt to be a potential persecuting object that has to be controlled and appeased (Rosenfeld 2001).

The skin can then become both a vehicle for the expression of raw, unprocessed emotions and acquire a separate life of its own when, in phantasy, it is felt to be the recipient of the infant's projections, the embodiment of the object that the child is identified with. While itching is a way of relating to this object-skin, it also serves the purpose of resolving the impossible primitive love/hate relationship that has not been mediated by thoughts. In this regard, Anzieu stressed that the relationship between the pruritus, the compulsion to scratch, in the dermatoses and in generalized eczema expressed the fragility of the ego-skin as a circularity between autoerotic and self-punitive mechanisms, partly trying to reverse the displeasure to pleasure. He reminds us of Spitz's question as to whether the child with eczema is demanding to be touched by the mother or whether what it shows is his narcissistic isolation, where the child provides what the mother has not (Anzieu 1995).

Since Freud, psychosomatic symptoms have been considered as complementary elements to understand the patients, whereas nowadays those body expressions are analyzed to produce modifications. A large number of physicians have understood this, and, therefore, refer patients to psychotherapeutic or psychoanalytic treatment. This means a big change to be accounted for, accepting the multi-factorial character of those symptoms.

One of the obstacles in the cure in current clinical practice is the emergence of the psychosomatic phenomenon that has compelled therapists to transform this problem into

further knowledge. Aisemberg proposed the idea of two psychic functioning, the neurotic and the non-neurotic one, based on Freudian conceptualizations of mixed neuroses and actual neuroses. This field refers to the quantity of somatic excitation which has failed to transform into drive, which has no psychic inscription yet, and which sort-circuits to the soma. Defence against this destructive excitation may be suppression of affect, mainly of aggression, and an equivalent to foreclosure of representation, as Green (1998) points out.

Drawing on the ideas Freud set down in the Project (1885), psychoneurotic functioning is built out of the memory trace left by the experience of satisfaction with the primary object, whereas the non-neurotic one derives from the sensorial traces left by the experience of pain which have not been transformed into psychic tissue, experiences of pain which have not been bound, that is, Rosemberg's (1991) lifeguard masochism as psychic survival. Psychosomatic phenomenon as a *mise en scéne* of the investment of those sensorial traces that have not been processed, so the challenge in analytical work consists in production constructions that transform them into psychic tissue. This is the field of repetition (Aisemberg 2007, 2008; Freud 1914, 1920; Green 2000; Marucco 2007) beyond the pleasure principle, the evil compulsion, to follow Bolognini (2006), repetition compulsion of the archaic, traumatic perpetual traces that find expression in different short-circuits: (a) to the body, giving rise to somatosis; (b) to the act, with acting-outs and accidents; (c) to the mind, emerging as a hallucinatory episode in a non-psychotic person.

This field of repetition is related to Thanatos, to helplessness anxiety, to early traumas, or pre-psychic traumas, as Rousillon (1991) names them, which, not having been transformed into psychic structures, keep the primitive traces split, that is, proper unconscious (Aisemberg 2005, 2007, 2008). Such traces, once invested, come into the scene and become the object of exploration in contemporary psychoanalysis, thus enabling us to create something new between patient and analyst, similar to the artist who, by his/her work, can alone transform his/her primitive traumatic traces into figurations (Aisemberg, et al. 2000). As already stated, there is a structuring functioning stemming from endosomatic excitation that results from inner and external perceptions of the relationship with the object, which is transformed intro drive, and this is inscribed as psychic representation, this being the dynamics that prevails in the field of psychoneurosis.

Instead, when endosomatic excitation fails to transform, has no psychic representation, does not turn into drive, and is not translated into a psychic representation, it remains on the border between soma and psyche yielding primitive inscriptions. This non-structuring functioning

may be the origin of somatic disorders, among others. The structuring organization originates from the experience of satisfaction.

Need or self-preservative drive sets this circuit in motion. It is the perception of the experience of satisfaction with the primary object that will be the foundation of pleasure and sexuality and be inscribed as memory trace. This trace will, in turn, be invested by the drive psychic representative, eliciting a thing-representation. Anaclisis provides the functioning of the partial sexual drive and the structure of desire. Now the psychic representative is liable to repression: the ideational-representative on the one hand, and the quantum of affect on the other hand, will follow different pathways. The repressed unconscious (Freud 1915a, b, c) is being constructed. Thing-representation is articulated with the drives and also with the language, giving rise to word-representation. Instead, if the experience of pain is not bound by lifeguard masochism, it leads to disinvestment, splitting and short-circuits. This is endosomatic excitation that has no psychic resolution, that has no mental representation, and that is inscribed only as sensorial traces. This is the proper unconscious that never become conscious. The excess of unbound endosomatic excitation that is not translated is a quantity that disorganizes, that disobjectivizes, reminding the Green's description of the death drive, or destruction drive, when it is oriented towards the interior (Aisemberg 2005, 2007, 2008a, 2000b). In contrast, Eros organizes and objectives the psyche, starting from the memory trace of the experience of satisfaction, and builds the structuring circuit mentioned above.

In the field of psychosomatic medicine, it is believed that emotions and personality can influence bodily functions and contribute to the aetiology and pathogenesis of disease.

During the middle decades of the twentieth century, the psychoanalytic approach to patients with somatic diseases was influenced, for the most part, by two psychosomatic theories. Both theories were based on Freud's concepts of repression and intrapsychic conflict; they differed, however, over the meanings (or lack of meanings) attributed to disease. One theory originated by George Goddrek assumed that somatic diseases have primary symbolic meaning. This theory was essentially an extension of Freud's view of conversion hysteria, in which somatic symptoms are considered an expression of an unconscious fantasy in "body language"; as an such the symptoms carry "hidden" meaning which is considered directly accessible to psychoanalytic interpretation in the same way as a dream.

The notion of psychosomatic illness was introduced by the psychoanalyst James Halliday within the movement of psychosomatics directed in the USA by Franz Alexander. It was entirely based on a theoretical conception that links somatic illness with a dysfunctioning of the emotions.

Franz Alexander developed his doctrine of psychosomatic medicine from the notion of organ neurosis. The Ferenczi's definition relates the entity of organ neurosis to hysteria on the one hand, and to organic disease on the other hand. But it also gives an indication of an aetiological order, since it links this new entity with conflicts of a psychical order. It is worth recalling that actual neurosis is a psychical organization that is accompanied clinically by disturbances of a depressive and anxious nature and by diverse somatic disturbances affecting different organs, which are akin to what doctors refer to as functional disorders.

Franz Alexander's theory proposed that somatic disease, like Freud's concept of the actual neuroses, are asymbolic (without meaning), and are a consequence of interactions between constitutional dispositions and physiological changes that accompany chronic states of emotional arousal. Treatment was aimed at interpreting and resolving the unconscious conflicts thought to be maintaining emotional arousal.

Under Franz Alexander's influence, Freud's view of actual neurosis underwent a theoretical deviation in the direction of a medicalization. This medicalization was based on some conceptual operations: for the referent of the drive, Alexander substituted the referent of emotion; for the drive trajectory, Alexander substituted the direction linking emotion to the autonomous nervous system; for the Freudian principle of constancy, Alexander substituted the principle of physiological homeostasis.

On these new bases of physiopathological and medical order, Alexander was to build a new classification of psychosomatic illnesses. When an emotion finds itself repressed repeatedly at a psychical level, owing to certain conflicts, it follows the trajectory of one of the paths of the autonomous nervous system, either the sympathetic pathway or the parasympathetic pathway, and reaches an organ or a specific system of organs. Alexander defined two groups of psychosomatic disease, those of a "sympathetic" and "parasympathetic" type. The first group includes diseases such as migraine, high blood pressure, hyperthyroidism, functional cardiac disorders, osteoarticular disorder, and diabetes. The physical conflicts leading the onset of these disease involve the repression of hostile and aggressive emotions. Instead of finding an outlet towards motricity, the latter are diverted via the sympathetic pathway towards certain system of organs, which, under normal conditions, prepare the organism for reaction of struggle and fight. The second group include illness such as gastric ulcers, digestive disorders, states of colitis, but also asthma attacks. The psychic conflicts that lead to the onset of these diseases involve the repression of specific emotions linked to needs of dependency and protection by the object. Rather than finding a psychical and relational expression, by way of a regression to passivity, these emotions are diverted towards the

56

parasympathetic pathway until they reach the systems of organs that, under normal conditions, are responsible for the restoration of the resources of the organism.

Franz Alexander's psychosomatic approach attributes the somatic disorder of disturbed emotional states to certain specific physical conflicts.

As mentioned above, Pierre Marty and the Paris School of Psychosomatics have elaborated an original and rigorous conception of the process of somatization, which rests on two theoretical foundations: the psychoanalytic evaluation of the patient's mental functioning and the economic dimension of the relations between the mind and the somatic system.

For Marty, psychosomatic praxis is divided into two processes of somatization, which are linked to two different levels of mental functioning: (a) when the drive excitations prove to be of average importance and do not accumulate too much in a subject whose mentalization is otherwise good, one is fortunate in only witnessing the onset of somatic affections which in most cases are spontaneously reversible; (b) when the instinctual and drive-based excitations prove to be important and accumulate in a subject, whose mentalization is otherwise poor, there is a risk of witnessing the onset of evolutive and severe somatic affections. Thus, the process of somatization through regression is usually contrasted with the process of somatization through the progressive disorganization.

During the 1970s, a third major psychosomatic theory emerged, which extended Alexander's theory by proposing that pathogenic states of emotional arousal are a consequence of impairments in the symbolic function itself. This theory, as Greco (1998) points out, shits the focal point from whether or not somatic diseases have psychological meanings to a higher level of abstraction in which explanations are sought for the subjective conditions that allows for the development of pathologies that lack symbolic meaning. In contrast to the two earlier theories, this theory gives important roles to trauma and dissociation, and has implications for the therapeutic techniques that go beyond interpretation of repressed conflicts.

The traditional psychoanalytic view of symbol formation is derived from Freud's early work on the interpretation of dreams, and from his discovery with Breuer that the symptoms of hysteria carry hidden meanings (Freud,1896). For Jones (1916), "only what is repressed needs to be symbolized". Thus, the emphasis is on unconscious representations of repressed libidinal and aggressive wishes that lie behind the manifest symbol (Deri, 1984).

Symbolization is a broader concept than symbolism, and emphasizes function rather than concept; it includes secondary process as well as primary process thought, and is considered a process of linking and meaning-making (Aragno 1997, Freedman 1998).

The distinction between symbolism and symbolization has important implications for treatment. Whereas, with symbolism, the analyst's task is to provide the *real* meaning for the symbol and thereby discard the symbol itself, with the broader concept, the aim of psychoanalytic treatment is to enhance the patient's capacity for symbolization, as both Green (1975) and Deri (1984) have highlighted.

Both conceptualizing symbolization as a development achievement, psychoanalysts could begin to observe varying degrees of impairment in this capacity, particularly in patients with histories of deprivation or psychic trauma (Krystal 1978). While investigating the communicative style of patients with the same type of diseases as Alexander studied, Nemiah and Sifneos (1970; Nemiah et al. 1976) observed that many of the patients manifested a restricted imagination and a deficit in the ability to symbolically represent and verbally express emotions; they labelled this deficit *alexithymia*. They noted that the paucity of fantasy, along with an externally oriented cognitive style, correspond to the phenomenon of *pensée opératoire* described by Marty and de M'Uzan (1963). Although subsequent research has shown that alexithymia is not specific to, or an invariable feature of, any group of disease (Taylor 2004), this construct made the symbolic dimension relevant to Alexander's theory by proposing that the pathogenic impact of emotion on the body is a consequence of a failure to adequately symbolize, and thereby contain, distressing emotional states.

Our understanding of how emotional experience is represented in the mind increased over the past decade as a result of the theoretical contributions and empirical investigations of Bucci (1997a). In her multiple code theory of emotional information processing, the fundamental organizing structures of human emotional life are referred to as *emotion schemas*. Bucci (2008) described there as "particular types of memory schemas that develop on the basis of repeated interactions with others from the beginning of life and that form the basis of personality organization". They determine how we perceive and respond to other "and are themselves continuously affected and changed by new interpersonal experience".

According to the multiple code theory (Bucci 1997a), emotion schemas begin to develop during infancy in a *non-verbal* form. This includes *subsymbolic* processes, which are the patterns of sensory, visceral, and kinaesthetic sensations and motor activity experienced during states of emotional arousal, and also *symbolic imagery*, such as the object or person associated with the emotion. As the child develops language, *verbal symbols* (words) are incorporated into the emotional schemas. The different components are connected, to varying degrees, by the *referential process* such that dominant emotion schemas from the

non-verbal system can be translated into logically organized speech. This is not a transformation of one modality to another, but a connecting of the separate components of the emotion schema, thereby allowing for a transformation of the meanings represented in them (Bucci 1999).

Normal emotional development depends on the integration of sensory, visceral, and motoric elements in the emotional schema, together with images and words. There are different degrees of interaction among in the subsymbolic and symbolic verbal and non-verbal components in normal everyday functioning, with each component able to function effectively in its own modality (Bucci 2007). However, the integration within emotion schemas is significantly impaired in individuals who experience developmental deficiencies, serious conflicts, or psychic trauma, as the connections are disrupted or even fail to form. The dissociation or desymbolization within the schemas creates a potential for high arousal of the somatic and motoric components, as these are no longer organized and regulated through links with the symbolic components. As Bucci (1999, 2008) explains, dissociations between or within the components, and the defences employed by the person in an attempt to repair the schemas, are likely to result in pathological symptoms, the nature of which depends on the level of dissociation and the strategies used to manage the affective arousal when subsymbolic components are activated.

Bucci's (1997b) proposed that when simply the primary object of the emotion schema has been dissociated, in the service of the defences, the mind may try to repair the dissociation by using a part of the body to organize the schema, thereby creating a hypochondriacal or conversion symptom with the symbolic meaning. More severe dissociations, as occurs in post-traumatic states, can result in states of prolonged activation of subsymbolic processes with upsurges of emotional arousal that are beyond the person's capacity to self-regulate and may be triggered by stressful events or by cues related to the original trauma.

Exploring clinical work with patients who suffer from severe somatosis, an unwritten history of early mournings and traumas that not have been processed is often found. The difficulty these patients have in coping with psychic pain, as well as with emotions in general, may lead them to a somatic course of mourning. Sometimes, it is not only their own mourning or traumas that have not been processed, but also identifications with parents who could not work through theirs. Moreover, several retrospective studies with very large samples have shown strong support for an association between childhood trauma and the development of somatic disease in adult life. The Adverse Childhood Experiences Study in San Diego, California (Dube et al. 2009, Felitti et al. 1998) and the National Comorbidity Survey in the

United States (Goodwin & Stein 2004) found that self-reported childhood trauma was associated with an increased risk for a broad range of physical illness, including cardiovascular, digestive, respiratory, and autoimmune diseases, which could arise many years after the exposure. The types of trauma included sexual, physical, and emotional abuse, as well as exposure to household dysfunction such as parental separation or divorce, domestic violence, and parental substance abuse or mental illness. There is evidence also that traumatic experiences in adulthood can have consequences for physical health in later years. Several follow-up studies of Vietnam War veterans with chronic post-traumatic stress disorder have reported a higher lifetime prevalence of various somatic diseases as many as twenty years after military service (Boscarino 1997, 2004, Friedman & Schnurr 1995).

Notwithstanding the importance of these correlational studies, they do not explain how emotions associated with unsymbolized psychic trauma may contribute to changes in physical health. The causal mechanisms are likely to be complex and involve various coexisting pathways. There is now substantial evidence that emotional stress directly affects the nervous, endocrine, and immune systems; moreover, these systems communicate with one another via bidirectional pathways, thereby forming an arrangement of reciprocally regulating subsystem within the body that interface via the brain with mental processes and with the larger social system (Eskandari & Sternberg 2002, Glaser & Kiekolt-Glaser 2005, Kiekolt-Glaser et al. 2002, Sternberg 2000, Taylor 1992). In earlier contributions (Taylor 1987, 1992), a psychobiological dysregulation model of disease has been proposed. Perturbations in one or more components of the feedback loops between the various bodily systems may lead to changes over time in the rhythmic functioning of one or more of the systems, thereby creating conditions conducive to disease activity.

Because of dissociation, people often fail to remember the details, or even the occurrence, of childhood traumas. Traumatic memories, however, are encoded in the procedural or implicit memory system, which is mediated, at least in part, by the amygdala, which does not forget (Yovell 2000). Even though early trauma has a distorting effect on the developing personality, memories of traumatic childhood experiences may lie dormant for decades, but eventually be awakened by an appropriate stimulus, such as a stressful emotional state, perhaps associated with separation, loss, or personal threat (Siegel 1995). The emotional memory may be experienced somatically only, and not attributed to past childhood events, especially when it is dissociated from verbal and non-verbal symbolic components in the emotion schema which are necessary for an explicit memory of the original trauma (Bucci 2007, 2008, Siegel 1995).

60

Consistent with contemporary recommendations for the psychoanalytic treatment of traumatized individuals (Cohen 1980, Bromberg 1998), as already stated, Bucci (2007, 2008) emphasizes that to bring about changes in the organization of the emotion schemas it is necessary that the patient experience some aspects of the affective core of the dissociated schema in the therapeutic sessions. Since the mode of mental organization following psychic trauma is repetition-compulsion, some aspects of the original trauma will inevitably re-emerge in the transference, with a potential for enactments and for re-traumatization if the therapist is perceived as the original predator and is provoked to act. In the context of the new interpersonal relationship with the analyst, however, and aided by his or her containing function, there is the opportunity to gradually symbolize the dissociated painful emotion by connecting somatic experiences with imagery and language. As imagery initially heightens activation of subsymbolic elements in the schema, patients are likely to experience the affective arousal as overwhelming and disorganizing, and sometimes fear that they are going mad. There is also a risk that activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis will aggravate a patient's somatic disorder, and even be a threat to life. It is, therefore, important for the therapist to regulate the intensity of the emotional arousal while enhancing the referential process, and, together with the patient, reflect on the retrieved memories and the meanings the patient has given to them.

In addition, some research has found an association between insecure attachment and increased somatization in adults. In a study published in 2018, the association between attachment insecurity and mentalization deficits were examined in psychiatric patients diagnosed with medically unexplained somatic symptoms (MUSS). Somatic symptom severity experienced by MUSS patients was related to attachment anxiety and alexithymia. Findings may indicate that individuals with an anxious attachment style have difficulties in clarifying own emotions, and this may in turn results in somatic experience of emotional distress and risk for development of MUSS (Riem et al. 2018).

The capacity for symbolic functioning breaks down when adults experience massive psychic trauma, but more commonly in individuals who experience serious traumatic events in childhood and there is no parent who is able to contain the overwhelming affects and render them bearable for the child. Unable to mentally represent the unbearable emotional states so that they can be "digest" though dreaming and thinking, the traumatic emotions are dissociated, but are prone to return by way of somatic illness. The purpose of the psychoanalytic treatment consists into transforming the suffering and pain of severe somatosis into psychic suffering and pain, creating an external-internal space for this aim.

Psychoanalytic therapy of somatically ill patients requires identification and activation of dissociated emotional states so that unsymbolized trauma, with the aid of the analyst's containing and symbolizing ("alpha") functions, can be transformed into psychic structure.

Chapter 2

Materials and methods

2.1 Aims and scope

The present research provided for the collection of data from hospitalized patients presenting medically unexplained physical symptoms (MUPS) referring to different hospital wards, aiming to the following endpoints: 1) to draw a clinical and socio-demographic profile of hospitalized patients with MUPS; 2) to explore psychopathological correlates of SSD diagnosis; 3) to estimate economic costs related to healthcare utilization of MUPS.

2.2 Sample

The cross-sectional research consisted in the evaluation of data referring to all hospitalized patients admitted between 2008 and 2018 in the wards of a teaching hospital in Northern Italy, ASST (Azienda Socio-Sanitaria Territoriale) dei Sette Laghi, Ospedale di Circolo of Varese (Deliberate n. VIII/4221, February 28th, 2007).

The research involved the divisions of Internal Medicine, Neurology, Infectious Disease, Orthopedics, Otorhinolaryngology and Emergency ward; Short Stay Unit data were available from 2014, Emergency and Transplant Surgery data from 2015 and Psychiatry data from 2012. Data from Short Stay Unit and Emergency and Transplant Surgery were available from the opening year of these wards. Data from Psychiatry ward were computerized from 2012. Emergency ward data collected referred to the period from November 2017 to November 2018. All data were recruited between January 2018 and January 2020.

Hospital discharge letter were analyzed by three psychiatry section clinicians from the hospital software. The clinicians were not directly involved in analyzed patients' diagnosis and treatment.

Data from patients fulfilled the following inclusion criteria: age > 18; be an inpatient in the teaching hospital; present symptoms with apparently no medical cause, or whose cause remains unclear (Medically Unexplained Physical Symptoms); have a diagnosis of *Somatoform Disorder* or *Somatic Symptoms Disorder and related disorders* by non-specialists (according to DSM-IV-TR and DSM-5; since Italian statistical medical recording

is ICD, diagnosis have been made through ICD code conversion Table); present all test clear. No excluding criteria were used.

Some 'diagnostic' labels have been taken into consideration. They describe different groups of patients but they also overlap considerably. In the research, the most frequent terms used to describe the group of symptoms frequently referred to as 'medically unexplained' were: somatoform disorder, functional disorder or functional symptom, somatic symptom disorder, psychosomatic disorder, medically unexplained symptom, "unknown origin" diagnosis or symptom.

The following socio-demographic and clinical variables were evaluated: gender, age, marital status, employment, diagnosis or diagnostic hypothesis in admission and discharge, personal medical history, presence of previous or concurrent psychiatric comorbidities, length of hospitalization, healthcare costs, medical examinations, psychiatric evaluation, pharmacological treatment.

The economic costs of each hospitalization were obtained from the economic value sheet combined with the discharge letter uploaded on the electronic register of the hospital. When unavailable, the average costs of hospitalization for each patient were estimated by the Management control division of the hospital. The costs of laboratory and instrumental examinations were found on the document "Nomenclature tariff of the specialist outcare patient" (Ministerial Decree 216, January 12th, 2017) DPCM 2017) of the Italian National Health System.

All patients provided a general written informed consent to processing personal data as part of the routine quality check processes.

Patients' data were made anonymous, obscuring sensitive information used in the research to protect the recognizability of the patients, according to the Italian legislation (D.L. 196/2003, art. 110 - 24 July 2008, art. 13).

To summarize epidemiological and clinical characteristics, descriptive statistics (which include means, standard deviation and demographic variables percentages) were computed.

To better detect the clinical and socio-demographic characteristics of the patients, hospital wards were grouped into different macro-areas: Medical wards: Internal Medicine, Neurology, Infectious Disease, Short Stay Unit; Surgical wards: Emergency and Transplant Surgery, Orthopedics; Emergency ward; Psychiatry; Otorhinolaryngology.

Statistical analyses were performed on data from medical specialties, including surgical wards, Psychiatry and Otorhinolaryngology. Emergency ward data were not computed because of the lack of patients' personal information.

2.3 Statistical analysis

Analyses were conducted to investigate specific issue regarding the probability of having a diagnosis of somatic symptoms disorder in our sample of patients with MUPS. In particular, chi-square tests (χ^2) were used to investigate whether there were differences in the distribution of the diagnosis of somatic symptoms disorder in the two genders, as well as in the diverse conditions of civil status and employment. Two multiple logistic regression models were used to evaluate whether a series of medical and psychiatric conditions were associated with increased probability of having a somatic symptoms disorder diagnosis. In particular, a model with medical diseases as independent variables (including previous medical history, neurological anamnesis, fibromyalgia, neoplasms, metabolic diseases, autoimmune diseases, endocrinological diseases, infective diseases, medical diseases, surgery, and accidents) was tested, and a second model with psychiatric disorders as independent variables (Depressive Disorder, Anxiety Disorder, Personality Disorder). In both models, all independent variables were dichotomic categorical variables, with a value of 0 indicating no pathology in anamnesis, and a value of 1 indicating the presence of pathology.

All analyses were conducted through the software IBM® SPSS® Statistics version 25.0 was used [26].

Results

Socio-demographics and clinics

Socio-demographics and clinical characteristics of the sample are showed in table 2.

Table 2. Socio-demographic characteristics of the sample

	Male		Female	
Age (years ± SD)	47 ± 17.0		44 ± 15.9	
	Number	% (of 82)	Number	% (of 191)
Gender	82	30	191	70
Marital status				
Married	31	37.8	76	39.3
Single	17	20.7	49	24.6
Divorced	3	3.7	21	10.5
Widowed	1	1.2	9	4.1
Not available	25	31.7	45	23.5
Occupation				
Salaried	27	35.3	81	40.8
Retired	25	30.5	18	8.4
Housewife	0	0.0	33	16.2
Unemployed	9	12.2	13	5.6
Student	4	4.9	9	3.9
Invalid	1	1.2	8	3.2
Not available	13	18.3	41	20.9

The overall hospitalizations detected were 306. The total number of patients with MUPS considering that three patients had more hospitalizations in the research period was calculated. The distribution of patients in different wards is shown in table 3. The prevalence of patients with MUPS is shown in the same table, considering the percentage of people hospitalized more than once under 10%.

In Short Unit Stay the prevalence of MUPS was 0.98 % (on 5'397 overall hospitalizations), considering the percentage of people hospitalized more than once under 10%.

The average length of hospitalization in different wards was the following: Medical Wards (7 days); Surgical Wards (5 days); Psychiatry (8 days); Otorhinolaryngology (7 days).

Table 2. Distribution of patients with MUPS in hospital wards

Ward	Patients (N)	Hospitalizations (N)	Male/Female ratio	Age (Mean) Range	Prevalence (%)
Medical Wards				18–86	
Neurology	125	144	1/3	44.0	3.87
Internal Medicine	59	61	1/5	49.0	0.44
Short Unit Stay	50	53	2/3	49.0	0.98
Infectious Disease	7	7	2/5	50.0	0.16
Surgical Wards				19–71	
Emergency Surgery	10	10	1/1	42.1	0.96
Orthopedics	2	2	1/0	36.5	0.02
Psychiatry	12	14	3/10	49.5 22–67	0.42 -
Otorhinolaryngology	14	15	2/3	43.5 18–60	1.51

As shown in table 4, 46% of the sample (n=126) patients present no psychopathological comorbidities, of which 65.8% (n=83) are women and 34.1% (n=43) are men.

Table 4. Psychiatric comorbidity in patients with MUPS

1) Previous diagnosis		n	(%)
-Anxiety Disorder	Male	13	25.5
	Female	38	74.5
-Depressive Disorder	Male	3	17.6
	Female	14	82.4
-Substance Abuse	Male	3	100.0
	Female	0	0.0
-Somatoform Disorder	Male	2	70.0
	Female	1	30.0
-Personality Disorder	Male	0	0.0
	Female	2	100.0
-Comorbidity AD[1]; PD[2]; SFD[3]	Male	0	0.0
	Female	3	100.0
AD[1]; SFD[3]	Male	0	0.0
	Female	2	100.0
ED[4]; PD[2]; SFD[3]; AD[1]	Male	1	100.0
	Female	0	0.0
AD[1]; DD[6]; SFD[3]	Male	0	0.0
	Female	1	100.0
PD[2]; SFD[3]	Male	0	0.0
	Female	1	100.0
ED[4], SFD[3], AD[1], SA[4]	Male	0	0.0
	Female	1	100.0
ED[4]; AD[1]; SFD[3]	Male	0	0.0
	Female	1	100.0
ED[4]; PD[2]; SFD[3]; AD[1]	Male	0	0.0
	Female	1	100.0
Others	Male	1	9.1
	Female	10	90.9
-Other Post-Traumatic Stress Disorder	Male	0	0.0
	Female	2	100.0
Parasuicide	Male	0	0.0
	Female	1	100.0
2)Discharge diagnosis			
-Depressive Disorder	Male	9	53.0
	Female	8	47.0
-Anxiety Disorder	Male	4	18.8
	Female	15	81.2
-Somatoform Disorder	Male	2	28.5
	Female	5	71.5
-Substance Abuse	Male	0	0.0
	Female	2	100.0
-Personality Disorder	Male	1	50.0
	Female	1	50.0
-Comorbidity			

AD[1]; SFD[3]	Male	1	100
	Female	0	0.0
DD[6]; SFD[3]	Male	0	0.0
	Female	1	100.0
3) No diagnosis			
	Male	43	34.1
	Female	83	65.8

AD[1]: Anxiety Disorder; PD[2]: Personality Disorder; SFD[3]: Somatoform Disorder; ED[4]: Eating Disorder; SA[5]: Substance Abuse; DD[6]: Depressive Disorder

In previous medical history, 36% of patients (n=101) patients presented at least one psychiatric disorder in comorbidities, of which 77.2% (n=78) were women, and 22.7% (n=23) were men. The most frequent detected diagnosis was: 1) Anxiety disorder (50%; 2) Depressive disorder (15%); 3) Somatoform disorder (3%); 4) Substance abuse (3%). At discharge, 18.9% of patients (n=53), of which 66% (n=35) women and 33.9% (n=18) men, were diagnosed a psychiatric disorder afresh. The most frequent diagnosis was: 1) Depressive disorder (37%); 2) Anxiety disorder (35%); 3) Somatoform disorder (15.5%). The diagnosis of somatoform disorder was formulated in 7.9% of case, in 5% of case the diagnosis was in comorbidity with other psychiatric disorders; in 2.9% of cases without comorbidities.

A psychiatric consultation was requested in 75 admissions and a psychopharmacological treatment was set in 157 cases; in 52 cases the therapy was prescribed by a psychiatrist. Not including the number of hospitalizations in psychiatry, 138 (50.5%) patients did not receive any psychiatric treatment. The pharmacological treatment consisted in benzodiazepines (10.5%) and Selective Serotonin Reuptake Inhibitors (9.5%), in 30.4% the treatment consisted in combinations of different classes of drugs.

Considering the overall hospitalization, the most common symptomatology found for patients with MUPS are: headache (21.9%); pain (14%); syncope (8.8%); vertigo (4.6%). Symptoms per unit are shown in table 5.

6291 accesses to Emergency ward in patient with MUPS were observed; this sample is composed by 5735 subjects, 55% of the sample are women (n=3142), 45% are men (n=2590). The average age of the sample is 52 years. 6005 patients were discharged, 20 patients were sent to outpatient clinic, 243 patients left the emergency ward before concluding the exams, 30 patients refused a hospitalization, and 2 patients were transferred to another hospital. The most frequent symptoms determining the access resulted: abdominal pain (18.9%; n=1191).; non-specific chest pain (18.7%; n=1175); lower back pain (12.3%; n=775); headache (9%; n=571).

Table 5. Symptoms per unit

Hospital Ward	Symptoms
Short Stay Unit	Syncope (N = 13); Pain (N = 16); Paraesthesia (N = 5); Headache (N = 9); Vertigo (N = 4); Motor deficit (N = 2); Neurological dysfunction (N = 1); Postural instability + Loss of consciousness (N = 1); Fainting (N = 1); Aphasia (N = 1); Headache + Paraesthesia (N = 1)
Neurology	Headache (N = 50); Paraesthesia (N = 19); Pain (N = 8); Neurological dysfunction (N = 14); Motor deficit (N = 9); Loss of consciousness (N = 4); Motor deficit + Paraesthesia (N = 2); Headache + Vertigo (N = 3); Fainting (N = 2); Headache + Paraesthesia (N = 4); Vertigo (N = 2); Aphasia (N = 1); Headache + Pain (N = 1); Headache + Motor deficit (N = 1); Headache + Fainting (N = 1); Dysphagia (N = 1); Fibromyalgia (N = 1)Postural instability (N = 1); Hypochondria (N = 1); General malaise (N = 1); Blurring (N = 1); Paresis (N = 1); Loss of consciousness + Pain + Paraesthesia (N = 1)
Infectious Disease	Pain (N = 4); Urinary disorders (N = 1); Enteritis (N = 1); Fever (N = 1)
Internal Medicine	Pain (N = 9); Syncope (N = 5); Headache (N = 5) Fainting (N = 3); Paraesthesia (N = 3); Vertigo (N = 3); Fever (N = 3); Vomit (N = 2); Absence (N = 2); Dyspnoea (N = 2); Asthenia (N = 2); Asthenia + Vertigo + Fainting (N = 1); Pain + Impotence (N = 1); Weight loss + Night sweats (N = 1); Headache + Pain (N = 1); Haemorrhage (N = 1); Headache + Aphasia (N = 1); Fainting + Paraesthesia (N = 1); Pain + Nausea (N = 1); Fainting + hypokalaemia (N = 1); Vertigo + Nausea (N = 1); Pain + Nausea (N = 1); Chest tightness (N = 1); Pain + Nausea + Haemorrhage (N = 1); Weight loss (N = 1); Blood pressure increase + Palpitation (N = 1); Dysphagia (N = 1); Syncope + Headache (N = 1); Drowsiness (N = 1); Agitation (N = 1); Tremor (N = 1); Vertigo + Malaise (N = 1);
Emergency Surgery	Pain (N = 8); Pain + Fever (N = 1); Headache + Paraesthesia (N = 1)
Orthopedics	Pain (N = 2)
Psychiatry	Agitation (N = 5); Anxiety (N = 4); Syncope (N = 2); Paraesthesia (N = 1); General malaise (N = 1); Cognitive impairment (N = 1)
Audiovestibology	Hypoacusis (N = 6); Vertigo (N = 5); Vertigo + Pain (N = 1); Chronic Dizziness (N = 1); Postural instability (N = 1); Fainting (N = 1); Fainting + Vertigo (N = 1);

Evolution of the diagnostic criteria from somatoform disorder (DSM-IV-TR) to SSD (DSM-5).

32 patients (19 women and 13 men) of the total sample who did not receive a diagnosis of somatoform disorder, fulfill the diagnostic criteria of DSM-5 Somatic Symptoms Disorder, based on the discharge letter. 6 patients had a psychiatric consultation during hospitalizations.

16 patients had a previous psychiatric diagnosis (Anxiety Disorder n=10; Depressive Disorder n=4; Substance Abuse (n=1); Anxiety Disorder/Eating Disorder n=1), 7 patients received a psychiatric diagnosis at the discharge (Anxiety Disorder n=4; Depressive Disorder n=2; Personality Disorder n=1) and 9 patients had no previous psychiatric diagnosis and they did not receive a psychiatric diagnosis at discharge.

Psychopathological correlates of SSD diagnosis

Chi-square tests showed that the distribution of somatic symptom disorder diagnoses was not significantly different in any of the two genders ($\chi^2(1) = 0.31$; p = 0.58). Also, no differences were found with regard to levels of employment ($\chi^2(8) = 5.71$; p = 0.68) or civil status ($\chi^2(4) = 4.38$; p = 0.36).
Logistic regression models are presented in table 6.

Table 6. Multiple logistic regression predicting the probability of having SSD diagnosis from medical and psychiatric diseases

	OR	CI for OR	SE[1]	Wald χ^2 (df = 1)
MEDICAL DISEASE[2]				
Fibromyalgia	0.39	[0.05, 3.35]	1.09	0.72
Previous medical history	1.20	[0.52, 2.79]	0.42	0.18
Neurological disorders	0.34	[0.13, 0.90]	0.50	4.75*
Neoplasms	1.04	[0.26, 4.13]	0.70	0.00
Metabolic disorders	2.11	[0.76, 5.91]	0.52	2.05
Autoimmune diseases	0.70	[0.16, 3.06]	0.75	0.22
Endocrine diseases	2.41	[0.62, 9.31]	0.69	1.63
Infectious diseases	1.83	[0.41, 8.13]	0.76	0.63
Medical diseases	2.10	[0.86, 5.13]	0.46	2.64
Surgical diseases	0.41	[0.14, 1.21]	0.55	2.62
Accident	1.44	[0.42, 4.88]	0.62	0.34
PSYCHIATRIC DISEASE[3]				
Depressive Disorder	1.54	[0.40, 5.95]	0.69	0.39
Anxiety Disorder	2.43	[0.94, 6.26]	0.48	3.39
Personality Disorder	16.18*	[2.42, 108.03]	0.97	8.26*

[1]*SE* = Standard Error; *OR* = Odds Ratio [Exp(B)]; N = 273; *p < .05
[2]$R^2 = 0.13$; omnibus $\chi^2(11) = 17.96$; p = 0.08.
[3]$R^2 = 0.10$; omnibus $\chi^2(3) = 12.16$; p < 0.01.

The table includes Odds Ratios (*OR*), indicating the increase in the probability of occurrence of the SSD diagnosis, and their corresponding Confidence Intervals (*CI*) and p-values. *CI*s including the value of 1 indicate no significant relationship. Standard Errors (*SE*) associated with the coefficient and Wald χ^2 are also reported. The Wald χ^2 tests the null hypothesis that there is no association: if significant, the probability of occurrence of the SSD diagnosis is significantly associated with the corresponding predictor. As can be seen, the model including medical diagnoses as independent variables indicated that the presence of a neurological disease in medical history was negatively associated with the presence of a diagnosis of somatic symptom disorder (*OR* = 0.34; Wald $\chi^2(1)$ = 4.75, p = 0.03). However, it has to be noted that the overall model was not significant ($\chi^2(11)$ = 17.96; *p* = 0.08; Negelkerke R^2 = 0.13), meaning that medical diseases did not explain a significant percentage of variance in the dependent variable. Given this, a Phi-correlation coefficient among neurological anamnesis only and somatic symptom disorder diagnosis to further explore this association was computed: the correlation was negative and significant (ϕ = -0.13; p = 0.03).

Logistic regression model including psychiatric diagnoses as independent variables was significant ($\chi^2(3)$ = 12.16; p < 0.01; Negelkerke R^2 = 0.10). The model correctly classified 92.7% of participants, and indicated that a personality disorder diagnosis in patients with MUPS was associated with increased probability of having a diagnosis of Somatic Symptoms Disorder (*OR* = 16.18; Wald $\chi^2(1)$ = 8.26, p < 0.01). A marginally significant positive association (p = 0.06) also emerged with anxiety disorder, but not with depressive disorder.

Healthcare costs

Table 7 shows the overall estimated cost of hospitalizations for patients with MUPS and the costs divided by the hospital wards.

Table 7. Costs of hospitalizations (Euro)

Ward	Hosp	ALH (days)	MUPS			Overall	%
			Total	Each	Exams	Total	MUPS/ Overall
Neurology	144	9	328'192.09	2'263.4	71'441.89	17'474'510	1.9%
Internal Medicine	61	8	147'976.16	2'425.8	13'704	43'509'770	0.3%
Short Stay Unit	53	4	71'853.8	1'335.72	10'383.95	6'529'696	1.1%
Infectious Disease	7	8	13'482.65	1'926.1	9'782.80	31'259'630	0.04%
Emergency Surgery	10	5	12'393.54	1652.47	2'375.58	12'403'892	0.09%
Orthopedics	2	3	2'101.6	1050.82	791.86	76'801'450	0.002%
Psychiatry	14	8	34'129.61	2'437.83	5'541.03	11'539'717	0.3%
Otorhinolaryngology	15	7	9'965.88	664.72	5'905.23	6'648'790	0.1%

[1]Hosp: Hospitalization; [2]ALH: Average Length of Hospitalization

The total amount is 475'409.73 € with an average cost per year of 47'540.973 €. The highest costs were observed in medical wards, such as Neurology (328'192.09€) followed by Internal Medicine (147'976.16€). The overall estimated cost of examinations, which include blood tests and instrumental examinations, is 119'926.34 €. The overall estimated cost of hospitalizations in surgical wards is 14'495.14 €.

Chapter 4

Discussion

The research was carried out in a secondary setting. Clinical and diagnostic features of somatoform disorder have been debated by authors over the years, without reaching a consensus on which one could be the best and more useful diagnostic classifications. As in previous studies, MUPS were chosen as the basic diagnostic feature to the first selection of the patients (Haller et al. 2015; Rask et al. 2017; Houwen et al. 2917; Sharpe et al. 1992). MUPS still remain the main feature of all the diagnostic labels proposed (official ones and alternative ones), except for Somatic Symptom Disorder (according to DSM-5). This section was introduced in order to change the diagnostic paradigm and facilitate the diagnosis, especially for non-specialists (APA, 2013; Husing et al. 2018).

In this study, it emerges that a diagnosis of SSD seems more inclusive than diagnosis of somatoform disorder, with 32 patients (11.7%) fulfilling the diagnostic criteria of SSD, which is more than those who received a diagnosis of somatoform disorders (7.9%). This difference, retrospectively observed, could be partly due to a bias linked to the study design since it was not always possible to deduce the way patients present and perceive their symptoms from the discharge letter.

The present research confirms the gender trend observed in another primary care study (Kroenke et al. 1998; Kroenke et al. 1997; Rask et al. 2017) with a high prevalence of females with MUPS. Although this prevalence emerged, no statistically significant correlation between the female gender and SSD was detected. The average age of hospitalized patients with MUPS is 45 years, with a prevalence of married and employed people, contrary to what is observed in the literature (Fink et al. 1999; Sharma et al. 2018). This result could be influenced by the lack of almost 20%–28% of patients' information.

The study highlights a relevant comorbidity of MUPS with other psychiatric disorders (39% in previous medical history and in 16% as a new psychiatric diagnosis). Consistent with previous studies (Kleinstauber et al. 2014; Zonneveld et al. 2013; De Waal et al. 2004), the most frequently detected disorders were Anxiety Disorder, Depressive Disorder and Substance Abuse.

A psychiatric consultation was requested for 75 admissions in 306 hospitalizations; this result is in line with a previous study in outpatients (Poloni et al. 2018). The discrepancy between the admissions for medically unexplained symptoms and request of specialist

consultation could lead to a misdiagnosis or to a treatment proposal not in line with management guidelines of MUPS (Van der Feltz-Cornelis et al. 2010).

The most prescribed treatments were SSRIs and benzodiazepines. In the literature, it emerged that SSRIs are preferred alone or in combination with antipsychotics (Van Driel et al. 2018, Albert et al. 2016; Diurni et al. 2009). This result is consistent with what emerged in evidence-based literature. In a recent meta-analysis, it emerged that the new generation of antidepressants have very low-quality evidence regarding their effectiveness, even if their effectiveness is balanced against high rates of adverse effects (Kleinstauber et al. 2014). No data are available for benzodiazepines, but German guidelines for somatoform disorder discourage the use of anti-anxiety medications, especially in elderly people (AWMF 2012; Callegari et al. 2006; Baranzini et al. 2009).

An eventual efficacy of any type of psychotherapy that presents some evidence of being effective was not evaluable (Van Dessel et al. 2014; Kroeke & Mangelsdorff 1989), because this information was not available in the patients' discharge letters.

Regarding the data on the wards involved in the presentation of MUPS and the most common symptoms presented by the patients, these data differ from the literature, especially concerning Internal Medicine or Primary Care. For example, Kroenke and Mangelsdorff conducted a longitudinal study on the common symptoms in an internal medical setting, highlighting that the most frequent symptoms were chest pain, fatigue and dizziness (Kroeke & Mangelsdorff 1989). This difference could be due to the large number of neurologic patients in our sample, although the subgroup of patients referring to the Emergency Ward was considered, lower back pain, non-specific chest pain, headache and abdominal pain formed the most common symptomatology.

With regard to the correlation between medical anamnesis and SSD, there is no evidence that a history of medical disease is associated with a diagnosis of SSD. In other words, patients with MUPS and a neurological diagnosis in medical history may be less likely to receive a somatic symptom disorder diagnosis compared to patients with MUPS and no neurological diagnosis in anamnesis, although further study is necessary to confirm this datum. It is possible to assume that having already received a diagnostic label of a previous neurological disorder, patients are subsequently not diagnosed with appropriate codification of MUPS (Lee et al. 2016).

From our analyses, a Personality Disorder diagnosis in patients with MUPS was associated with increased probability of having a diagnosis of Somatic Symptoms Disorder. A marginally significant positive association also emerged with Anxiety Disorder, but not with

Depressive Disorder. This interesting result highlights the impact of the previous diagnoses on formulating a diagnosis of SSD in patients presenting MUPS. Further investigations are needed to understand those psychopathological correlations.

From our cost analysis, the neurology ward had the highest overall healthcare expenditure, including the highest cost for laboratory and instrumental exams. This observation could due to the type of examinations, which are predominantly procedures associated with huge healthcare costs. It is interesting to note that psychiatric hospitalization costs incur higher costs than those related to emergency surgery and infectious disease. This could be due to the long hospitalization durations in psychiatry and because patients in emergency surgery did not receive any surgery after clean investigations. With regard to patients admitted in infectious disease, hospitalizations were shorter than in psychiatry and any medications received were not expensive.

As shown in table 7, the ratio between costs for MUPS in hospitalized patients and overall costs related to hospitalizations for each ward is higher in Neurology (1.9%) than other specialties. This is in line with the prevalence of clinical presentation, as already described in the text. As widely described in the literature, this could be used as a guide to reduce any repetitive investigations and to evaluate the need of a psychiatric consultation early. In fact, psychiatric consultation has been identified as a way to support and implement the diagnostic process in order to reach an earlier person-centered psychiatric intervention, while also evaluating personal resources (Van der Feltz-Cornelis et al. 2010; Grassi et al. 2017; Poloni et al. 2010; Poloni et al. 2013). The present study takes into consideration the costs related to part of the diagnostic process, raising the hypothesis that total healthcare costs for patients with MUPS are even more extensive (Kroeke & Mangelsdorff 1989). As shown in the professional literature, this may only be the tip of the iceberg (Rask et al. 2017) and it represents the reason why it was not possible to compare our data with healthcare costs derived from previous American and European studies in the professional literature (Zonneveld et al. 2013; Rask et al. 2017).

Chapter 5

Conclusions

Medically unexplained symptoms are very common in the general population, and in primary care they may lead to high healthcare costs because they are responsible for so many consultations. Most medically unexplained symptoms are transient and only a small proportion become persistent and are potentially disabling and expensive to healthcare and society. It is these persistent symptoms that are diagnosed as somatoform disorders, currently classified in the chapter "Somatic Symptom Disorder and Related Disorders" in the DSD-5 (APA, 2013).

Regarding the types of treatment for medically unexplained symptom and somatic symptom disorders, and their efficacy, it is clear that there is evidence of efficacy and effectiveness, though this trends to be stronger in some conditions than others. The evidence is stronger for some pharmacological treatments than for psychological treatments partly because of the universal use of placebo tablets and the lack of an attention-placebo in psychological treatment trials.

With regard to therapeutic ingredients, it is evident that the so-called 'non-specific' aspects of treatment, such as time spent with the patient, the doctor's recognition of the reality of symptoms, and empathy and supportive approach, are important. In addition, specific relevant educational material, self-help manuals and a diary to better understand links between symptoms, behavior and thoughts are relevant first-line treatments.

As regards more intensive psychological treatments, the use of specialist cognitive interpersonal techniques needs to become much more widespread.

As far as it is known, few studies on patients with medically unexplained symptoms admitted to hospital exist in the professional literature. The strengths of the present study consist in the investigation of a large number of patients with MUPS; to study clinical, socio-demographic variables and psychopathological correlations involved in the development of Somatic Symptom Disorder; to provide a financial economic estimate of hospitalization costs of patients with MUPS.

The study presents some limitations, such as the small sample size from non-medical specialties, limiting the possibility to extend the statistical analyses to the whole sample due to the lack of patients' personal information.

Further investigations of this research project could possibly extend the study in other areas, such as General Practice and to extend the research to clinics and outcare patient facilities.

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PORTFOLIO

Doctoral student: Ivano Caselli

Doctoral period: October 2017-November 2020

Supervisor: Professor Camilla Callegari

Training activity in PhD program (University of Insubria)

- Seminar "On inflammation and depression, of what…? The effects of inflammation on behavior", Varese, 23rd March 2018

- Seminario "La Legge 180 del 1978: incontro tra etica, diritto e medicina", Varese, 20 giugno 2018

- English learning process through the MacMillan English Campus (MEC) software

- Second Insubria International School in Methodology, Ethics and Integrity in Biomedical Research, Center of Research in Medical Pharmacology, University of Insubria, Varese, 12-16 November 2018

Attended conferences and seminars

- "Malintesi nella vita amorosa: dalla simbiosi narcisista al riconoscimento della complessità edipica", 26 settembre 2020, seminario on line.

- XII Congresso AGIPPsA "Identità adolescenti. Alla ricerca di sé nella società complessa", Università degli Studi Milano Bicocca, Milano, 20-21 Ottobre 2017

- Seminario "C'è una specificità nella psicoterapia con persone lesbiche o gay? Il lavoro clinico con pazienti omosessuali e con coppie genitoriali", Hotel Marriott, Milano, 3 febbraio 2018

- Convegno "Gli interventi sanitari, giudiziari e di ordine pubblico relativi ai pazienti psichiatrici autori di reato", Varese, 22 marzo 2018

- Convegno "Esiti in psichiatria: qualità e quantità di vita", Bormio, 5-8 aprile 2018

- Seminario "Perché la psicoanalisi è terapeutica?", Hotel Marriott, Milano, 14 aprile 2018

- Convegno "Schizofrenia oggi", Milano, 22-23 maggio 2018

- Congresso Società Italiana di Psichiatria Sezione Regionale Lombarda "Dalla Psichiatria alla Salute Mentale: una cultura clinica inclusiva dei nuovi bisogni per nuovi servizi", Milano, 20-22 giugno 2018

- Seminario Area G "Il tempo post-moderno e la clinica psicoanalitica", Milano, 27 ottobre 2018

- "Verso una psichiatria di precisione. Poliedricità e personalizzazione dei trattamenti terapeutici". Sala Kursall Palace Grand Hotel Varese, 22 marzo 2019

- Seminario "Il trauma. Dalle neuroscienze alla psicoanalisi" di Franco De Masi, Milano, 30 marzo 2019

- "Il mestiere di psicoterapeuta. Formazione, sviluppo professionale ed efficacia clinica", 3-4 maggio 2019, Università degli Studi di Milano-Bicocca, Piazza dell'Ateneo Nuovo, 1

- "Milanopsichiatria. Informare e capire per prevenire e curare", Milano, 13-16 maggio 2019

- 7th International Congress - Infections & Transplantation, Varese, 23-25 May 2019

- Convegno Internazionale "Genitori e figli, terapeuti e pazienti. La libertà di scegliere nelle relazioni educativa e terapeutica", Università di Milano Bicocca, 21 settembre 2019

- "Elementi innovativi in neuropsicofarmacologia e nuove frontiere terapeutiche", XXI Congresso Nazionale Società Italiana di NeuroPsicoFarmacologia, Milano, 29-30-31 gennaio 2020

- "Percorsi di cura: relazione e dialogo tra ricerca e pratica clinica", Novara, 14 febbraio 2020

Organization of training courses

- "Quale amore…" Il paziente altamente problematico: stati di intossicazione, autori di reato, gestione delle misure di contenzione, TSO: presentazione di casi clinici - Supervisione in èquipe - 14 maggio, ASST Sette Laghi, Varese.

- "Quali elementi decisionali per l'eleggibilità al trapianto di rene: fattori etnoculturali e problemi etici. "Una nuova vita (im)possibile?", ASST dei Sette Laghi, Varese.

Publications

Caselli I., Poloni N., Ceccon F., Ielmini M., Merlo B., Callegari C., A systematic review of factitious disorders: psychopathology and diagnostic classification. Neuropsychiatry Journal (London) 2018;8 (1): 281-292.

Ielmini M., Poloni N., Caselli I., Diurni M., Bianchi L., Vender S., Callegari C., Efficacy and tolerability of two different kinds of titration of paroxetine hydrochloride solution: an observational study. Psychopharmacology Bulletin 2018:3(33).

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Papers submitted (peer reviewed journals)

Poloni N., Ielmini M., Caselli I., Lucca G., Isella C., Buzzi A.E., Rizzo L.R.M., Intronini G., Callegari C. The use of mechanical restraint in a psychiatric setting: an observational study. Journal of Psychopathology, 2020 May, *under review*.

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Scientific posters

Ielmini M., Caselli I., Poloni N., Pagani R., Introini G., Diurni M., Ceccon F., Giana E., Callegari C., L'uso delle misure contenitive in psichiatria: uno studio osservazionale. 12° Congresso Nazionale SIP "Le nuove frontiere della psichiatria sociale: clinica, public health e neuroscienze", Napoli, 2018.

Poloni N., Ielmini M., Caselli I., Pagani R., Zizolfi D., Pettenon F., Callegari C., Paroxetine vs vortioxetine for depressive symptoms in postmenopausal transition: a preliminary study. Congresso Nazionale di Psichiatria, Bormio, 5-8 aprile 2018

Zizolfi D, Poloni N., Ielmini M., Milano A., Miccicchè R., Calzolari R., Sani E., Caselli I., Cavallini G., Callegari C., The role of resilience and recovery style in schizophrenia: promote quality of life and psychosocial functioning in psychotic patients, Congresso Nazionale di Psichiatria, Bormio, 5-8 aprile 2018

Callegari C., Caselli I., Poloni N., Isella C., Ielmini M., Test farmacogenetici e riduzione di accessi ai servizi di emergenza e giorni di ricovero. Analisi "mirror" della durata di 2 anni

in pazienti affetti da disturbo bipolare, Congresso di Psichiatria Biologica, Napoli, 2-4 ottobre 2019

Teaching activities and invited speeches

- World Cultural Psychiatry Association, "Achieving global mental health equity: making cultural psychiatry count", 5th World Congress of the World Cultural Psychiatry Association, New York City (NYC), 11-13 October 2018

- Supervisione in équipe "Pazienti borderline e contesto familiare: emozioni a contrappeso", 12 novembre 2018, ASST Sette Laghi, Varese (Italy)

- Simposio parallelo "Dal concetto di somatizzazione al disturbo da sintomi somatici"; relazione dal titolo "Aggiornamento sul Disturbo da Sintomi Somatici: gestione dei pazienti con sintomi inspiegabili dal punto di vista medico (MUPS)", SOPSI 2019, 20-23 febbraio 2019, Rome (Italy)

- Seminario Area Medica – Esame di stato per Abilitazione Medico Chirurgo "Urgenze ed emergenze in psichiatria: come orientarsi", 4 luglio 2019, Varese (Italy)

- Simposio parallelo "Modelli e prospettive di intervento per disagi emotivi transculturali geograficamente diversificati - Il disagio psicopatologico nei migranti del territorio varesino: uno studio epidemiologico", XXIV Congresso Nazionale SOPSI 2020, febbraio 2020, Rome (Italy)

- Subject Expert in the teaching of Psychiatry at Degree Course of Medicine and Surgery, University of Insubria (from June 2020).

- Neuroscience Scientific Day, "Dissociative disorders and brain dysfunctions: findings from scientific literature"; Università degli Studi dell'Insubria, Online Event, 16/09/2020

Participation to other projects

- Joining to the VESPA protocol ("Assessing tolerability and efficacy of Vortioxetine versus SSRIs in elderly patients with depression: a pragmatic, multicenter, open-label, parallel-group, superiority, randomized trial") promoted by the School of Specialization in Psychiatry of the University of Verona. The study involves 14 Italian psychiatric centers engaged in the recruitment of elderly patients with major depression aiming to compare the tolerability, safety and efficacy of vortioxetine *versus* other SSRIs antidepressants in terms of the occurrence of adverse effects, mortality, suicidal events, quality of life and comorbidities. The subjects involved will be evaluated after 1, 3 and 6 months through the administration of the following rating scales: *Montgomery – Åsberg Depression Rating Scale* (MADRS), *Antidepressant Side-Effect Checklist* (ASEC), *EuroQual 5 Dimensions* (EQ-5D), *Charlson Age-Comorbidity Index* (CACI).

- Collaboration with the Postgraduate School of Psychiatry of the University of Verona in research on the use of second generation long-acting antipsychotics in clinical practice in Italy. The project involves the realization of several multicenter longitudinal observational studies aiming the investigation of the characteristics of the pharmacological prescription and the differences over the use of first generation long-acting antipsychotic drugs.

- Study on the use of pharmacogenetic testing to support the treatment of bipolar disorder and other psychiatric disorders. Pharmacogenetic testing (PGTs) are proving useful for clinicians in identifying better tolerated and more effective pharmacological treatments by studying the correlations between individual genetic variants and pharmacological response. The first phase of the study involves the recruitment of patients who meet the diagnostic criteria for bipolar I and II disorders, according to DSM-5, who undergo the Neurofarmagen® pharmacogenetic testing (AB-BIOTICS, SA, Barcelona, Spain) and a second phase of study involves the evaluation of patients affected by a wider diagnostic spectrum.

- Collaboration in the administration of psychometric tests and in the drafting of the text of the article "Are Clinical and Psychosocial Criteria Enough for Deciding Who is Eligible for Kidney Transplantation? The Value of Proportional Ethical Judgment.

Case Report" by Alessandra Agnese Grossi, Ivano Caselli, Alessia Petrolo, Daniela Dalla Gasperina, Paolo Antonio Grossi, Camilla Callegari, Mario Picozzi.

- Design of the study and drafting the manuscript "Clinical implications of subjectivity in patients with schizophrenia spectrum disorders: an observational study" by Ielmini M., Caselli I., Gasparini A., Amorosi S., Poloni N., Callegari C. [Abstract. The paper assumes that nowadays, mental illness can no longer be considered as a mere list of symptoms corresponding to localized brain dysfunctions but rather as a disturbance of the patient's subjectivity. Thus, a solid, qualitative study of patients' subjectivity could represent a useful tool in the complex evaluation of efficacy of pharmacotherapy in schizophrenic persons. In this perspective, authors performed a phenomenological oriented investigation on 49 patients, diagnosed with schizophrenia spectrum disorder, who were receiving long-acting injectable (LAI) antipsychotic therapy. From data analysis, authors found a positive correlation between general psychopathology and the use of long-acting injectable antipsychotic therapies, highlighting the necessity of a careful investigation of patients' subjectivity in a phenomenological way as an irreducible part of both psychopathological and psychopharmacological matters.]

- Conduction of a systematic review of studies on brain dysfunctions in dissociative disorders. [Background and objectives. Dissociation is a mental process which involves disruptions of usually integrated functions of consciousness, perception, memory, identity, and affect. Psychological trauma, stress such as severe and chronic childhood abuse or neglect, has been shown as implicated in the development of dissociation, suggesting an interaction between genetic, neurobiological and cognitive predispositions and stressful life events. Neuroimaging research in psychiatry has been increasingly used in recent years to identify some of the neurobiological mechanisms of psychiatric disorders. The research involves paper on studies of any type regarding neuroimaging, neural correlates and biomarkers in dissociative disorders aiming to give an overview of the studies in neuroimaging research published in professional literature through a systematic review of the most relevant findings in associations between dissociative disorders and brain dysfunction. Studies on Dissociative Disorders (DD) based on Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th edition criteria – DSM-5, or

119

DSM-IV-TR criteria were included; diagnosis based on International Classification of Diseases criteria 10 version – ICD-10, were also included. We chose to include also studies on Post-traumatic Stress Disorder (PTSD) with dissociative symptoms (PTSD+DS), and Acute Stress Disorder (ASD) with dissociative symptoms (ASD+DS) based on DSM-5, or ICD-10 criteria. A keyword search of the scientific literature published in English from 1980 to 2019 was conducted].