Mindfulness and Bodily Distress

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Fjorback LO, Walach H. Meditation Based Therapies – A Systematic Review and Some Critical Observations. Religions and Psychotherapies. 2012; 3: 1-18.

Fjorback LO, Arendt M, Schröder A, Rehfeld E, Oernbol E, Walach H, Fink P. Mindfulness Therapy for Somatization Disorder and Functional Somatic Syndromes: randomized trial with one-year follow-up, active control. Journal of Psychosomatic Research, 2012. In press.

Fjorback LO, Carstensen T, Arendt M, Rehfeld E, Oernbol E, Walach H, Fink P. Mindfulness Therapy for Somatization Disorder and Functional Somatic Syndromes: analysis of economic consequences alongside a randomized trial. Journal of Psychosomatic Research, 2102. In press.

OUTLINE

The present thesis proposes that mental health can be improved by mental training, just like physical (and mental) health can be improved by physical training. We added mindfulness training to the treatment of patients who experience multiple, persistent, and disabling physical symptoms that cannot be explained by a well-defined medical or surgical condition. We term illnesses that are characterized by such symptoms 'bodily distress syndrome' (BDS). We acknowledge that emotions are involved in any serious illness, but the stress response may be functioning abnormally in patients suffering from BDS. The mind is closely connected with the body, in particular with the immune system and the automatic nervous system, which means that emotional regulation and stress regulation may be improved by such training [1].

INTRODUCTION

Towards a mindfulness treatment approach

The introduction provides a brief overview of the concept of BDS and discusses why from a theoretical point of view mindfulness may be helpful. In the recent years, we have seen encouraging evidence that psychological treatments can improve the health-related quality of life of patients suffering from medical and psychiatric conditions such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and somatization disorder. Even so, the need for approaches that can be deployed to further the development of self-regulatory and self-care skills remains strong. The theoretical model for including mindfulness training in the treatment of BDS is based on identified neurobiological impairments in these patients and the neurobiological improvements that mindfulness training may offer. The overall goal is to improve the care for patients suffering from these conditions. The chapter raises the following topics: mental health, BDS, stigmatization, epidemiology, etiopathogenesis, the biology of emotions, treatment, and the potential of mindfulness, and presents a theoretical model for including mindfulness in the treatment of BDS.

Mental health

Mental health per se, unlike physical health, has only recently become a subject of medical research; until the late nineties [2], research was confined to the study of mental disorders, and mental health was defined, largely by default, as the absence of a psychiatric illness [2]. We do not define physical health only as the absence of illness; rather, it is common sense that many things influence psychical health, e.g. exercise, nutrition, and other aspects of daily living. It is beyond question that physical training has an impact on the brain, immune, and endocrine functions [3]. The same mechanisms may hold true for mental training, and this thesis explores whether patients suffering from BDS may be committed to such mental training in the form of mindfulness therapy, which is a mindfulness program specifically targeted patients suffering from BDS.

Bodily distress syndrome

There is an ongoing debate about the classification and the diagnostic criteria for medically unexplained symptoms, functional somatic syndromes, somatization, somatization disorder, and

other somatoform disorders, which are about to change in the revision of the 11th International Classification of Diseases (ICD-11) and the American Psychiatric Association's Diagnostic and Statistical Manual of mental Disorders (DSM-V). The diagnostic issues have been discussed intensely and described in detail elsewhere [4,5]. The present thesis uses the term BDS because it is developed from empirical research, and it covers the most important functional somatic syndromes [5,6]. Thus, BDS is a classification that may unite functional somatic syndromes and somatization disorder. The BDS concept is based on specific symptom clusters, and it includes most patients with somatoform disorders, despite psychological symptoms or behavioral characteristics not being part of the diagnostic criteria [7]. Also, BDS is a neutral label which is easier to communicate across specialties. In this study, we included the multi-organ type BDS that requires functional somatic symptoms from at least three out of four bodily systems: the cardiopulmonary, gastrointestinal, musculoskeletal, or general symptoms, and moderate to severe impairment in daily living, and at least six months of duration (Table 1). For the randomized controlled trial, we only included chronic cases defined as cases whose symptoms had lasted at least two years.

Table 1. Diagnostic criteria for bodily distress syndrome.
Fink et al (2007) [5]

Symptom groups	
Musculoskeletal	**Gastrointestinal**
Muscular ache or pain	Abdominal pain
Pain in the joints	Nausea
Feelings of paresis or localized weakness	Frequent loose bowel movements, diarrhea
Back ache	Feeling bloated/full of gas/distended
Pain moving from one place to another	Regurgitations, burning sensation in chest
Unpleasant numbness or tingling sensations	Constipation
Pain in arms or legs	Vomiting
General symptoms	**Heart and lung**
Concentration difficulties	Palpitations/heart pounding
Impairment of memory	Hot or cold sweats
Excessive fatigue	Breathlessness without exertion
Headache	Hyperventilation, dry mouth
Dizziness	Trembling/shaking, churning in stomach, flushing or blushing
Symptoms from at least three out of the four different symptom groups, and at least three symptoms from each of the three symptom groups Duration: a minimum of six months Impairments in daily life	

Stigmatization
Somatization has been known in medicine since ancient times and has almost always caused stigmatization as evidenced by such concepts as 'hysteria', which dates back to about 1900 BC and was described in Egyptian papyruses [8]. Although the medical profession has gained much ground since ancient times, somatization remains a puzzle. Medical professionals may find somatization difficult, and patients may be told that 'it's all in their mind' or 'they just have to live with it, and if they coped better they would not experience all these symptoms, and use time and money in the health care system' [9-12]. The 'understanding' of the concept of somatization disclosed by such utterances may be rooted in the mind/body dualism deeply embedded in modern medicine, which tends to classify symptoms and diseases as either physical or mental. Chronic illnesses without organ pathology are a source of confusion for physicians often taught that 'if it is not organic, it must be psychiatric'; the prevailing paradigm simply makes it difficult to believe in the reality of an illness without organ pathology [13]. The physicians may think that the patients are faking and are untreatable, especially if they decline psychosocial treatment. The patients, on their part, may also believe that they may be helped only by means of medication prescribed to treat a biomedical problem. Furthermore, psychological or psychiatric treatment may seem inappropriate to a person with somatic complaints, and it may be perceived as unnecessarily stigmatizing [7]. Thus, the sharp division of a health care system into 'mental' and 'physical' domains is problematic in the light of current research which argues that the problem of BDS is one that encompasses both the body and the mind [7] .

Epidemiology
BDS is common and costly, although only the bodily symptoms which are persistent and lead to impairment or distress are diagnosed as disorders [7]. It is estimated that these disorders occur in approximately 6% of the population, 16% of primary care attenders, and up to 33% of patients in secondary care clinics [7,14-18]. BDS correlates with female sex, fewer years of education, low socioeconomic status, other psychiatric disorders (especially anxiety and depressive disorders), and recent stressful life events [19,20]. There is some evidence for genetic predisposition [21]. Also, having a parent with poor health or high neuroticism, persistent abdominal pain as a child, childhood abuse, physical illness, a negative illness belief, and unemployment may be associated with BDS [22-25]. When the disorders occur concurrently with a physical illness and anxiety/depression, the impairment seems to have an additive effect. A high number of symptoms is associated with a high level of disability [7]. In addition, functional somatic syndromes are associated with physical illnesses [7,26-28].

The onset of functional somatic syndromes may be associated with prior gastrointestinal infection, anxiety, depression, neuroticism, recent stressful life event, and health anxiety [29,30]. Predictors of the onset and the persistence of functional somatic syndromes include female gender, older age, fewer years of education, lower socioeconomic status, unemployment, a reported history of sexual abuse/other childhood adversities, multiple symptoms, concurrent chronic physical illness or psychiatric disorder, social stress, and reinforcing social factors such as illness benefits[20,23,31-33].

For patients suffering from irritable bowel syndrome, a successful contact with a gastroenterologist that is followed by improvement in symptoms of irritable bowel syndrome is associated with reduced anxiety, reduced fear of cancer, greater likelihood of attributing symptoms to stress and less catastrophizing in relation to bodily symptoms [7].

The impairments of BDS are comparable with those of depressive disorders or a general medical disease. Due to these impairments

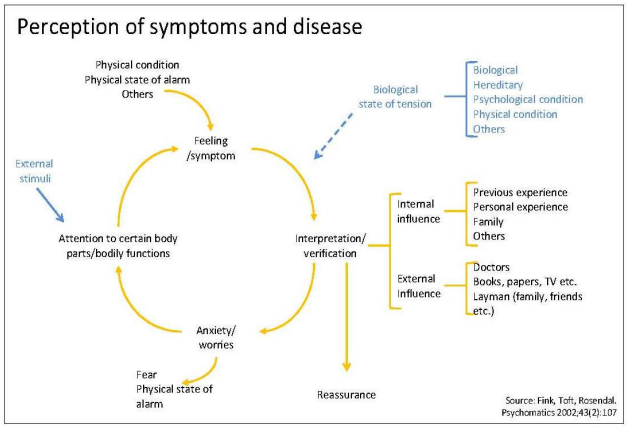
and the numerous investigations made to rule out any medical conditions, BDS is expensive in terms of health care use and time missed from work [5,7,16,34-47]. In the Netherlands, medically unexplained symptoms and somatoform disorders form the fifth most expensive diagnostic category [29,48]. The costs appear to be higher than those incurred by stroke and cancer. The high health care costs do not include time lost from work and the reduced productivity, or the time of carers. The money is spent on medical consultations and expensive investigations, which lead to little or no health gain [7]. The greater societal costs are evident by the fact that these diagnoses account for 6-10% of early retirement pensions in Denmark [5,49].

Etiopathogenesis

The causes of BDS are complex and involve both pathophysiological, psychological, and social mechanisms. The complex interface of biological, psychological, and behavioral mechanisms is not unique to BDS; indeed, it plays an important role in the symptom expression of all chronic medical and psychiatric illnesses [50]. In the search for a pathophysiological basis, research has focused more and more on the central nervous system [51]. It has been suggested that the pathology of the hypothalamic pituitary-adrenal axis and the autonomic regulation of physiological arousal may play a role [52]. This suggestion finds support in the growing body of evidence for one or more of the following pathophysiological manifestations once BDS has developed: sensory amplification, attenuated hypothalamic-pituitary function, lability of the autonomic nervous system, and psychological and behavioral factors [53]. The etiopathogenetic models of BDS are multifactorial, but they differ in their emphasis on biological vs. cognitive/behavioral or cultural factors.

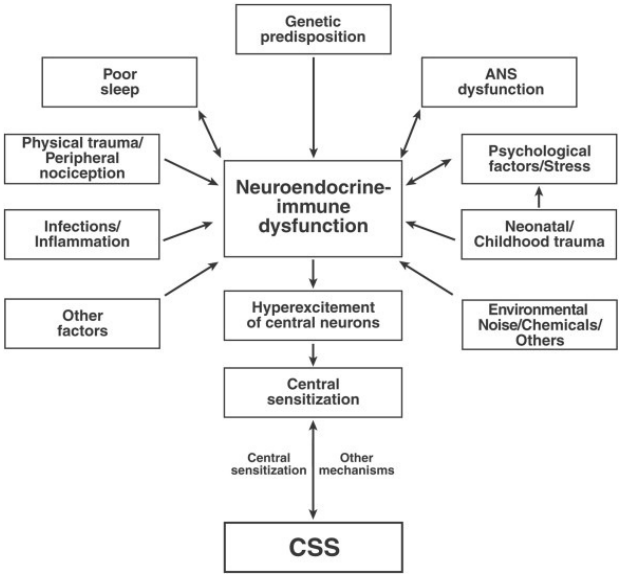
The perception of symptoms and disease model [54] (Figure 1) emphasizes cognitive/behavioral factors and describes the risk of health anxiety, excessive medical consultations, and expensive investigations. Yet, the model also acknowledges that symptoms are initiated by a physical state that may be similar to what is suggested in patients suffering from asthma.

Figure 1. Perception of symptoms and disease model. Fink (2002)



The central sensitization model (Figure 2) emphasizes the role of biological factors [55,56], a similar model is used to describe the relationship between emotions and asthma [57]. Research directed toward understanding the pathophysiology of asthma has previously ignored the role of the brain. But research now suggests that the insula and anterior cingulated cortex are major components of circuitry through which emotional and cognitive processes and peripheral inflammation are mutually influential. Substance P, a neuropeptide involved in inflammation and the signaling of noxious stimulation to the brain, is one factor through which stress and emotions may promote inflammation and vice versa [58]. Several groups have demonstrated that patients with fibromyalgia have cerebrospinal fluid concentrations of Substance P that are approximately threefold higher than those of normal controls [53,59,60]. Also, Substance P dysregulation may be involved in irritable bowel syndrome [58]. These observations may challenge the dichotomous view that classifies illness as either organic or nonorganic [50]. Brain imaging studies have compared measures of brain activity between patients suffering from different functional somatic syndromes or somatoform disorders and controls, and reported differences in regional cerebral blood flow in subcortical structures: thalamus [61-63], basal ganglia [62-66] and brainstem [67], and in the cortical regions [64-71], but the descriptions are too inconsistent to be of any help [72]. However, one study using patients diagnosed with BDS with no co-morbidity described impairments of sensory processing [51]. Contrary to expectations, the patients had a pain threshold that was higher than that of the controls. Yet, the patients and controls reached unbearable pain at the same temperature. In addition, the patients had a significantly lower response to painful stimulation in the contralateral secondary somatosensory cortex and bilateral prefrontal cortex than the healthy controls. The patients demonstrated a lower increase in regional cerebral blood flow in the inferior parietal lobule, which is involved in sensory-discriminative and semantic judgmental processing. Therefore, it is suggested that these patients have an impaired ability to evaluate and categorize their painful sensations. This claim is further supported by different activations of the prefrontal cortex; which is thought to play a regulatory role in the processing of pain, especially in emotional and cognitive modulation of pain experiences. This may indicate a deficiency in the cognitive regulation of pain perception in patients suffering from BDS [51].

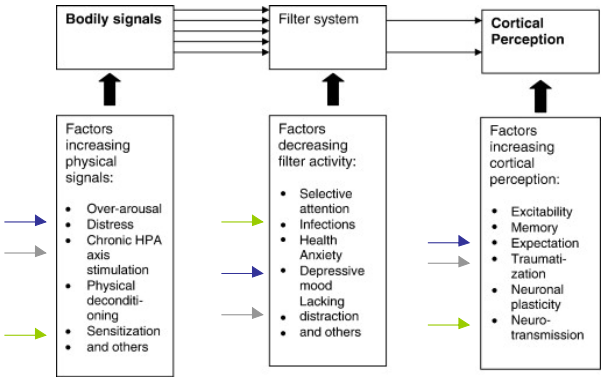
Figure 2. The central sensitization model, Yunus (2007)



CSS= central sensitivity syndromes (covers BDS); ANS= autonomic nervous system.

The perception-filter model [73] (Figure 3) suggests that due to an impaired filter system, more bodily sensations reach cortical perception in patients suffering from BDS. It was formerly believed that sensory processing was a passive, stimulus-driven device, but now perception is viewed as an active and highly selective process [74,75]. This model includes depression as a factor that can decrease the filter activity, which is also relevant for other disorders. Research has demonstrated that chronic diseases characterized by dysregulation of inflammation are particularly susceptible to exacerbation by stress and emotions. Likewise, rates of depression and anxiety are overrepresented in individuals suffering from chronic inflammatory diseases [58,76,77] .

Figure 3. Perception-filter model, Rief (2007)



HPA= hypothalamic pituitary-adrenal.

In addition, a hypothetical model (Figure 4) for the cause of BDS has been offered [78]. This model is global and emphasizes a developmental perspective that involves predisposing, precipitating, and perpetuating factors.

Figure 4. Hypothetical model explaining the cause of functional somatic syndromes (covers BDS), Henningsen 2007

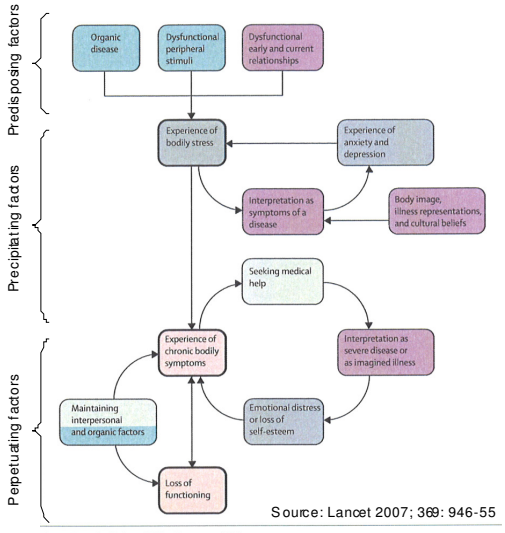


Figure: Hypothetical model for the cause of FSS
Pink=core symptoms of FSS. Grey=accompanying symptoms. Purple=psychological and sociocultural factors. Green=behavioural and interpersonal factors. Blue=organic factors.

The biology of emotions

Any kind of complex behavior, such as the regulation of emotions and of illness perception and illness behavior, is the result of complex interactions of different functional systems in the brain. The frontal lobe is a critical zone for regulating emotions, and the parietal lope is an area where representations from the senses come together, whereas the amygdala is critical for automatic, negative, but also for positive emotions, and for fear in particular. The hippocampus plays an important role in emotions, because it is essential for our appreciation of the contexts of events and for recruiting routines that assist in the regulation and inhibition of automatic emotional responses [79]. Some emotional disorders involve abnormalities in the hippocampus, particularly depression and posttraumatic stress disorder, likely due to the comparative density of cortisol receptors in the hippocampus [80-82]. Destructive emotions are an expression of an emotion whose expression is not constructive in a particular situation although the emotion itself may be adequate in the situation. For instance, it is natural for a person to experience sadness when a loved one dies. But a depressed person experiences sadness in contexts that are not appropriate [2]. Similarly, it is natural to experience bodily symptoms when the body is ill or stressed, but a person suffering from BDS experiences bodily symptoms even though no pathology can be found, and the person might not even experience stress. In neuroscience, it is now hypothesized that the frontal lobes, the amygdalae, and the hippocampus change in response to experience [83]. They are parts of the brain that are affected by the emotional environment in which we are raised and which are shaped by repeated experience. This phenomenon – 'neural plasticity'- has been traced down to the level of gene expression [2], and new neurons have been shown to grow throughout man's entire life span. The amygdala plays a key role in the circuitry that activates emotion, while the prefrontal cortex does much of the regulation, especially inhibition [1]. The frontal lobes, the amygdalae, and the hippocampus are extensively connected to the body, in particular the immune system, and the autonomous nervous system. This implies that emotional regulation and the stress regulation in the body and the mind are highly connected [84,85]. When we think, feel, and act, we may actually change our brain and body as modern neuroscience suggests [2].

Emotional regulation is relevant to BDS patients because emotion regulation and pain or symptom regulation are associated; the comorbidity of mood disorders and pain syndromes has been shown to be high [86]. Among chronic pain patients and healthy individuals, a heightened experience of negative affect has been shown to be associated with poorer pain outcomes [87,88]. Moreover, integrative neuroimaging, behavioral, and physiological methods may have provided novel evidence that emotion regulation and pain regulation skills are a shared ability that is reflected in the functioning of the amygdala [88].

Treatment

Psychosocial interventions may alter a raised physical symptom perception threshold, neuro-endocrine-immune dysfunction, and maladaptive perception. Moreover, an increase in the prefrontal cortical volume following individual cognitive behavioral therapy (CBT) has been found in patients with chronic fatigue syndrome [89]. The rehabilitative approach combined a graded increase in physical activity with a psychological approach that addressed thoughts and beliefs [89]. Reviews have concluded that graded exercises and CBT may have a therapeutic potential for BDS patients [78,90-92]. A large study on chronic fatigue syndrome

confirmed the beneficial effect of CBT and graded exercises. The three-arm study found that individual CBT and individual graded exercise therapy were associated with less fatigue and a better physical function, and it was recommended that patients attending secondary care with chronic fatigue syndrome should be offered individual CBT or individual graded exercise therapy alongside specialist medical care [93]. Yet, it should be observed that 3158 patients were screened for eligibility in order to include 641 patients. Moreover, the treatment was comprehensive: at least three sessions of specialist medical care were offered and provided by doctors with specialist experience in chronic fatigue syndrome, plus up to 14 individual therapy sessions, and an additional booster session. The effects of CBT on somatization disorder are tested in two studies. Allen [94] found that individual CBT added to psychiatric consultation improved physical function compared with psychiatric consultation alone. Whereas a CBT intervention by the family physicians was unable to facilitate improvement of physical function [95].

A Cochrane review on exercise for treating fibromyalgia found that supervised aerobic exercise training had beneficial effects on physical capacity and fibromyalgic symptoms. However, adherence to many of the interventions was poor [90]. A Cochrane review on psychological therapies for the management of irritable bowel syndrome concluded that CBT and interpersonal psychotherapy may be effective immediately after finishing treatment, but the quality of the studies was sub-optimal [91]. A review of the treatment for somatoform disorders concluded that CBT is the best established treatment for a variety of somatoform disorders; that a consultation letter to the primary care physician was associated with some benefit; and that there was preliminary but non-conclusive evidence for an effect of antidepressants [96].

However, among the most severe disorders in this area randomized controlled trials are few. Also, research in functional somatic syndromes and somatization disorder is even more limited as these disorders are heterogeneous and lack a clear definition. Recently, a new intervention entitled Specialized Treatment for Severe Bodily Distress Syndromes (STreSS) [97,98] was developed at a general hospital by our group of psychiatrists specialized in functional somatic syndromes. The STreSS model is based on a CBT approach and aimed at overcoming shortcomings in the classification and the organization of care by treating patients with various functional somatic syndromes under one unifying diagnostic label, BDS. The STreSS model has been tested in a randomized controlled trial, and it was found effective in improving self-reported physical health when compared with enhanced usual care [97].

A literature search for mindfulness and functional somatic syndromes identified only randomized controlled trials of patients diagnosed with fibromyalgia. Three studies have been conducted and none of them showed convincing results, but they gave some indications as to possible avenues for therapeutic improvement. Sephton et al. showed that the mindfulness program Mindfulness-Based Stress Reduction (MBSR) alleviated depressive symptoms in one study [99]. In this self-selected sample, a high proportion of the respondents who initially scheduled did not attend the intake interview, and 282 individuals were screened for eligibility in order to include 91 participants. Functional impairment, pain, and sleep quality were measured prior to randomization, but the results of these outcomes were not reported. Demographic characteristics of the patients were as follows: the mean age was 48.4 (SD 8.9) years, 66.7% had >14 years of education, and 60.7% had an income >$40,000. In another study, Astin et al. [100] were unable to show a difference between a treatment combining MBSR and Qi Gong and an educational program. Also, the demographic characteristics of their population showed a high social status among participants, as over 80% had taken at least some college courses, their average age was 47.7 (SD 10.6) years. A high drop-out rate of up to 49% made it difficult to draw any final conclusions. While both groups improved, they showed no differences between groups. A similar finding was observed in a recent study [101]. Being the largest and one of the few actively controlled studies, it shows a small difference between MBSR and the active control in fibromyalgia patients. The subjects had a higher mean age (53,4 years; SD 8.7) than the subjects in the two previous studies; in the MBSR intervention arm, 35.5% of the participants were working and 37.7% retired. Thus, participants showed a similarly high social status.

The potential of mindfulness

Mindfulness practice is the practice of a non-judgmental awareness that aims at the experience of nonduality. Nonduality in this context means that reality is ultimately neither physical nor mental. From a traditional Buddhist point of view, we all have destructive emotions. This is reflected in the first and second of the four noble truths that life is suffering and that the source of suffering is greed, which is the basis of all destructive emotions. But if we really investigate our emotions, analyze them, and look at their effects, we can attenuate negative emotions and cultivate positive emotions as reported in a recent study [102]. According to research, mindfulness training may be a practice that promotes neural plasticity [84,103-105]. Mindfulness can be defined as a moment to moment non-judgmental awareness [106]. It correlates with a meditative state called 'open awareness' where one is very fresh, the senses are very alert, but one consciously chooses not to mentally engage, judge, identify with whatever is coming to the senses [2]. The neural process that might correspond to this state of awareness has been investigated by Richard Davidson et al. Their investigations demonstrated a shift of brain function to left frontal dominance in response to emotional triggers that were associated with an approach state of mind with more positive emotion. And the left shift in emotion-regulation circuits was correlated with improved immune function [107]. An increased thickness in the prefrontal area, insula, and hippocampus has also been found; the degree of thickness correlated with the length of time practicing mindfulness meditation [108-111]. The insula transmits data from the body to the brain and is especially thought to be important for a physiological kind of awareness [112]. Neural integration is the linkage of anatomically or functionally differentiated neural regions into an interconnection of widely distributed areas of the brain and body proper. One example would be the balance of such functions as brakes and accelerator branches of the automatic nervous system. The middle prefrontal regions may monitor the sympathetic and parasympathetic activity and then be able to alter it, a mechanism of 'bodily regulation' [113].

Mindfulness practice starts by observing the body and holding the awareness of the body with a friendly non-judgmental attitude. Daniel Siegel has proposed that the ability to observe the body is a sixth sense that may enhance stress regulation or 'bodily regulation' [113]. The next step is to observe the mind, notice when thoughts and emotions arise. The Tibetan word for meditation means 'familiarization'. The point is not to try to block arising

thoughts, but to not let them invade the mind. What people do in meditation is to familiarize themselves with a new way of dealing with thoughts that come to their minds [2]. When a powerful thought of strong attraction or anger arises, you recognize it: 'Oh, that thought is coming'. An example often given is that of a thief coming into an empty house. There is nothing to lose for the owner and nothing to gain for the thief. This is an experience of freedom. You do not become apathetic, but you gain mastery over your thoughts. This can only happen through sustained training and genuine experience [2]. Daniel Siegel has proposed that the ability to observe the mind is a seventh sense that may enhance attention and emotion regulation [113]. The last step is to move toward acceptance and to observe relationships; the relationship toward yourself, the situation you are in, and the connection with others [113]. Daniel Siegel has proposed that the ability to observe relationships is an eighth sense that may enhance communication skills. This eighth relational sense enables one to be 'feeling felt' by another and to feel being a part of a larger whole. Also, it enables one to become friends with oneself.

A brain perspective on a mindful way of being may reflect a primary neural circuitry in which we (1) perceive the outside world through our first five senses, (2) have interoception of our bodily sixth sense, (3) achieve mindsight for the mental processes of our own and others` minds in our seventh sense, and (4) have a direct sensation of our resonance with something larger than our day-to-day adaptive self in our eighth sense. Living within the directness of these eight senses may enable us to be grounded in the physical world, the body, our mind and our relationships [113].

A theoretical model for mindfulness therapy

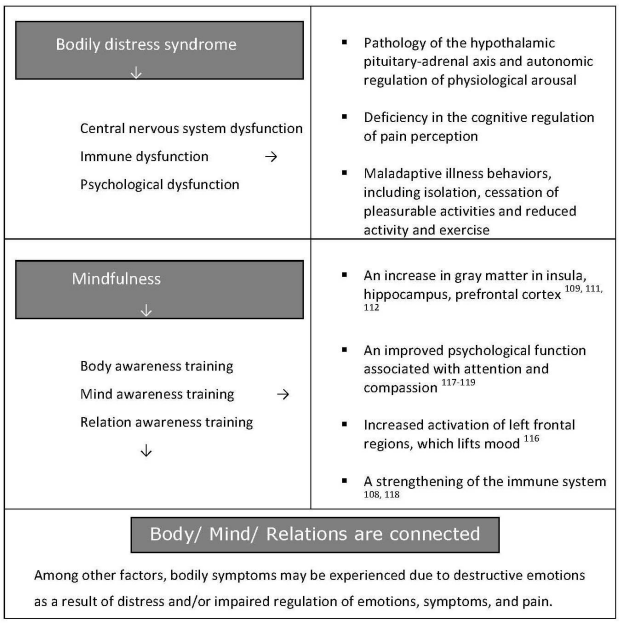
A theoretical model for mindfulness therapy is summarised in Table 2.

The co-occurrence of negative affect and pain is well recognized [87,114], and an impaired ability to evaluate and categorize painful sensations could indicate a deficiency in the cognitive regulation of pain perception in patients suffering from BDS. This may be due to changes in the parietal and prefrontal cortex, which are the areas that sustained training of mindfulness may improve. Impairments of sensory processing may also lead to repetitive overloading, which may in turn lead to fear of movement and unhealthy coping strategies. Patients often describe that they shift between ignoring and being totally overwhelmed by somatic symptoms. A patient described this inability to detect and react to bodily sensations as a state of stress in the body that he is not aware of.

In contrast, mindfulness training may improve stress and emotion regulation, and it may train patients' in the ability to notice when bodily sensations, thoughts, and emotions arise and help them embrace these sensations in a friendly, non-judgmental awareness. Mindfulness training may enable one to notice the selective process or the automatic filters that regulate the flow of energy and information in what may be considered the mind. By investigating healthy minds, modern neuroscience suggests that mental health can be improved by mindfulness training [79,115]. The mind is extensively connected with the body, in particular with the immuno-endocrine system and the autonomous nervous system. Hence emotional regulation and stress regulation may be improved by such training.

In summary, BDS is a major public health issue possibly associated with the pathology of the immuno-endocrine and autonomic nervous system. BDS patients are often stigmatized, and effective treatment is rarely delivered, leaving these patients isolated, left by themselves, vulnerable to potentially harming medical and/or alternative treatments. There is accordingly a need for non-harming practical tools that patients can learn to master so that they can improve the ability to take responsibility for their own health and wellbeing. Planning this PhD project, I therefore aspired to design a project that could develop and evaluate a mindfulness treatment approach for those most severely disabled patients who suffer from multi-organ BDS.

Table 2. A theoretical model for mindfulness therapy



Mindfulness practice is often explained as a state of being in the now, but it also includes knowing the past, knowing what has lead to this moment, and moreover it includes the future, because this moment has already gone. Therefore, it is important to know in which direction one is going: is it a helpful or hurtful direction? A constructive or destructive direction? In mindfulness practice, yoga is used for body awareness training, meditation for mind awareness training, and compassion for mindfulness training, which is described as the heart of mindfulness practice [116].

GENERAL DISCUSSION AND CONCLUSION

What is gained by a mindfulness approach?

Development of a mindfulness treatment approach

The present thesis has contributed to the development of a mindfulness approach as treatment for Bodily Distress Syndrome which is an important and widespread condition. Before a detailed discussion on the findings, a more critical issue could be raised; namely, if it really was necessary to develop a mindfulness approach for BDS considering the many treatment methods already available: STreSS-1; individual CBT; individual psychodynamic psychotherapy; graded exercises therapy; psychiatric consultation intervention; specialist medical care; MBSR; MBCT; yoga; meditation; mindfulness training offered in Buddhist settings, etc.

With great respect for these different resources, I found it advantageous (and very exiting) to conduct a structured treatment of mindfulness therapy that drew on my background in medicine, CBT, yoga, meditation, and mindfulness. By using this knowledge and experience, I may have helped BDS patients to navigate in a complex world where they can be totally lost. One patient, for example paid $ 20.000 for anti-HIV medication prescribed from a private physician despite the fact that he was not HIV-positive. Another had slept throughout his 20s doped from the morphine prescribed by his family physician. Having teeth removed, repeating cortisone injections, months and years of bed rests, repeating explorative surgeries, and a variety of treatments performed by spiritual hands and crystals are an incomplete list of the many options the BDS patients make use of.

A published example is Michael Brown [117] who for 10 years had been preoccupied with the task of attempting to cope with and heal himself from a painful condition (Horton's syndrome). In his book The Presence Process - a healing journey into present moment awareness he describes a momentary experience of 100% present moment awareness, facilitated by the ingestion of peyote cactus: 'I felt complete. I felt whole. I felt physically present, mentally clear, emotionally balanced, and spiritually connected'. Unlike the BDS patients in the present trial, Michael Brown resolved what he believes was an unconscious emotional condition that manifested as a painful ailment. Michael Brown continues: 'However, if we want to neutralize the causal emotional charge that is unconsciously driving us to manifest accidents that are injuring us to disease that are physically, mentally, or emotional debilitating to us, then a medical practitioner is possible the last person that we may consider approaching'.

No matter what we believe as medical practitioners, the fact remains that the majority of the referred BDS patients have experienced an odyssey of treatments through the health care system and through alternative treatments. Safety guidelines are therefore highly recommended, as also explained by David M. Eisenberg [118], Director of the Division for Research and Education in Complementary and Integrative Medical Therapies and the Osher Institute at Harvard Medical School:

Even in my primary care clinic in a university hospital, if I asked ten patients were they using or thinking about using alternative unproven techniques, three or four or five would say yes. And then it hit me, maybe the strategy was to document the extent to which Americans in academic hospitals were using these things. Document how much money they were spending and then bring it to my academic colleagues and try to make the argument that we must out of concern for patients figure out which were safe, which were dangerous, which saved money, which cost money [119].

When it comes to BDS patients, modern medicine and alternative treatments seem to have forgotten Hippocrates' guiding of doing no harm. The word mindfulness means to 'remember'; remember the body, the mind (intelligence), and the heart (kindness). This is so obvious and trivial, but it may, nevertheless, be exactly what is called for in modern medicine. Teaching how to feel whole, physically present, mentally clear, and emotionally balanced may, indeed, be an integrated part of modern medicine. Mindfulness therapy is definitely not a miraculous cure I invented, and many new questions have been raised, but I 'remembered', expanded my knowledge, shared it with the patients, and had great fun.

What is new?

The present study is a continuation of the STreSS-1 trial which did not include yoga, meditation, or mindfulness training. The present study, which is also called the STreSS-2 trial, can therefore be seen as a new, original contribution; not solely as CBT framed as an updated version.

The MBSR program is a practical manual for 'Full Catastrophe Living, Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness' [106] and to 'Heal Thy Self' [120]. MBSR is an invitation to embark upon a journey of self-development, self-discovery, learning, and healing [106]. Growth, development, and maturation as a mindfulness practitioner and mindfulness teacher are critical parts of a process that is not painless [121]. One of the key principles of the MBSR program is a medically heterogeneous environment, in which people with a broad range of medical conditions participate in classes together without segregation by diagnosis or conditions. This approach focuses on what people have in common rather than what is special about their particular disease. The participants share being alive, having a body, breathing, thinking, feeling, perceiving, an incessant flow of mental states, including anxiety, worry, frustration, irritation, anger, sorrow, helplessness, despair, joy, and the capacity to cultivate a moment-to-moment awareness by directing attention in particular systematic ways [122].

In contrast, MBCT was developed as a prevention program for formerly depressed patients, and the MBCT program focuses more on thoughts. Like in the MBCT program, we adapted the MBSR program by targeting a specific patient population; but in contrast to the MBCT program, mindfulness therapy focuses much more on the body. Since the BDS patients start out with a problem in their body and a desire for a new body, learning how to be present in the very body they try to escape from is a very practical and useful skill.

The hospital setting and our medical background may be important factors as we used analogies to chronic medical conditions and gave specific medical feedback. Also, the medical assessment is important because it ensured that the patients received the right diagnosis, which is the basis for the right treatment. Mindfulness is not a cure one can use when nothing else is working, but it may very well be the right treatment if the body is distressed to a level where it is no longer functioning. In mindfulness therapy, the core focus is observing what is present in the body, and by doing so insights may arise, for example: 'I noticed that I am able to regulate the level of stress in the body', 'I noticed that I hate myself', 'I noticed that I feel isolated most of the time, but in class it is as if everything is okay, as if I am okay', 'Now, I have tools so I can work without becoming ill', 'I never believed in any of this, but experiencing a body without a simple symptom totally blew me away', 'Not much happened but I quit the painkillers', 'I realized that I am not the only one suffering, but that it is a human condition just like happiness', 'I realized that by keeping my focus on the pain, humour suddenly appeared' .

The introduction highlights the fact that BDS patients are suffering, and that mindfulness means to work with the very stress and pain that causes the suffering [106]. According to the Buddha himself, we are all suffering; but for BDS patients, the physical suffering is so present that it cannot be ignored. However, BDS patients do not come to the hospital saying: 'I am suffering' but they do come with a body they want to have fixed. The tools offered by medicine, including psychiatry, are intended to fix or

attack the symptoms, not to release suffering or promote flourishing [2,123]. Moreover, courses on the mind and body or on mental health are not part of a professional education in medicine. However, this may be changing since an intensive educational program in mindfulness, communication, and self-awareness has been tested in a before-and-after design for primary care physicians, and this program is associated with improvement in primary care physicians' well-being, psychological distress, burnout, and the capacity for relating to the patients [124]. Apparently, there is a growing interest in the possible effectiveness of bringing mindfulness into secular settings within mainstream society, including medicine. How to engage BDS patients in the work of observing and embracing a painful and/or fatigued body, how to inspire them to use what is now known from modern medicine (physical exercises, healthy nutrition, healthy relationships, CBT, etc.), and how to engage in their everyday lives is an ever evolving process, in which I believe mindfulness therapy is a contribution.

SUMMARY OF FINDINGS IN RELATION TO AIMS

The aim of this PhD thesis was to create a mindfulness treatment approach for BDS by:

1) Developing a theoretical model for including mindfulness in the treatment of BDS

By practicing body awareness, mind awareness, and communication skills patients may develop self-regulatory and self-care skills and improve their health. The theoretical model for including mindfulness training into the treatment of BDS rests on identified neurobiological impairments in these patients and the neurobiological improvements that mindfulness training may offer.

2) Reviewing mindfulness-based interventions

The overall results from the reviews [125, 126] and from the mindfulness literature indicate that MBSR and MBCT have something to offer. The reviews [125,126] recommended MBSR as a useful method for improving mental health; however, the lack of a long-term follow-up and active control groups are limitations in most studies. MBCT was recommended as a tool for preventing depressive relapse in recovered, recurrently depressed patients to prevent depressive relapse, but the implication of MBCT is challenged, especially the mindfulness teachers' lack of education is stated as problematic [127].

3) Testing the acceptability and feasibility of mindfulness therapy

The randomized controlled trial indicates that BDS patients are capable of and willing to engage in mindfulness therapy. This is an important finding since treatment adherence is reported to be problematic in this particular patient population [90,100]. This thesis showed that mindfulness therapy can safely and successfully engage BDS patients to take better care of themselves.

4) Evaluating the effect of mindfulness therapy

Mindfulness therapy was comparable to specialized treatment in improving the quality of life and symptoms of patients with BDS. Mindfulness therapy produced greater and more rapid improvements than specialized treatment. The observed improvements may reflect a clinically and socially significant change. Mindfulness therapy appears to produce improvements within the range of those reported in the STreSS-1 trial, where CBT was compared with enhanced usual care, and no improvements on the SF-36 scale were observed in the enhanced usual care group. This indicates that the changes accomplished with the two treatments mindfulness therapy and specialized treatment reflect real changes attributable to the interventions.

5) Evaluating the social and economic effects of mindfulness therapy

Mindfulness therapy had substantial socioeconomic benefits over specialized treatment. The costs incurred to cover permanent health-related benefits, especially disability pension, were significantly lower in the mindfulness therapy group than in the specialized treatment group over a 15-month follow-up period. The total health care utilization was reduced over time in both groups from the year before inclusion (mean $ 5,325 median $ 2,971) to the year after inclusion (mean $ 3,644, median $ 1,593) ($p=0.0001$). There was no difference between the two groups.

6) Analyzing the social and economic consequences of BDS

The BDS patients had accumulated significantly more weeks of unemployment and sickness benefit 5 and 10 years before inclusion ($p<0.0001$) than the population controls.

In conclusion, the social and economic consequences of BDS are significant and mindfulness therapy may have a potential to significantly improve the quality of life and symptoms, prevent social decline, and reduce societal costs.

GENERAL DISCUSSION OF METHODS

Design

Selection bias

The intervention was delivered only to patients with a strong treatment need due to the BDS and was restricted to patients who had been ill for at least two years. This may have skewed the recruitment by increasing the rate of the most severe cases. The BDS patients enrolled in the trial may not be representative of all patients suffering from somatization disorder or functional somatic syndromes as the recruitment may have been biased towards those willing to engage in a psycho-social treatment. The fact that our research clinic is placed at a general hospital may have ensured a higher acceptability of participation than if it had been placed at a psychiatric hospital. Another possible selection bias could stem from the fact that we recruited our study participants from individuals seeking help within the health care system. However, most of the patients did not seek help due to BDS, but due to particular physical symptoms, and the physicians only referred patients whose symptoms could indicate BDS. The trial may have limited generalizability because of volunteer bias, although we only included referred patients. Furthermore, doctors may not have referred patients with a low treatment motivation. Our experience speaks against this possibility, because many of the patients were highly skeptical at the beginning of the clinical assessment. Some patients remained highly skeptical almost until the very end of the treatment. In the specialized treatment group, the patients very often began the consultation after the assessment by stating: 'So, you also believe that it is just in my mind'. This dual way of thinking deeply embedded in our culture makes it hard to grasp the idea that the problem of BDS (and most other illnesses) is one that encompasses both the body and the mind. In the mindfulness therapy group, some patients were exited, other highly skeptical in the beginning; most patients very quickly found it difficult especially the yoga practice, and they found it very painful to simply observe the symptoms; however, towards the end, most patients were sad that the group was ending. Finally,

selection bias could be present due to mindfulness, yoga, and meditation, so that only patients interested in these practices were willing to participate. Nevertheless, the participation rate was extraordinarily high. We may have been very successful in convincing the patients to participate in the clinical trial. Although we tried only to include motivated patients by telling them that mindfulness therapy may be very challenging, and that they should only participate if they were, indeed, willing to engage in the treatment; even so very few declined participation, possibly owing to a thorough clinical assessment and the lack of alternative treatment options.

Assessment

We made a comprehensive life-time review of case notes and clinical records from primary care physicians, ambulatory care, and hospital wards. We subsequently used the SCAN interview as our main diagnostic instrument. This may constitute limitations due to the diagnostic algorithms deployed in the SCAN interview. Currently, SCAN is the most comprehensive diagnostic tool available to explore BDS and functional somatic syndromes as it covers almost all physical symptoms experienced by humans. But it does not include the counting of tender points (diagnostic criteria for fibromyalgia) or a detailed specification of bowel movements (diagnostic criteria for irritable bowel syndrome). Using criteria for various other syndromes may therefore have complemented the SCAN. On the other hand, these limitations are not specific for our study, and the use of SCAN strengthens our study because we interpreted the symptoms within a clinical context. Moreover, the assessments were performed by trained physicians with sufficient clinical expertise and all patients underwent a physical and neurological examination.

The randomized trial

In general, randomized controlled trials compromise if an intervention can work under ideal circumstances (efficacy trial with high internal validity), and if it does work in the real world (effectiveness trial with high external validity) [128]. We tried to mirror the real word and to achieve high external validity by having few inclusion and exclusion criteria; for example, allowing the participants to have comorbidities and take drugs. The sample resembles actual clinical patients, but the patients met all DSM or ICD criteria for the diagnosis given, which contributed to a high internal validity.

In the STreSS-1 trial, primary care physicians and all hospital wards in the western part of Denmark were reached by posted mail. All the BDS patients had a theoretical chance of being referred to the trial. Inclusion for the present STreSS-2 trial began when the inclusion for the STreSS-1 trial had ended, at which time physicians had become used to referring patients. The enrolment of the participants into the present trial may therefore be said to reflect a clinical practice that is practicable and manageable. However, since the physicians may have seen an effect from the STreSS-1 trial, they may have referred more severe and more intractable patients to the STreSS-2 than to the STreSS-1 trial. We raised the age criteria to 50 years (45 in STreSS-1); and contrary to the practice in STreSS-1, we did not exclude those in litigation.

We considered all functional somatic syndromes fulfilling the criteria for multi-organ BDS and did not restrict the inclusion criteria to single syndromes. Nor did we exclude patients due to a lack of suitability for the intervention or lack of motivation.

We had no passive control group and therefore cannot, in theory, establish causality between improvement and mindfulness therapy or specialized treatment. However, since the STreSS-2 trial began when the STreSS-1 trial ended, we decided to use our knowledge from the STreSS-1 trial and aimed at sharing this knowledge with all the patients. It was deemed unethical to compare the mindfulness therapy group with a group of patients recruited from a waitlist or treatment as usual since individual CBT and psychiatric consultation intervention have previously been found to have positive outcomes [129,130]. We, therefore, decided to do our very best in the control group and to establish a strong, active control group. However, the present results remain relevant even if the population may have been selected and we lacked a passive control group.

A randomized controlled trial cannot examine aspects like: the result of unspecific factors, regression towards the mean, or the natural history of the disorder. Since positive findings were maintained at the 15-month follow-up and the participants had been ill for at least two years prior to the treatment (on average 13.5 years), it is hardly likely that the observed effect is attributable to the natural history of the disorder or to regression towards the mean, although the study design cannot completely rule out this possibility.

Active ingredient

Mindfulness therapy is composed of many elements and the study design cannot determinate the active ingredients. Some of the strong elements are: 1) connection to the body, 2) connection to the mind, 3) connection to self and others. The yoga practices: body scan (yoga nidra) and hatha yoga are the tools systematically used to enhance the connection with the body. The meditation practices systematically used to discipline the mind consists of concentration on breath, the body as a whole, pain, sounds, thoughts, and emotions; these practices are used to keep the attention in the present, observing what is present in the awareness, and embracing whatever comes up with a friendly non-judgmental attitude. Connection to the self and others are practiced through deep listening. From a mindfulness perspective, deep listening is the greatest gift a teacher can offer, it is not just being silent, but it is being fully present with the patient. This presence may be explained as compassion in action or an ethical action that is believed to be the outcome and expression of a clear mind and an open heart.

Among clinicians, scientists, and even Buddhist masters, there is an ongoing debate about what mindfulness and its essence really is. Mindfulness is both a practice and an outcome. Some argue that the quality of attention is that which is most important [131, 132]; others claim that acceptance and the level of compassion are the most important elements [132]. It is claimed that the heeling is mediated by the teacher's authenticity and his or her ability to truly see the patient and act with compassion and ethics. If this truly is the essence of mindfulness, then this aspect of mindfulness may not be separated as a component only delivered to the mindfulness therapy group. Because if mindfulness is integrated into the person that delivered the specialized treatment, then it is not possible for such a person to spend eight or nine hours with a patient not being mindful; they may connect and mindfulness is being communicated. Conversely, if mindfulness is mainly engaging in formal practices, it may be separated. This type of communication is of course, not exclusive to mindfulness;

it may be expressed as a common humanity and it equals the therapeutic alliance in psychotherapy.

Data

Processing of questionnaires

The data were designed and processed using the TELEform software program, which allows optical reading of data. The research secretaries were provided with guidelines on how to handle cases of doubt. The project head and the statistician were responsible for the further collation of data.

Questionnaire

The SF-36 is an established instrument, widely used and well-validated in the general population [133,134], in primary care [134] and in various medical conditions [135]. But it may not be accurate in measuring BDS patients' self-reported health [136-138]. The SF-36 questionnaires were filled in prior to the clinical assessment, and it is possible that this influenced the patients' self-reported health. In order to be taken seriously, they may have attributed their limitations to physical rather than emotional problems. Also, to keep up appearance or because of insufficient knowledge, they may have scored their physical functioning better than it actually was. For example, if one never gets out of the home (which was very common), then one does not know whether it is difficult to walk a distance or climbing the stairs. A cross-sectional study suggested that the PCS and the MCS component scores of the SF-36 may not be valid in patients with BDS and proposed a new aggregate score, the Perceived Physical Health (PPH) score, including physical functioning, bodily pain, and vitality [139]. However, improvements assessed with the PCS and the PPH showed similar results in the BDS patients [97]. Health profiles have been compared between different medical and psychiatric conditions [140]. The BDS patients included in this trial scored physical functioning almost within normal range; but role physical, bodily pain, general health, vitality, and social functioning scores were scored about ten points worse than in patients suffering from both a psychiatric condition and a severe chronic medical condition such as congestive heart failure, chronic obstructive pulmonary disease and/or advanced diabetes; while scores of role emotional and mental health were about the same as in this group of patients suffering from both mental and physical conditions.

One SF-36 question asks: 'compared to one year ago, how would you rate your health in general now?' The other questions refer to the past four weeks. But there may be recall bias anyway because the current state at a particular day a patient answers the questionnaire influences recall. The SF-36 questionnaire asks questions like: 'Is it problematic?', 'Do you have difficulties?' or, 'Within the past four weeks did you cut down on the amount of time you spent on work', 'Accomplished less than you would like'. We have no idea what the person did accomplish; we only know how he or she judged accomplishment. The scoring could reflect a pattern of perfectionism rather than the impairment itself. People adapt to the current state and memory is fallible and more a construction than a fact, so the questionnaire will inevitable give rise to some bias. The mentioned biases will underestimate a possible effect.

Register data

Denmark runs a nationwide centralized register of personal information where every citizen is awarded a unique personal identification number. Virtually every government agency and all central registries in Denmark receive information about a person from the database in which data are continuously updated with all relevant health-related and other information. This unique data pool allows every citizen to be followed closely from birth to death.

The registers have almost full population coverage, and no informed consent is required to use data from those registered. The data can be used in an anonymous form. In the DREAM database, persons supported by their spouse, e.g. housewives and persons 'dropped out' of society, i.e. people who receive no employer or transfer payment, are not registered and they are therefore counted as self-supporting. However, these groups are considered to represent only a minor proportion according to the Danish Ministry of Employment.

Analysis

In the analysis phase, we accounted for confounding by matching and stratification. We used intention to treat analysis [141,142] and multiple imputation [143] in an appropriate manner. No participants were excluded from the final analysis. We decided to use simple descriptive analyses of workability, as these data have never been presented before and a pure description is highly valuable for hypothesis-generating research to be tested in future trials.

Generalizability

The population studied is a selected group in the sense that they are likely to be the most severe, the most unusual, and most intractable patients compared with the entire cohort of persons suffering from bodily distress. In principle, socio-demographic bias should not influence the selection of patients as the health care in Denmark is free of charge for all citizens. Immigrants were excluded, but they constitute less than 10% of the Danish population so this bias is hardly a problem. The results from the study may be generalizable to a Scandinavian population between 20-50 years of age who suffer from multi-organ BDS.

GENERAL DISCUSSION OF RESULTS

Clinical importance

The magnitude of the statistically significant differences observed may or may not be sufficient to make clinicians and health care planners consider changing their current practices. To interpret outcomes and to facilitate such decision-making, we displayed outcomes directly by units and by the percentage of patients who improved. The evaluation of whether the outcome is clinically important can be evaluated through clinical knowledge and the literature. A meta-analysis concluded that compared with CBT for depression or other mental disorders the efficacy of CBT for medically unexplained symptoms seems to be lower [144] and only small between-group effect sizes are found when compared with treatment as usual or a waitlist [144,145]. Moreover, patients presenting in primary care with physical symptoms have been followed for five years, and it was reported that poor baseline functional status, illness worry, and longer symptom duration predicted a lack of resolution [146,147].

Thus, it is unlikely that the patients enrolled in the present study would have improved without the interventions since they had poor baseline functioning, high scores of illness worry, and very long symptom duration. At the end of treatment, a statistically significant higher number of patients randomized to the

mindfulness therapy group (28%) than to the specialized treatment group (10%) reported a marked improvement (PCS >1 SD), OR=3.21 [1.05-9.78]. A value of OR> 2 marks a clinically important difference [128]. The standards for Cohen's d effect size are approximately 0.2 small, 0.5 moderate, 0.8 large as a rule of thumb; whether it is a clinically important difference is a matter of clinical judgment, not a statistical one [128]. Judgment depends on how serious the disorder is, how big the difference is, what that represents in terms of behavioral change, how difficult it is to change, and how costly the intervention is [128]. Our results highlight the fact that BDS implies a social decline for some. BDS is a significant and costly illness from which even young and well-educated persons may suffer. The improvement in PCS score outcome may not be huge; still, the use of register-based data afforded us with an excellent opportunity to gain insight into possible behavioral changes. Overall, an intervention that is safe, is acceptable to the patients, may prevent social decline, and may even reduce total health care costs, is sufficiently encouraging to warrant future further investigation. Suffering from somatic symptoms is stressful, suffering from somatic symptoms without having a diagnosis or an explanation may be even more stressful. Both intervention groups had improved outcomes for illness worry, anxiety, depression, and somatic symptoms. Thus, receiving the BDS diagnosis may have a therapeutic effect. Reducing the level of distress seems to be relevant as stressors perceived as inescapable or unavoidable evoke the strongest adverse biological consequences [53]. In the specialized treatment group the BDS diagnosis was individualized and supplemented with an individual treatment plan which improved treatment to a point that seems to be clinically important.

Treatment response equals disability pension?

However, the participants randomized to specialized treatment did not improve in terms of their PSC scores until the 15-month follow-up. All participants whether they were randomized to the mindfulness therapy group or the specialized treatment group received information containing with a definition of stress: when the demands exceeds the resources, one can cope either by decreasing the demands or enhancing the resources. We speculated if a treatment response could be explained by receiving disability pension (decreasing the demands). We analyzed if a clinically significant treatment response (PCS change score> ½SD) at 15-month follow-up was associated with receiving disability pension. 13/27 (48%) of those receiving disability pension in the specialized treatment group at the 15-month follow-up improved, 7/27 (26%) did not reach a clinically significant treatment response, and 7/27 (26%) were lost at follow-up. In the mindfulness treatment group, 4/15 (27%) of those receiving disability pension improved, 6/15 (40%) did not reach a clinical significant treatment response, and 5/15 (33%) were lost at follow-up. Thus, receiving disability pension in general cannot explain a clinical treatment response, and a clinical treatment response was not at all associated with disability pension in the mindfulness therapy group. For some BDS patients, disability pension is the only realistic solution, but from a therapeutic point of view, it is not a very ambitious treatment, and the therapeutic ambitions should be raised, at least for the younger part of the population.

Possible risk factors

We found results suggesting that accumulated weeks of unemployment or sickness benefits are possible risk factors for chronic and severe multi-organ BDS. We do not know if accumulated weeks of unemployment or sickness benefits five and ten years before inclusion were simply leading to a future BDS, or the reason for accumulated weeks of unemployment or sickness benefits was BDS. But these measures were assessed at different time points, and the results certainly point towards the existence of an association. Many patients have an understanding of a very sudden onset of their illness. However, we found impaired working capability five and ten years before study enrolment. These results point to a clinical relevance of vulnerability factors; they suggest that BDS may be detected much earlier; and they offer valuable information that may be used to inform in possible prevention programs or treatment initiatives. These findings also suggest that there may be opportunities for arresting or maybe even preventing the BDS patients' odysseys through the health care system and/or alternative treatments that could save financial resources which could be better used for prevention and treatment programs.

Comparison with other studies

An overall comparison with other studies is difficult, because of the variability in the populations studied, the diagnostic criteria used, the interventions delivered, and the types of measures deployed. In former randomized controlled trials testing mindfulness interventions, the typical participant is a white, middle-aged, middleclass, well-educated woman. In this study, the majority were out of work and had little or no education. Our findings suggest that even a socially marginalized population with chronic bodily distress is willing to participate and engage in a treatment that requires a high level of patient involvement. We checked if having an education was associated with a clinical treatment response and found absolutely no association (the results are not reported). We have previously reported that the BDS population group was just as educated as the matched population controls; we believe that this similarity reflects the age group (20-50); if the subjects had all been 50 years of age, a difference in education is highly probable, since it is likely that more population controls than BDS patients would have achieved an education by the age of 50.

Previously, four other mindfulness interventions have reported change scores of the SF-36. The PCS scores for woman with cancer improved from 38 to 40 [148], the MCS scores improved from 32 to 39 among emotionally distressed patients [149], bodily pain improved from 40 to 45 for older adults with chronic low back pain [150] and from 32 to 40 in woman with fibromyalgia [99]. Thus, improvements on the SF-36 have not been huge in previous randomized controlled mindfulness studies.

A comparison of SF-36 change scores following CBT and the results of the present study are hampered by the fact that the CBT interventions were of different duration and mostly are individual CBT. Moreover, there is variability in the diagnostic criteria, the severity, and the duration of illness. In general, the less severe cases seem to be those who have achieved the highest level of improvements. CBT plus specialist medical care improved the SF-36 physical functioning score from 39 to 58 [93] in patients suffering from chronic fatigue syndrome, but the study excluded patients with a physical functioning > 60; in our mindfulness therapy group, the mean physical functioning was 60 at baseline.

The StreSS-1 trial reported an effect size of 0.51; 95% CI 0.19-0.83 on the primary outcome, which should be compared with an effect size of 0.42; 0.17-0.68 in the present STreSS-2 trial. But the group size (12 versus 9) and the age (≤50 versus ≤45) were higher,

the social marginalization was worse, and the intervention covered a shorter period (3 versus 4 months) in STreSS-2. CBT was compared with enhanced usual care in the STreSS-1 trial, and no improvements on the SF-36 scale were observed in the enhanced usual care group, which indicates that the changes found in the two treatments mindfulness therapy and specialized treatment in the present study reflect a real change attributable to the interventions.

In the STreSS-1 trial 73% reported a positive change and 25% a marked improvement, while 68% reported a positive change and 29% a marked improvement in the STreSS-2 trial. Both trials reached high effect sizes for illness worry and small effect sizes for anxiety and depression. We therefore conclude that CBT in STreSS-1 and mindfulness therapy in STreSS-2 were equally effective. The data on disability pension have not yet been analyzed in the STreSS-1 trial.

The benefit observed following specialized treatment is in line with previous research which has reported effect of individual CBT [92], specialist medical care [93], and psychiatric consultation intervention [92].

CONCLUSION

A mindfulness approach can safely be integrated into the treatment of BDS and it improves health.

Patients with BDS are currently being largely neglected which results in enormous societal costs and much human suffering; consequently much benefit could be reaped if health care professionals and planners gave higher priority to BDS. There is no 'gold standard' for BDS management. However, the STreSS-1 trial proposed a stepped care model [97,98] and suggested that the application of such a strategy would lead to improved health care and has the potential to save costs. The present STreSS-2 trial provides encouraging preliminary evidence for the effect and cost-effectiveness of mindfulness therapy. Mindfulness therapy is a useful complementary treatment in the management of BDS; it offers an additional intervention option to be integrated into the stepped care model. Doing no harm and improving treatment for BDS patients require close collaboration across medical specialties. The BDS diagnosis has shown its potential to facilitate the delivery of evidence-based care across medical specialties, as it has now been tested in two randomized controlled trials where it has proved its clinical usefulness for hundreds of patients.

Instead of telling patients that they just have to 'live with their symptoms' and that 'there is nothing to be done', we can now offer evidence-based treatments based on the results achieved by the STreSS-1 and STreSS-2 trials. One model does not fit all the patients, thus having more treatment options is an advantage. Mindfulness therapy may be used as a specific prevention program for high-risk groups and may be added at all levels in the stepped care model. Although encouraging, large-scale multicenter trials are needed for further evaluation.

RESEARCH PERSEPCTIVES

Perspectives for the use of the BDS diagnosis and a mindfulness approach

Expertise in behavioral medicine or mind/body medicine is rarely present in routine medical settings. This may result in an insufficient knowledge of BDS and a problematic communication between the patients and the medical practitioners. For example, the referred BDS patients reported that the most common responses they receive from their physicians are: 'You are going to have to learn to live with this' or 'Your symptoms are not real or that rare that I have no idea about their origin'. BDS clinics using a unified approach for the various functional somatic syndromes and psychiatric conditions are rare or non-existing in most countries. The successful biomedical revolution and the diagnostic confusion of BDS may have contributed to a neglect of BDS in clinical practise and health care planning. However, a BDS research clinic is establish at the general hospital, Aarhus University Hospital, Denmark [98].

In line with previous research, this thesis confirmed that BDS is a common, costly, and highly debilitating condition [94]. And the results of this thesis give hope to a much earlier delivering of safely guidelines, prevention, and treatment initiatives, which seems to be a better use of the financial resources.

The relationship between emotion and symptom expression is being studied in chronic medical conditions [57,58,107], and the BDS diagnosis has the potential to expand this research field, because the unifying approach is useful, non-stigmatizing, and may resolve the confusion related to classification. The BDS diagnosis is easy to communicate across medical specialties and makes sense to the patients, because it does not define symptoms as 'mental' and not 'physical', but unifies medical conditions and psychiatric disorders.

The unified integrated approach may fill the gab between medicine and psychiatry. The STreSS-1 trial may educate patients and health care practitioners in BDS [97]. The MBSR program may teach patients how to learn to live with this [106]. The MBCT program may teach formerly depressed patients how to recognize when the mind is operating in maladaptive modes of mind [151]. And Mindfulness therapy may teach BDS patients how to recognize when the body is operating in destructive patterns. The patients learn that they have a real disorder; that the disorder most likely is an imbalance in the autonomic nervous system; that catastrophizing thinking, inactivity, and overloading make the symptoms worse; that connecting to the body can improve health; the imbalance in the autonomic nervous system can be balanced by this connection; symptoms, emotions, and thoughts come and go, which one will notice when observing the awareness, the mind, and the body.

In order to detect decisive ingredients, future studies could include neurobiological measures. Functional brain imaging has shown impairments of the sensory processing in BDS patients, which may indicate a deficiency in the cognitive regulation of symptom perception [51,72]. The emotion and cognitive regulation are connected with the immune system, the endocrine system, and the autonomic nervous system [83,84]. Thus, practicing emotional regulation skills may improve mental and physical health. In addition, research suggests that basic functions associated with the prefrontal cortex may emerge following mindfulness meditation [113]. These functions include regulation of the body systems, balancing emotions, attuning to others, modulating fear, responding flexibly, and exhibiting insight and empathy [113]. Functions that may be investigated through a combination of neuroscience, qualitative studies, and effect trials, because many of the cognitive and emotional regulatory processes implemented in the prefrontal cortex operate relatively automati-

cally and are opaque to direct self-reporting and are represented only indirectly in self-reported measures [1].

This phenomenon may have been present in our trial in which it was not unusual that patients were almost unable to climb the stairs to attend the mindfulness therapy program, which was located at the third floor (without an elevator); but by the end of treatment, they had no trouble climbing the stairs; however, when we asked them about their improvement, they often stated that they did not realize that so much had changed.

Neuroscientific work has uncovered components of emotion regulation that could not have been discovered through self-report methods, these components may be investigated in BDS patients. Thus, neuroimaging, behavioral, and biological measures may complement the evaluation of treatment effect in future trials.

Our trial was carried out at a highly specialized research clinic at a general university hospital. Many patients had to travel 2-3 hours to attend assessment and treatment. A similar treatment may be delivered at local clinics. When treating BDS patients at local clinics, physicians are recommended to ensure proper medical diagnoses. A proper BDS diagnosis is not achieved only by filling out a questionnaire. The BDS diagnosis is a clinical diagnosis similar to depression; and the level of impairment, the number of symptoms, and the duration of this illness are to be interpreted in a clinical context. It is common sense that all medical and mental illnesses are being diagnosed and addressed. Mindfulness therapy, MBSR, and MBCT are complementary and participatory treatments; they are not alternative treatments, for example for cancer. The success and the failure of the implementation of mindfulness therapy at local clinics need to be investigated to determine the boundary conditions for a nationwide application. Sufficient training and education in mindfulness and CBT are highly recommended. MBCT is now being recommended by the UK's best practice advisory board for NHS-NICE (National Health Service-National Institute of Health and Clinical Excellence). However, challenges related to the implementation of evidence-based mindfulness approaches are being reported from the UK [152]. Few teachers are competent in its delivery, and several reviews, books, and papers have pointed to the importance of the teachers' competence [121,125,153-155] . According to Jon Kabat-Zinn, the practice of mindfulness is not just a good idea, and there is a great risk that mindfulness will be grasped and understood in a limited way, simply as a concept. Thus, a training of teachers is recommended, and the implementation of mindfulness therapy in other settings needs to be evaluated.

The training of mindfulness teachers and an analysis of the effect of mindfulness therapy delivered at local clinics are under preparation. Also, mindfulness therapy for patients with shoulder impairments (impingement- or rotator cuff syndrome) is under preparation. The shoulder patients' experience of mindfulness therapy will be investigated in a qualitative anthropological PhD study. Also, an ongoing qualitative PhD study is investigating how BDS patients experience stress in their daily lives before and after mindfulness therapy. In addition, the effect of pharmacotherapy and acceptance and commitment therapy is currently tested in ongoing STreSS-3 and StreSS-4 trials where specialized treatment is included for all patients.

Large-scale multicenter trials are needed to explore the effectiveness and cost-effectiveness of mindfulness therapy. The effect of longer treatment times, the inclusion of booster sessions, and whether integrating mindfulness therapy with specialized treatment yields a better outcome may be explored.

ABBREVIATIONS

BDS	Bodily Distress Syndrome (a novel unifying diagnostic category)
BDS, single-organ type	BDS type characterized by symptoms primarily from one bodily system
BDS, multi-organ type	The most severe form of BDS, characterized by symptoms from at least three bodily systems
CI	Confidence Interval
CBT	Cognitive Behavioural Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification Diseases and Health Related Problems
MBCT	Mindfulness Based Cognitive Therapy
MBSR	Mindfulness Based Stress Reduction
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard Deviation
SF-36	Medical outcomes study short form 36 questionnaire
SF-36 MCS	SF-36 Mental Component Summary
SF-36 PCS	SF-36 Physical Component Summary
SF-36 PPH	SF-36 Perceived Physical Health (an alternative to the SF-36 PCS)
STreSS	Specialized Treatment for Severe Bodily Distress Syndromes
STreSS-1	The first clinical trial assessing the efficacy of STreSS
STreSS-2	The second clinical trial assessing Mindfulness therapy
TAU	Treatment as usual

SUMMARY

We have created a mindfulness approach to treat patients who experience multiple, persistent, and disabling physical symptoms that cannot be explained by a well-defined medical or surgical condition. Randomized controlled trials in this area are few, and research is hampered by the lack of clear definitions. Bodily distress syndrome (BDS) or bodily stress is an empirically defined definition unifying various conditions such as fibromyalgia, chronic fatigue syndrome, and somatization disorder.

In the present PhD, we explored whether patients suffering from BDS may be committed to mental training in the form of mindfulness therapy, which is a mindfulness program specifically targeted patients suffering from BDS.

The theoretical model for including mindfulness training in the treatment of BDS is based on identified neurobiological impairments in these patients and the neurobiological improvements that mindfulness training may offer. BDS is a major public health issue possibly associated with the pathology of the immuno-endocrine and autonomic nervous system. BDS patients are often

stigmatized, and effective treatment is rarely delivered, which leaves these patients isolated, left by themselves, vulnerable to potentially harming medical and/or alternative treatments. Accordingly, there is a need for non-harming practical tools that patients can learn to master so that they can improve the ability to take responsibility for their own health and wellbeing.

Mindfulness-Based Stress Reduction (MBSR) is a group program that employs mindfulness practice to alleviate suffering associated with physical, psychosomatic, and psychiatric disorders. Mindfulness-Based Cognitive Therapy (MBCT) is designed to prevent depressive relapse.

Paper I and II present systematic literature reviews only of randomized controlled trials on MBSR and MBCT. The effect of MBSR has been explored on fibromyalgia in three studies, none of them showed convincing results, but gave some indications as to improvement. The reviews recommended MBSR as a useful method for improving mental health; however, lack of long-term follow-up and active control groups are limitations in most studies. MBCT was recommended as a tool for preventing depressive relapse in recovered, recurrently depressed patients, but the implication of MBSR and MBCT is problematic, especially due to the lack of well educated mindfulness teachers.

We combined MBSR with cognitive behavioral therapy, CBT, specifically targeted BDS. Paper III provides original data from 119 patients enrolled in a randomized clinical trial, mindfulness therapy for BDS. The randomized controlled trial indicates that BDS patients are capable of and willing to engage in mindfulness therapy. This thesis showed that mindfulness therapy can safely and successfully engage BDS patients in mindfulness practice. Since individual CBT and psychiatric consultation have previously been found to have positive outcomes for BDS patients, we compared mindfulness therapy to an active control group entitled specialized treatment in which an individual treatment was planned in collaboration between the patient and a MD specialized in BDS, CBT, and psychiatry. Mindfulness therapy was comparable to specialized treatment in improving the quality of life and the symptoms of the patients with BDS at 15-month follow-up.

For primary outcome physical health (PCS) at 15-month follow-up, different developments over time for the two treatment groups could not be established ($F(3,2674)=1.51$, $p=0.21$). However, in the mindfulness therapy group, PCS significantly changed at the end of treatment and this change remained at 15-month follow-up, whereas no significantly change was seen in the specialized treatment group until at the 15-month follow-up. In the mindfulness therapy group, 26%; CI, 14-38 reported a marked improvement (> 1SD) at the end of treatment compared with 10%; CI, 2-18 in the specialized treatment group. This amounts to a statistically significant difference between the groups (OR=3.21; CI, 1.05-9.78, $p=0.04$). The results are indicating that mindfulness therapy produced greater and more rapid improvements than specialized treatment.

Mindfulness therapy appears to produce improvements within the range of those reported in the STreSS-1 trial, where CBT was compared with enhanced usual care, and no improvements on the SF-36 scale were observed in the enhanced usual care group. This indicates that the changes accomplished with the two treatments mindfulness therapy and specialized treatment reflect real changes attributable to the interventions.

The economic effects of mindfulness therapy are evaluated in paper IV by the use of original register data from the 119 enrolled patients and a matched control group of 5950 individuals. Mindfulness therapy had substantial socioeconomic benefits over specialized treatment. The costs incurred to cover permanent health-related benefits, especially disability pension, were significantly lower in the mindfulness therapy group than in the specialized treatment group over a 15-month follow-up period; 25% from the mindfulness therapy group received disability pension compared with 45% from the specialized treatment group ($p=0.025$).

The total health care utilization was reduced over time in both groups from the year before inclusion (mean $ 5,325, median $ 2,971) to the year after inclusion (mean $ 3,644, median $ 1,593) ($p=0.0001$). There was no difference between the two groups.

Five and ten years before their inclusion, the BDS patients were less self-supporting than an age-, gender- and ethnicity-matched population control group; the BDS patients accumulated more weeks of sickness benefit and unemployment. Thus, the included BDS patients may have been ill and in high risk for a social decline five and ten years before they received a proper diagnosis and treatment.

In conclusion, the social and economic consequences of BDS are significant and mindfulness therapy may have a potential to significantly improve function, quality of life and symptoms, prevent a social decline, and reduce societal costs.

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