How to treat Bodily Distress Syndrome/
functional somatic syndromes.
Results from a highly specialised university clinic

Prof. Per Fink
MD, PhD, Dr.Med.Sc.

www.functionaldisorders.dk
Overview

• The Concept - the BDS and Health/Illness anxiety diagnoses

• Organisation of treatment (business model)

• Treatments
The Research Clinic for Functional Disorders (1999-)

- The Head and Heart Centre, Aarhus University Hospital
- Catchment area ~ 2-3 million people
- Patients referred from primary care physicians and hospital wards
- Multidisciplinary team, around 30-40 clinicians/researchers
- Involved in approx. 20 ongoing research projects
- Training of medical and psychology students, GPs and other doctors, psychologists, social workers etc.
### Functional somatic syndromes according to specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterology</td>
<td>Irritable bowel syndrome (IBS), non-ulcer dyspepsia</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>Pelvic arthropathy, premenstrual syndrome, chronic pelvic pain</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>Fibromyalgia, lower back pain</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Atypical or non-cardiac chest pain, syndrome-X</td>
</tr>
<tr>
<td>Respiratory medicine</td>
<td>Hyperventilation syndrome</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Chronic fatigue syndrome (CFS, ME)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Tension headache, non-epileptic seizure</td>
</tr>
<tr>
<td>Dentistry</td>
<td>Temporomandibular joint dysfunction, atypical facial pain</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>Globus syndrome</td>
</tr>
<tr>
<td>Allergy</td>
<td>Multiple chemical sensitivity (MCS)</td>
</tr>
<tr>
<td>?</td>
<td>Electricity hypersensitivity</td>
</tr>
<tr>
<td>?</td>
<td>Infrasound hypersensitivity</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>WAD – Whiplash ass. disorder</td>
</tr>
<tr>
<td>Anaesthesiology</td>
<td>Chronic benign pain syndrome</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Somatoform disorders, Neurastenia, Dissociative (conversion)</td>
</tr>
</tbody>
</table>
Prevalence self-reported functional somatic syndromes in the general Danish population

<table>
<thead>
<tr>
<th>Have you been told by a physician that you suffer from any of the following conditions?</th>
<th>Males N=3460</th>
<th>Females N=4040</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td>0.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td>IBS</td>
<td>7.6%</td>
<td>15.2%</td>
</tr>
<tr>
<td>CFS/ME</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>MCS</td>
<td>1.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>WAD</td>
<td>2.1%</td>
<td>3.7%</td>
</tr>
<tr>
<td>One of above</td>
<td>10.0%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Two or more of above</td>
<td>1.1%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Dantoft, T.M. et al Clinical Epidemiology 2017
Fractionated specialized clinics

- Infectious medicine
  - CFS

- Gastroenterology
  - IBS

- Rheumatology
  - Fibromyalgia

- Neurology
  - Headache

- Anaesthesiology
  - Pain

- Others

- Primary care

- Functional or idiopathic symptoms

- CFS clinic

- IBS clinic

- FM clinic

- Headache

- Pain clinic

- Others

(+/- multidisciplinary clinics)

Gen. medicine

General psychiatry
- Somatoform and related disorder

CL-psychiatry

Fink et al. Current state of management and organisation of care in: Medically unexplained symptoms, somatisation and bodily distress: Developing better clinical services. Cambridge University Press 2011
Specialized clinic for Bodily Distress Syndrome including functional somatic syndromes

Infectious medicine
CFS

Gastroenterology
IBS

Rheumatology
Fibromyalgia

Neurology
Headache

Anaesthesiology
Pain

Others

Functional disorders / Bodily distress
If necessary, separate programs for various syndromes

Primary care
Functional or idiopathic symptoms

General psychiatry
Somatoform and related disorder

CL psychiatry

Fink et al. Current state of management and organisation of care in: Medically unexplained symptoms, somatisation and bodily distress: Developing better clinical services. Cambridge University Press 2011
Functional somatic syndromes and disorders  
- common factors

- The common basis is that:
  - the diagnoses are solely based on the patients’ reports on subjective complaints
  - no true biomarkers or paraclinical tests can objectively verify the diagnoses
  - the complaints are mainly unspecific symptoms that are common in the general population

Fink P. J Psychosom Res. (in press 2017)
Functional disorders and syndromes

- Diagnostic constructs based on 3-4 different principles:
  - Symptoms or symptom counts
  - Symptom pattern/illness picture
  - Psychological and behavioural characteristics
  - Assumed aetiology (i.e. Central Sensitivity Syndrome) or illness attribution ("Blame–X syndrome")

Fink P. J Psychosom Res. (in press 2017)
### Symptom groups are stable across studies

#### Table 1.2 Symptom clusters or factors in patients presenting with bodily distress

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment instrument</th>
<th>Setting</th>
<th>Symptom cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al. (1996) (8)</td>
<td>CIDI</td>
<td>Primary care</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Liu et al. (1997) (45)</td>
<td>DIS</td>
<td>General population</td>
<td></td>
</tr>
<tr>
<td>Robbins et al. (1997) (46)</td>
<td>CIDI</td>
<td>Primary care</td>
<td>Musculoskeletal/pain</td>
</tr>
<tr>
<td>Gara et al. (1998) (44)</td>
<td>CIDI, DIS</td>
<td>Primary care, neurological, internal medicine</td>
<td>Cardiopulmonary</td>
</tr>
<tr>
<td>Fink et al. (2007) (7)</td>
<td>SCAN</td>
<td>General population</td>
<td></td>
</tr>
<tr>
<td>Rosmalen et al. (2011) (47)</td>
<td>PHQ-15</td>
<td>General population</td>
<td></td>
</tr>
<tr>
<td>Kroenke et al. (1998) (48)</td>
<td>PHQ-15</td>
<td>General population</td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2011)(49)</td>
<td>PHQ-15</td>
<td>General population, primary care, neurological</td>
<td></td>
</tr>
<tr>
<td>Whitthöfft et al. (2012) (55)</td>
<td>PHQ-15</td>
<td>General population</td>
<td></td>
</tr>
</tbody>
</table>

**Symptom cluster: Gastrointestinal**: +

**Symptom cluster: Musculoskeletal/pain**: +

**Symptom cluster: Cardiopulmonary**: +

**Symptom cluster: Fatigue/general**: -

**Symptom cluster: Headache**: -

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CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; PHQ, Patient Health Questionnaire.

*a* Confirmatory analyses of 3 and 4 factor models previously reported by Kroenke et al. and Fink et al.  
*b* General population.  
*c* Primary care.  
*d* Somatic anxiety

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Fink & Schröder *J Psychosom Res* 2010, Budtz-Lilly et al. 2015
Bodily distress syndrome = BDS, suggested diagnostic criteria

1. Types
   1. Multi-organ type >=3 symptoms from 3-4 organ systems
   2. Single-organ type >=3 symptoms from 1-2 organ systems
2. The symptoms are distressing or cause substantial distress
3. Relevant differential diagnoses have been ruled out
4. Duration > 6 mdr. (ICD-11 PC)

<table>
<thead>
<tr>
<th>No</th>
<th>Organ systems</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 3 Cardiopulmonary /autonomic arousal</td>
</tr>
<tr>
<td></td>
<td>Palpitations, heart pounding, precordial discomfort, breathlessness without exertion, hyperventilation, hot or cold sweats, trembling or shaking, dry mouth, churning in stomach, &quot;butterflies&quot;, flushing or blushing</td>
</tr>
<tr>
<td></td>
<td>≥ 3 Gastrointestinal arousal</td>
</tr>
<tr>
<td></td>
<td>Frequent loose bowel movements, abdominal pains, feeling bloated, full of gas, distended, heavy in the stomach, regurgitations, constipation, nausea, vomiting, burning sensation in chest or epigastrium</td>
</tr>
<tr>
<td></td>
<td>≥ 3 Musculoskeletal tension</td>
</tr>
<tr>
<td></td>
<td>Pains in arms or legs, muscular aches or pains, feelings of paresis or localized weakness, back ache, pain moving from one place to another, unpleasant numbness or tingling sensations</td>
</tr>
<tr>
<td></td>
<td>≥ 3 General symptoms</td>
</tr>
<tr>
<td></td>
<td>Concentration difficulties, impairment of memory, fatigue, headache, dizziness</td>
</tr>
</tbody>
</table>
Implications for new classification

• Bodily distress syndrome
  – Severe (multi-organ system type)
  – Moderate (single-organ system type)
    • CP type
    • GI type (incl. IBS)
    • MS type (incl. Fibromyalgia)
    • General symptoms type (incl. CFS/ME)

• Health anxiety
• Others

Fink P. & Schröder A. *J Psychosom Res* 2010
Central sensitization can be defined as an amplification of neural signaling within the CNS. When the response is prolonged, central sensitization becomes a pathological state characterized by a dysfunctional response to different and normally non-noxious stimuli that can manifest itself as pain hypersensitivity.
"Because the BDS concept is developed by psychiatrists it is a mental disorder."

Yunus MB Current Rehumatology Review 2015
Bodily distress syndrome (BDS). The FIP study. Labour market drop-out at index consultation in primary care

<table>
<thead>
<tr>
<th>Labour market drop-out</th>
<th>Bodily Distress Syndrome</th>
<th>Control</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-organ type (n=124) (a)</td>
<td>Multi-organ type (n=35) (b)</td>
<td>Control (n=880) (c)</td>
</tr>
<tr>
<td>Available for labour market</td>
<td>79.0 %</td>
<td>69.0 %</td>
<td>92.9 %</td>
</tr>
<tr>
<td>Partial/full disability pension</td>
<td>17.5 %</td>
<td>27.6 %</td>
<td>3.3 %</td>
</tr>
<tr>
<td>Age retirement pension</td>
<td>3.5 %</td>
<td>3.5 %</td>
<td>3.8 %</td>
</tr>
</tbody>
</table>

**Risk of new awards of full or partial disability pension.**  
Ten years of follow-up, primary care. Bodily distress

<table>
<thead>
<tr>
<th>Hazard ratios (95%CI)</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference group (n=880)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BDS, single-organ type (n=124)</td>
<td>5.8 (3.6;9.3)</td>
<td>4.9 (2.8 ; 8.4)</td>
</tr>
<tr>
<td>BDS, multi-organ type (n=35)</td>
<td>8.0 (3.8;16.9)</td>
<td>8.7 (3.7 ; 20.7)</td>
</tr>
</tbody>
</table>

*Adjusted: Age, gender, chronic illness, major depressive episode, anxiety disorder and intervention

Bodily distress - a spectrum

The healthcare system is contacted

Normal physiological reaction
Temporary symptoms
Mild bodily distress
Severe bodily distress

Symptoms & complaints
Multiple symptoms
Multisomatoform disorder
Bodily distress syndrome
- Functional somatic syndrome
- Somatoform disorders
Bodily Distress Syndrome

Conclusion

- The construct is empirically based on patients from different clinical settings
- It is based on the identification of symptom patterns (not symptom count)
- It does not include psychological or behavioral symptoms/criteria
- Despite this it includes almost all patients with DSM-IV somatoform disorder characterized by physical symptoms
- It includes almost all patients with the most common functional somatic syndromes
- It includes both patients with multiple symptoms and sub-categories.
Video BDS
Health / Illness anxiety
Health anxiety is relatively easy to diagnose. Patients accept the diagnosis and are pleased with the treatment. A range of well-documented treatment options exist.
# Diagnostic criteria for Health anxiety

<table>
<thead>
<tr>
<th>+</th>
<th><strong>1) Ruminations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a) If you think about having a disease or being seriously ill, do you find it difficult to get it off your mind again? Are you thinking about it constantly or are you winding yourself up?</td>
</tr>
<tr>
<td>+</td>
<td>b)</td>
</tr>
<tr>
<td>+</td>
<td>2) Suggestibility or auto-suggestibility</td>
</tr>
<tr>
<td>+</td>
<td>3) Preoccupation with health literature</td>
</tr>
<tr>
<td>+</td>
<td>4) Fear of contamination or poisoning</td>
</tr>
<tr>
<td>+</td>
<td>5) Fear of taking medicine</td>
</tr>
<tr>
<td>+</td>
<td>Specific: Mild or severe according to impairment</td>
</tr>
<tr>
<td>+</td>
<td>Lasts more than 2 weeks</td>
</tr>
</tbody>
</table>

Fink et al. *Am J Psych* 2004
Video HA
When the body says stop

ETIOLOGY

BDS

The are many causes for functional disorders.

The Danish Committee for Health Education
Etiology
(brief)

Vulnerability:
Biological, psychological and social heritage, social learning, previous illnesses, sexual abuse

Triggering factors:
Infection or other diseases
Physical or psychological trauma, stress or strain
The doctor
"Random” findings at examination

Illness

Chronic illness

Biological factors

- Increased symptom production
- Pathological central processing and modulation of body signals
The Research Clinic for Functional Disorders and Psychosomatics

Unspecific sensitivity to bodily symptoms

Bodily distress

Autonomic arousal & HPA axis hyperactivity

Cardio-pulmonary arousal

Gastro-intestinal arousal

Muskuloskeletal tension

General stress response

Fink P. et al Psychosomatic Medicine 2007
Women 6 weeks after sexual assault (n = 83)

Men and women 6 weeks after MVC (n = 948)

McLean et al, Pain 2014

Ulirsch et al, European J Pain 2013
Etiology (brief)

Vulnerability:
Biological, psychological and social heritage, social learning, previous illnesses, sexual abuse

Triggering factors:
Infection or other diseases
Physical or psychological trauma, stress or strain
The doctor
"Random" findings at examination

Maintaining factors:
Dysfunctional beliefs about symptoms and illness
Dysfunctional illness behaviour
Hypersensitisation and/or dysfunctional processing of symptoms in the CNS
The health system
Social and economical dependence

Illness

Chronic illness

Doctor, I feel worn out and unfocused

You just need a break and a change

Why don’t you take a long weekend and go raid England a little..
Evidence for antidepressants, aerobic exercise and psychological interventions in different subtypes of bodily distress

<table>
<thead>
<tr>
<th>Symptom profile (BDS subtype) and corresponding functional somatic syndrome or diagnostic label</th>
<th>Type of treatment</th>
<th>( + )</th>
<th>( +++ )</th>
<th>( +++ )</th>
<th>( ? )</th>
<th>( ++ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS type Chronic Fatigue Syndrome</td>
<td>Antidepressants</td>
<td></td>
<td>( +++ )</td>
<td>( +++ )</td>
<td>( ? )</td>
<td>( ++ )</td>
</tr>
<tr>
<td>MS type Fibromyalgia</td>
<td>Exercise</td>
<td>( +++ )</td>
<td>( +++ )</td>
<td>( ? )</td>
<td>( ? )</td>
<td>( + )</td>
</tr>
<tr>
<td>GI type Irritable bowel syndrome</td>
<td>Psychological treatment (mainly CBT)</td>
<td>( +++ )</td>
<td>( +++ )</td>
<td>( ++ )</td>
<td>( ++ )</td>
<td>( +++ )</td>
</tr>
<tr>
<td>CP type Non-cardiac chest pain</td>
<td>Multi-organ type</td>
<td>Multiple medically unexplained symptoms and somatization disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evidence ratings are based on meta-analyses or high-quality randomized controlled trials.

- \( +++ \) strong evidence
- \( ++ \) moderate evidence
- \( + \) weak evidence
- \( ? \) no evidence or lack of studies

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Reality</th>
</tr>
</thead>
</table>
| The patients misinterpret normal physical sensations as indication of severe disease | The case in health anxiety but not in BDS.  
The patients have their symptoms                                      |
| Preoccupation with their physical health and bodily sensations            | Suffering from symptoms                                                                          |
| High health care use - frequent attenders                                 | The patients cannot get any help or explanations  
A problem of the health care system                                         |
| It is a chronic illness                                                  | The same spectrum as in other disorders/diseases                                                  |
| Unresponsive to therapy                                                  | Quite good treatment results even in the chronic group                                             |
| The symptoms represent a (disguised) mental disorder                     | The problem is physical symptoms.  
It is a distinct disorder of its own                                            |

Fink P. Psychosom Res (in press 2017)
Bodily distress - a spectrum

The healthcare system is contacted

Normal physiological reaction
Temporary symptoms
Mild bodily distress
Severe bodily distress

Prevention
General population, doctors etc.

Managed in primary care
collaborative care with specialist

Treated in specialised care
multidisciplinary team
Functional Disorders and Medically Unexplained Symptoms
Assessment and treatment

Edited by Per Fink and Marianne Rosendal

NB: Free download as e-book during this conference!

Can also be purchased at Aarhus University Press
http://en.unipress.dk/
Price $35
RCT studies – Research Clinic for Functional Disorders

BDS- multiorgan type
1. Specialized Treatment for Severe bodily distress Syndrome (STreSS-1). **CBT** vs. control.

2. **Mindfulness** therapy for Bodily distress syndrome
   Fjorback LO et al. J.psych.res., January 2013

3. **Imipramine** versus placebo for multiple functional somatic syndromes (STreSS-3): a double-blind, randomised study
   Agger J et al. Lancet psychiatry, 2017

4. a) **ACT** in small groups vs. large groups
   b) ACT vs. standard treatment
   Under analyze

Health anxiety
5. ACT in groups vs. wait-list
   Eilenberg T. et al Psychological med 2015

6. **Internet based treatment** of Health Anxiety
   Ditte ? Under patient inclusions

Whiplash (WAD)
6. The effect of an educational video following acute whiplash trauma. A randomised controlled trial
   Petersen MM et al. under analyze

BDS-Multiorgan type -Adolescents
7. Acceptance and Commitment group therapy for adolescents with a range of functional somatic syndromes: randomized trial
   Rask C, Schröder A et al

Post-concussional syndrom (together with Neurological rehabilitation)
8. Early intervention for impairing post-concussional symptoms in adolescents and young adults:
   randomised trial
   Schröder A, Rask C et al
Assessment (4-6 hours)

- Review of medical records
- Screening questionnaires
- Biopsychosocial assessment
- Standardised psychiatric research interview (the SCAN modified)
- Physical and neurological examinations (not HA)
- Laboratory screening battery (not HA)
- Information about the diagnosis and guidance (psychoeducation)
Aim

To assess the efficacy of CBT group treatment (STreSS) for patients with severe FSS
(grouped under the unifying diagnosis multi-organ Bodily Distress Syndrome)

STreSS = Specialised Treatment for Severe bodily distress Syndromes
Outcome measures

Primary outcome measure:

- **Self-reported physical health at 16 months after randomization**, measured with SF-36-PPH (aggregate score of three SF-36 scales: physical functioning, bodily pain, vitality)*

Secondary outcome measures:

- Social level of functioning (SF-36),
- Emotional problems (SF-36, SCL-8 scale),
- Self-rated bodily distress (SCL-90 Somatisation subscale),
- Illness worry (Whiteley-7 scale)

Schröder et al. *J Clin Epidemiology* 2011
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bodily Distress Syndrome, multi-organ type, chronic (&gt; 2 years)</td>
<td>• No informed consent</td>
</tr>
<tr>
<td>• No severe psychiatric comorbidity (psychosis)</td>
<td>• Abuse of narcotics, alcohol or (non-prescribed) medicine</td>
</tr>
<tr>
<td>• Age 20-45</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Patients who understand, read, write and speak Danish (Scandinavian origin)</td>
<td>• Litigation</td>
</tr>
</tbody>
</table>
## Interventions

<table>
<thead>
<tr>
<th>Both groups:</th>
<th>Intervention group only:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. assessment</td>
<td>a. letter with recommendations</td>
</tr>
<tr>
<td>c. letter to GP</td>
<td>b. treatment manual</td>
</tr>
<tr>
<td>d. usual care</td>
<td>c. consultancy service</td>
</tr>
<tr>
<td></td>
<td>d. CBT in groups</td>
</tr>
<tr>
<td></td>
<td>e. close co-operation with employer or social authorities</td>
</tr>
</tbody>
</table>
Treatment manual

• Treatment delivered in groups of 9 patients by 2 psychiatrists
• Based on a cognitive-behavioural approach

Specialised Treatment for Severe Bodily Distress Syndromes (STreSS)

Aesop’s fable: “The hare and the tortoise”

“Slow but steady wins the race”

Emma Rehfeld, Andreas Schröder & Per Fink
The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Denmark 2009
Real disorder

Impact of beliefs

Neurobiological basis

Individual perpetuating factors (cognitive and behavioral)

Increasing healthy behaviour (individual treatment plan)

Relapse prevention / definition of individual goals for the next months

<table>
<thead>
<tr>
<th>Module</th>
<th>Week</th>
<th>Content and Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} Module</td>
<td>1</td>
<td>Introduction to STreSS</td>
</tr>
<tr>
<td>2\textsuperscript{nd} Module</td>
<td>2</td>
<td>Bodily symptoms and their interpretation</td>
</tr>
<tr>
<td>3\textsuperscript{rd} Module</td>
<td>3</td>
<td>Illness perceptions. Stress response. Treatment goals.</td>
</tr>
<tr>
<td>4\textsuperscript{th} Module</td>
<td>4</td>
<td>Negative automatic thoughts and dysfunctional behaviours</td>
</tr>
<tr>
<td>5\textsuperscript{th} Module</td>
<td>6</td>
<td>Cognitive distortions and emotional awareness.</td>
</tr>
<tr>
<td>6\textsuperscript{th} Module</td>
<td>8</td>
<td>From illness behaviour to health behaviour I</td>
</tr>
<tr>
<td>7\textsuperscript{th} Module</td>
<td>10</td>
<td>From illness behaviour to health behaviour II</td>
</tr>
<tr>
<td>8\textsuperscript{th} Module</td>
<td>12</td>
<td>Becoming your own therapist. Relapse prevention</td>
</tr>
<tr>
<td>9\textsuperscript{th} Module</td>
<td>16</td>
<td>How to maintain learned skills and coping strategies</td>
</tr>
</tbody>
</table>
278 consecutive patients, referred from primary and secondary care

114 excluded from clinical assessment
- 74 did not meet inclusion criteria
- 52 were not 20-45 years old
- 22 would not reach diagnostic criteria
- 40 met exclusion criteria
- 26 with current litigation claim

147 patients underwent clinical assessment

22 excluded from randomisation
- 20 did not reach diagnostic criteria
- 2 met exclusion criteria
- 1 with pregnancy
- 1 with current litigation claim

120 patients enrolled and randomised

54 allocated to STReSS
66 allocated to enhanced usual care
Trial profile
intervention and follow-up

120 patients enrolled and randomised

54 allocated to STReSS
- 45 (83 %) received STReSS
- 6 (11 %) did not receive STReSS
  - 2 felt too ill to participate
  - 2 did not want to work in a group
  - 2 were not able to spend the time
- 3 (6 %) discontinued STReSS
  - 1 moved to a secret address
  - 1 relapsed with alcohol abuse
  - 1 could not tolerate the group

66 allocated to enhanced usual care
- 66 (100 %) received enhanced usual care
  - No restrictions on psychological or pharmacological interventions
  - No restrictions on referrals to secondary care or to mental health services

44 followed for 16 months

54 analysed in ITT population
- 3 with baseline data only
- 51 with data at follow-up

50 followed for 16 months

66 analysed in ITT population
- 6 with baseline data only
- 60 with data at follow-up
### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>STreSS group (N=54)</th>
<th>Enhanced Usual Care group (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.4 (6.3)</td>
<td>36.2 (6.5)</td>
</tr>
<tr>
<td>Female gender</td>
<td>40 (74 %)</td>
<td>55 (83 %)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic school (7th — 10th)</td>
<td>31 (57 %)</td>
<td>36 (55 %)</td>
</tr>
<tr>
<td>Further education</td>
<td>23 (43 %)</td>
<td>30 (45 %)</td>
</tr>
<tr>
<td><strong>Work status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed or student</td>
<td>26 (48 %)</td>
<td>21 (32 %)</td>
</tr>
<tr>
<td>Of these on sick leave</td>
<td>7 (13 %)</td>
<td>8 (12 %)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>21 (39 %)</td>
<td>26 (39 %)</td>
</tr>
<tr>
<td>Disability pension or flexible work</td>
<td>7 (13 %)</td>
<td>19 (29 %)</td>
</tr>
<tr>
<td><strong>Number of functional somatic symptoms</strong></td>
<td>32.3 (7.5)</td>
<td>32.6 (10.0)</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>6.7 (3-14)</td>
<td>9.5 (4-15)</td>
</tr>
<tr>
<td>Clinician rated impairment in daily living</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>17 (31 %)</td>
<td>15 (22 %)</td>
</tr>
<tr>
<td>Severe</td>
<td>37 (69 %)</td>
<td>51 (78 %)</td>
</tr>
<tr>
<td><strong>Functional somatic syndromes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>30 (56 %)</td>
<td>41 (62 %)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>38 (70 %)</td>
<td>40 (61 %)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>19 (35 %)</td>
<td>24 (36 %)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>28 (52 %)</td>
<td>34 (52 %)</td>
</tr>
<tr>
<td>Hyperventilation syndrome</td>
<td>10 (19 %)</td>
<td>12 (18 %)</td>
</tr>
<tr>
<td>Tension headache</td>
<td>41 (76 %)</td>
<td>48 (73 %)</td>
</tr>
<tr>
<td>At least one of the above diagnoses</td>
<td>53 (98 %)</td>
<td>60 (91 %)</td>
</tr>
</tbody>
</table>

*Patients have long-lasting illness*

*Patients reach criteria for more than one functional somatic syndrome*
Patient characteristics II

<table>
<thead>
<tr>
<th></th>
<th>STreSS group (N=54)</th>
<th>Enhanced Usual Care group (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current psychiatric comorbidity (DSM-IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>9 (17 %)</td>
<td>14 (21 %)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>2 (4 %)</td>
<td>3 (5 %)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>10 (19 %)</td>
<td>12 (18 %)</td>
</tr>
<tr>
<td>At least one of the above diagnoses</td>
<td>16 (30 %)</td>
<td>24 (36 %)</td>
</tr>
<tr>
<td><strong>Lifetime psychiatric comorbidity</strong></td>
<td>31 (57 %)</td>
<td>40 (61 %)</td>
</tr>
<tr>
<td><strong>Health related quality of life</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived physical health score (15-65)</td>
<td>36.4 (8.8)</td>
<td>34.6 (7.5)</td>
</tr>
<tr>
<td>Social functioning score (0-100)</td>
<td>57.6 (24.6)</td>
<td>54.2 (29.7)</td>
</tr>
<tr>
<td>Mental health score (0-100)</td>
<td>61.6 (16.9)</td>
<td>59.3 (20.1)</td>
</tr>
<tr>
<td><strong>Illness severity</strong>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical symptoms score (0-4)</td>
<td>1.65 (0.67)</td>
<td>1.66 (0.71)</td>
</tr>
<tr>
<td>Illness worry score (0-4)</td>
<td>1.21 (0.57-1.86)</td>
<td>1.00 (0.57-1.86)</td>
</tr>
<tr>
<td>Depression / Anxiety score (0-4)</td>
<td>0.81 (0.50-2.13)</td>
<td>1.25 (0.63-2.00)</td>
</tr>
</tbody>
</table>

Data are number (%), mean (SD), or median (IQR).
Results
Effect of STreSS on primary outcome

Physical Health (Primary outcome)

<table>
<thead>
<tr>
<th>SF-36 Perceived physical health score</th>
<th>Enhanced usual care</th>
<th>STreSS</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>30</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>45</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>50</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- **Enhanced usual care**
- **STreSS**
- **Effect size**

- Improvement
- Norm

- Group * time: p<0.0001

**Treatment period**
- Baseline
- 4 months
- 10 months
- 16 months

**Follow-up period**
Illness severity more important than diagnostic label

Figure: Effect of cognitive-behavioural group treatment in various subgroups

Schröder et al. Lancet Psychiatry 2015
Is group CBT cost-effective over a medium-length period (16 months)?
Group CBT saved health care costs

Total annual healthcare costs

<table>
<thead>
<tr>
<th></th>
<th>1 year before</th>
<th>Treatment period</th>
<th>1 year after</th>
<th>2 years after</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUC</td>
<td>4106</td>
<td>976</td>
<td>4200</td>
<td>3937</td>
</tr>
<tr>
<td>STreSS</td>
<td>3544</td>
<td>2369</td>
<td>2250</td>
<td>2560</td>
</tr>
</tbody>
</table>

difference (bootstrap, ASL<0.05)

<table>
<thead>
<tr>
<th></th>
<th>no</th>
<th>yes (STreSS&gt;EUC)</th>
<th>yes (STreSS&lt;EUC)</th>
<th>yes (STreSS&lt;EUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline-adjusted difference (estimate):</td>
<td>-</td>
<td>+1545</td>
<td>-1569</td>
<td>-1133</td>
</tr>
</tbody>
</table>

… from the second year after treatment

Treatment costs in similar studies:

➢ Multi-centre study in Germany, individual psychodynamic therapy (Sattel et al. BJP 2012): 893 € (Chernyak et al. PLoS One 2014)


Schröder et al. J Psychosom Res 2017
Group CBT vs EUC:

\[ \Delta = 10.4 \text{ weeks} \]

(95% CI 3.5; 17.4)

Number of weeks where patients and population controls received benefits or were self-supporting.

Modified from: Schröder et al. *J Psychosom Res* 2017
Imipramine versus placebo for multiple functional somatic syndromes (STReSS-3): a double-blind, randomised study

Johanne L. Agger, Andreas Schröder, Lise K. Gormsen, Jens S. Jensen, Troels S. Jensen, Per K. Fink

Summary
Background Functional somatic syndromes, including chronic fatigue syndrome or irritable bowel syndrome, often co-exist. Treatment guidelines supported by high quality evidence exist for most functional somatic syndromes, but are lacking for multiple comorbid functional somatic syndromes. We aimed to assess the effect of the tricyclic antidepressant, imipramine, in patients with multiple functional somatic syndromes defined by the criteria for multiorgan bodily distress syndrome, a unifying diagnosis that encompasses most functional somatic syndromes and somatoform disorders.

Methods In this single-centre, double-blind, randomised trial done in a Danish university hospital setting, participants were patients consecutively referred (age 20–50 years) fulfilling criteria for multiorgan bodily distress syndrome with no concurrent comorbid depression or anxiety disorder. Participants were randomly assigned (1:1) to receive either 10 weeks of low-dose imipramine or placebo (oral daily doses of 25–75 mg). The hospital pharmacy handled randomisation (computer-generated) and masking, providing sequentially numbered packs of study drug that were given serially to the participants. All others involved were blinded to allocation. Primary outcome was...
Two separate trials running in parallel*:

1: Imipramine versus placebo, a double-blind randomized trial

2: ACT versus single consultation, a three-armed randomized trial, ACT delivered as
   - 9-session group therapy or
   - one-day workshop and follow-up consultation

Patients' preference*
Shared treatment recommendations in single FSS/single-organ BDS

- Psychotherapy\textsuperscript{1}
- Centrally acting drugs\textsuperscript{1}

Pharmacological recommendations in multiple FSS/BDS-multiorgan type
- No evidence

Why low-dose imipramine (TCA)?
- Pain modulating properties
- As effective as newer centrally acting drugs\textsuperscript{2}

\textsuperscript{1} Henningsen. Lancet 2007. \textsuperscript{2} Wolfe. Eur J Pain 2013
Multiple FSS ≈ multi-organ Bodily Distress Syndrome (BDS)

Aim

To test the effect of 10 weeks of low-dose imipramine in patients with multiple FSS in a double-blind, randomized trial

Agger JL. et al Lancet Psych. 2017
Hypotheses and outcome measures

Imipramine improves:

1. Patient-rated overall health

2. Physical, mental and social health (SF-36, SCL-92, Whiteley-7)
   - compared to placebo after 10 weeks of treatment

Clinical Global Improvement Scale CGI:
How do you consider your health status now compared with when you first came to the clinic?

- Much worse
- Worse
- Unchanged
- Better
- Much better

Agger JL. et al Lancet Psych. 2017
Treatment imipramine/placebo

methods

Agger JL. et al Lancet Psych. 2017
551 patients screened for eligibility

418 assessed for eligibility

133 excluded
124 did not meet criteria for multi-organ BDS/multiple FSS
9 did not meet criteria for origin, age (20-50) or duration (2 yrs)

161 excluded
57 treatment-demanding psychiatric disorder
45 received pain modulating drugs
19 had insufficient contraception
18 imipramine was contraindicated
8 treatment-demanding physical disease
14 other

138 randomized

118 declined to participate

Agger JL. et al Lancet Psych. 2017
138 randomized

70 allocated to imipramine
65 received at least one dose of study drug
8 discontinued intervention
4 due to adverse events
4 other
57 completed per protocol
65 included in ITT analysis

68 allocated to placebo
60 received at least one dose of study drug
7 discontinued intervention
3 due to adverse events
4 other
53 completed per protocol
60 included in ITT analysis
## Primary outcome

<table>
<thead>
<tr>
<th>CGI-5</th>
<th>Imipramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much worse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Worse</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Unchanged</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Better</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Much better</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>65</strong></td>
<td><strong>60</strong></td>
</tr>
</tbody>
</table>

OR for an improved outcome with imipramine of estimated 3.3 (95% CI 1.61-6.76); p<0.001

Agger JL. et al Lancet Psych. 2017
Secondary outcomes

Difference between groups adjusted for baseline (per protocol)

Conclusion and implications

Low-dose imipramine was superior to placebo in improving
• Self-reported overall health
• Physical health, somatic symptom burden and illness worry

Low-dose imipramine was NOT superior to placebo in improving
• Mental health and social functioning

Adverse events were common, but tolerable
Tolerability of adverse events may increase with regular contacts and psychoeducation
(only 4 (6%) dropout in imipramine group vs 3 (5%) in placebo group)
Current treatment of functional disorders
Modular treatment

Assessment
3-5 hours

BDS school
3 hours

Individual treatment plan

ACT
6 x 3 hours
8-10 patients

MBSR
9 x 3 hours
15-20 pat.

Consultation:
Adjust treatment plan

Imipramine?

Collaborative care?

General practitioner

Pedersen HF et al. Presentation at EAPM 2016, Luleå
Thank you!

Homepage: Functionaldisorder.dk