

Acceptance and Commitment Group Therapy (ACT-G) for health anxiety

A randomised, controlled trial

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THE 3 ORIGINAL PAPERS ARE

Paper I. Eilenberg T, Kronstrand L, Fink P, Frostholm L. Acceptance and commitment group therapy for health anxiety - Results from a pilot study. *J Anxiety Disord* 2013 Jun 19;27(5):461-8.

Paper II. Eilenberg T., Fink P., Jensen JS, Rief W., Frostholm L. Acceptance and Commitment Group Therapy (ACT-G) for health anxiety: A randomised, controlled trial. *Psychological Med* 2015;46(01):103-15.

Paper III. Eilenberg T, Frostholm L, Schröder A, Jensen JS, Fink P. Long-term consequences of severe health anxiety on sick leave in treated and untreated patients: Analysis alongside a randomised controlled trial. *J Anxiety Disord* 2015;32:95-102.

SETTING AND OUTLINE OF THE THESIS

Outline

The present thesis examines whether group therapy combining well-known cognitive-behavioral strategies with an acceptance-based approach (Acceptance and Commitment Therapy in groups, ACT-G) improves symptoms of illness worry (paper I) compared to a waitlist condition in patients with severe health anxiety (paper II). Furthermore, it is investigated whether persons with untreated severe health anxiety a) have higher levels of sick leave compared with the general population, and b) experience a decrease in sick leave in the year following ACT-G treatment (paper III). Throughout the thesis, the term health anxiety is used synonymously with designations such as hypochondriasis,

abridged hypochondriasis, hypochondrial disorder and illness anxiety disorder, unless differences between the diagnostic labels are discussed.

The thesis begins with a general introduction to health anxiety with special emphasis on classification of health anxiety and Perspectives on essential features and psychological treatment of health anxiety. The aims of this thesis are presented after that introduction.

The thesis deals with treatment of severe health anxiety and describes a pilot study testing the feasibility and acceptance of ACT-G for severe health anxiety (paper I) before initiating a randomised controlled trial (RCT). It continues to describe how ACT-G was implemented in an RCT and evaluates the treatment effect on illness worry and secondary outcomes of emotional distress, physical symptoms and health-related quality of life as well as the level of acceptance of the research diagnosis health anxiety¹ (paper II). The treatment manual can be requested from the author.

The thesis also concerns the influence of severe health anxiety on sick leave compared with a matched general population sample and explores the one-year treatment effect of ACT-G on sick leave among patients with severe health anxiety (paper III).

As the primary objective of this PhD project was conducting and evaluating the RCT trial, the general discussion on methods and results in this thesis will predominantly be focused on aspects of the RCT⁴.

The thesis continues with a general discussion on methods and a summary of results in relation to the aims of the thesis followed by an overall discussion of results, perspectives for further research, English and Danish summaries and a reference list.

Setting

Paper I provides original data from a pilot study (n=34) carried out at the Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Denmark between 2009 and 2010. Paper II provides original data from 126 patients enrolled in an RCT carried out at the Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Denmark between 2010 and 2012 (the trial is registered at clinicaltrials.gov, no. NCT01158430). Designing, conducting and evaluating the RCT trial were the primary objectives of this PhD project. Paper III provides original data from a national database on sickness-related benefits from the 126 patients enrolled in the RCT

and a matched general population sample of 12,600 individuals and assesses the effect of severe health anxiety on sick leave.

INTRODUCTION

Aims

A brief overview is given of how health anxiety has been conceptualised and classified over the years. The aim of the overview is to identify some of the key issues with respect to classification and labelling of the disorder that have caused major obstacles for research and may have hindered effective patient care ⁵. The introduction will initially present two vignettes to illustrate the multifaceted phenomenon of health anxiety. Furthermore, a brief overview of essential features of severe health anxiety will be outlined in order to give a better understanding of how health anxiety is currently treated. Finally, the new treatment approach Acceptance and Commitment Therapy (ACT) for health anxiety is described.

What is health anxiety?

Health anxiety may be seen as a multifaceted phenomenon ranging from mild and transient to severe and chronic conditions ⁶. Most people have experienced transient health anxiety at times when experiencing unpleasant and persistent symptoms. For some people, worry and rumination about illness becomes a maladaptive behaviour as the rumination and perceived risk are out of proportion with the objective degree of medical risk and hence cause great personal suffering and widespread impairment. The vignettes serve to illustrate two examples of patients both suffering from impairing health anxiety, but who show very different behavioural patterns.

Vignette 1.

Peter is a 45-year-old academic who suffers from a strong, bothersome inclination to always be afraid of being seriously ill. It is especially cancer that he fears. Peter remembers from his childhood that both his mother and grandmother often expressed concerns regarding illnesses. Peter's worries regarding illness changed dramatically as he himself became a parent at the age of 30. From this time whenever Peter is aware of the slightest change in bodily sensations, that be a headache or a mark on the skin, he is unable to concentrate on any task till his general practitioner (GP) reassures him that his symptoms are harmless and normal. Also, Peter is a frequent user of medical homepages trying himself to classify his symptoms. Peter's social relationships are burdened by his worries as he brings up topics regarding illness in most conversations. Over the years Peter experience that reassurance from his GP had less positive impact on his worries – he can no longer believe it when his GP tells him that he needs no more tests and that there is no need to worry. Even though, Peter no longer experiences a relief in worry when consulting his GP, he still frequently contacts him. Lately, Peter has made an appointment with a private hospital in order to get a brain scan, as he fears he has a brain tumour and his GP will not refer him to any more tests.

Vignette 2.

Ann is a 55-year old married woman working in a sales office. Ann starts training as a nurse at the age of 20. During her training as a nurse she becomes increasingly occupied by sensations in her body. More and more often when she in her training is confronted with symptoms of illness, she experiences the same symptoms herself. Ann is aware of this pattern and finds it very humiliating; still she is unable to control her rumination about illness. After one year of training as a nurse she decides to drop out. At first Ann finds a relief in illness worries, but in order to control her worries she has to perform a ritual of self-examination several times a day. Also, Ann finds that if she keeps herself very occupied all day she can keep the worries at a distance. To be able to sleep at night Ann has to take sleeping pills. Though Ann is severely impaired by her illness worries, and even unable to be in a relationship because of this, she never talks about her illness worries or have any contact with the health care system. She does not respond to the preventive check ups (e.g. mammography, smear test) offered in the health care system as she is too afraid of the results.

The behavioural patterns seen in the cases may be categorised as respectively care-seeking and care-avoidant behaviour ⁷. Yet, these patterns are not thought of as definitive characteristics of severe health anxiety, other characteristics could just as well have been highlighted. Primarily, the two cases are chosen to illustrate that patients with severe health anxiety may present quite differently, but still share the excessive ruminations with intrusive worries about harbouring serious illness and a persistent preoccupation with health leading to significant impairment. In the present thesis, the focus will be on patients suffering from severe and impairing health anxiety.

Diagnostic classification of health anxiety

The term hypochondriasis is for most people considered a stigmatising label that has a pejorative connotation as it implies that the symptoms are not real and that it is all “in your mind”, bordering on faking ⁸. Therefore, health anxiety has been suggested as replacement, and in the present thesis, this designation and diagnostic criteria will be used.

The view of health anxiety has changed significantly throughout times, yet the term hypochondria has been in use since ancient times. In 460 BC Hippocrates referred to it as the anatomical region that is located under the curvature and it was assumed that hysteria was due to a migrant uterus ⁹. From around the 19th century and until a renewed interest arose in the 1960s, this condition received scarce attention in the literature as hypochondria was considered a manifestation of neurasthenia ¹⁰. Hence, hypochondriasis was first included in the official classification system of DSM-II in 1968 ¹¹ as a neurosis under the designation hypochondrical neurosis and with a focus on *bodily preoccupation and fear of having a disease*. In 1980, with the introduction of the DSM-III ¹², it was added that the preoccupation and fear was characterised by *unrealistic interpretation* of physical signs and sensations and that these symptoms *could not be explained* by another disorder, nor could the patient's fear or belief be dismissed through *repeated medical reassurance*. In the DSM-III edition, hypochondriasis was now moved to the new diagnostic group of somatoform disorders including a group of mental disorder

ders that predominantly manifested themselves as physical symptoms. In the revised DSM-III¹³, a duration criteria of minimum 6 months was added. The definition of hypochondriasis was further refined in the DSM-IV edition¹⁴ in 1994 in which specific exclusionary criteria were added in order to better discriminate hypochondriasis from other disorders (e.g anxiety disorders, depressive disorders or other somatoform disorders) as well as the presence of significant distress or functional impairment. In cases where the full DSM-IV criteria for hypochondriasis are not met, due to one or more of the diagnostic features not being present, the condition has been called abridged hypochondriasis¹⁵.

In recent years, the DSM-IV hypochondriasis diagnosis has been criticised for being too restrictive^{15, 16} resulting in too low prevalence rates¹⁷ and neither satisfying clinical nor nosologic validity requirements¹. The empirical foundation for the DSM-IV criteria has been found poor as it has arisen from mainly clinical observations of patients in severely skewed psychiatric settings, even though the disorder is predominantly seen in medical settings¹. Especially criterion B regarding "appropriate medical evaluation and reassurance" has been criticised^{1, 15} as some patients deliberately avoid their general practitioner (GP) as a maladaptive avoidance (such as the patient in Vignette no 2) or due to dissatisfaction with previous health care experiences. Furthermore, criterion E regarding duration of symptoms for at least 6 months has been argued to be arbitrary and restrict the diagnosis to a chronic sample^{1, 18}.

In 2004, Fink et al.¹ introduced new and empirically-based positive diagnostic criteria for health anxiety, in which severe health anxiety is characterised by exaggerated rumination with intrusive worries about harbouring serious illness and a persistent preoccupation with one's health leading to significant impairment and a decrease in quality of life (see Table 1.1 for the research criteria for severe health anxiety). According to the new diagnostic criteria, health anxiety should no longer be a diagnosis of exclusion and may be helpful in providing patients with a positive explanation of their symptoms. In the trials of this PhD project, these diagnostic criteria have been used for inclusion.

Table 1. Diagnostic criteria for severe health anxiety¹

<p>Key criteria: Rumination with intrusive thoughts and ideas, and fears of harbouring an illness</p> <p>At least 1 of 5 sub-criteria;</p> <ol style="list-style-type: none"> 1) a) Worries, preoccupation or fear of harboring a severe physical disease <li style="padding-left: 20px;">b) Attention to an awareness of bodily functions 2) Suggestibility or autosuggestibility 3) Excessive fascination with medical information 4) Fear of being infected or contaminated 5) Fear of taking prescribed medication <p>Mild or severe according to influence on functioning and well-being</p> <p>Duration more than 2 weeks.</p>

This year, new diagnostic criteria for health anxiety have been introduced in DSM-V⁷, in which patients with former DSM-IV hypochondriasis are now subsumed under the classification of

Illness anxiety Disorder (excludes patients with moderate and severe somatic symptoms) or Somatic Symptom Disorder (SSD). It has recently been suggested that using the broadly defined DSM-IV hypochondriasis diagnostic criteria may result in a very heterogeneous sample^{1, 19} resembling the SSD criteria of the DSM-V more than that of the Illness anxiety disorder²⁰. The diagnostic health anxiety criteria used in the present thesis are found to be rather similar to the DSM-V Illness anxiety disorder, the difference between the two primarily being that the DSM-V diagnosis does not include the rumination symptom which is the key criteria of the health anxiety diagnosis, and furthermore the DSM-V diagnosis contrary to Fink et al.'s¹ excludes patients with moderate and severe somatic symptoms.

Overall, the lack of empirically valid diagnostic criteria have resulted in lacking expert consensus on how to classify or label patients with severe and persistent illness worry, which have hampered research and hence may have blurred the effect in trials of treatment for health anxiety. It is difficult to compare effects of treatment between studies when very different diagnostic labels and criteria have been used for inclusion. Furthermore, comparison between studies are also challenged by some studies identifying cases of health anxiety based on subjective scores on self-reported questionnaires on illness worry (with arbitrary cut-off criteria) compared to using diagnostic criteria for inclusion. This may potentially further blur the characteristics of the sample.

Boundaries of health anxiety and comorbidity

Like many clinical syndromes, health anxiety has characteristics that cross boundaries and suggest a shared aetiology with especially other somatoform disorders and anxiety disorders¹⁶. Health anxiety may be said to present with mixed symptoms of anxiety, such as rumination and catastrophic thinking, and somatic symptoms. Somatisation disorder and health anxiety share the presence of physical symptoms for which no organ-pathology can be found. Though, there is a difference in the way patients relate to symptoms and what is the main source of their distress. The majority of patients with somatoform syndromes experience that it is the somatic symptoms per se, such as unexplained pain, spasms, and fatigue, that cause distress, whereas for health anxiety, illness worry itself (rumination about the meaning, implication and consequences of the symptoms) is the primary problem suggested to arise from misperceptions of innocuous somatic symptoms²¹.

Although health anxiety remains classified as a somatoform disorder in the new DSM-V⁷, considerations regarding alternative classification as an anxiety disorder were made²² emphasising the conceptual relationship between health anxiety and anxiety disorders. Also, some evidence for phenomenological similarities between health anxiety and anxiety disorders have been shown²³⁻²⁵. A study comparing patients with hypochondriasis, somatoform disorders and anxiety disorder respectively on sociodemographic variables, psychopathology and treatment effects found that patients with health anxiety have an interim position between the two disorders, but is slightly closer related to anxiety disorders²⁶. Due to the chronic course seen in health anxiety and the pervasive impact on behaviour and cognition, some²⁷ have also suggested that the disorder may be better classified along Axis II as a personality disorder. The personality characteristic primarily found to be related to health anxiety is neuroticism^{28, 29}, and recently a long-term follow-up study has looked at personality, measured by an inventory of dimensions of temperament and character as a predictor for remission after treatment.

The study found preliminary evidence that patients with health anxiety, who have a less harm-avoidant temperament, for instance being less fearful and vulnerable, and a more cooperative character, such as more tolerant and forgiving, were associated with shorter remission time and full remission at follow-up³⁰. The literature has greatly debated whether health anxiety should be considered primary or secondary to other diagnoses such as depression, and it is now at large recognised that health anxiety can occur without past or current conditions³¹. Health anxiety is seen to co-occur with numerous psychiatric disorders, and more than half of patients with health anxiety may have a comorbid psychiatric disorder, the most prevalent being major depression or anxiety disorders^{1, 32}. Likewise, studies have found that between 1/5 and 1/3 of patients with health anxiety also fulfil diagnostic criteria for another somatoform disorder, the most prevalent being undifferentiated somatoform disorder and with the highest overlap seen among patients with full DSM-III or IV hypochondriasis^{1, 32}. Although studies show that around half of patients with health anxiety suffer from comorbid anxiety and depression, psychiatric comorbidity does not seem to predict the course of health anxiety or prevent patients with health anxiety from improving^{5, 33, 34}.

Prevalence of health anxiety

Health anxiety is common, yet prevalence estimates vary considerably across studies. A recent review¹⁷ of 55 papers based on 47 independent samples concluded that prevalence rates across the included studies were difficult to compare due to the heterogeneous nature of the studies such as use of different definitions and assessments and different populations, and therefore it is questionable whether reported prevalence rates reflect the same phenomena. Though, the review found a trend towards a significantly higher population prevalence rate in abridged forms of hypochondriasis (e.g. prevalence range for health anxiety was 2.1-13.1%) compared to full DSM-IV hypochondriasis (weighted prevalence of 0.40%, range 0.0-4.5%). Also, prevalence rates were found to be higher in general medical samples (prevalence of full criteria; range 0.3-8.5% and for health anxiety: range 4.5-30.6%) compared to clinical samples (psychiatric, psychotherapy and psychosomatic settings: range 0.4-7.4%). Due to the heterogeneous assessment methods and diagnostic definitions, calculated prevalence rates must be interpreted with caution.

The aetiology of health anxiety

Research in the aetiology of health anxiety is increasing, and a number of aetiological factors have been the focus of research: Family background and childhood experiences, stressful life events, sociocultural factors and genetic factors. So far most studies have failed to find direct evidence for genetic factors in health anxiety, and behavioural genetics suggest that health anxiety is moderately heritable, but is more strongly influenced by environmental factors³⁵. A study³⁶ investigated the role of genetic and environmental factors using a classic twin study method and found genetic factors to account for between 10-37% of the variance of excessive health anxiety. The authors concluded that health anxiety is largely a learned phenomenon and hence support the use of environmental interventions such as psychotherapy as treatment for health anxiety. Retrospective studies have shown that environmental factors such as traumatic childhood experiences, e.g. childhood abuse^{37, 38} and parental modelling of illness worry as well as sensitivity to somatic sensations³⁹ are associated with health anxiety. Still, the exact contributions of environmental and genetic factors to the development of health

anxiety are still largely unknown. It might be that genetic factors cause a proneness or sensitivity towards experiencing negative emotions or bodily sensations. Also, positive associations seen between environmental factors and health anxiety are most likely complex. For example, a recent study³⁸ on adverse childhood experiences and health anxiety in adulthood showed a significant positive association between the two and found that childhood experiences were predictive of health anxiety in adulthood, yet the unique contribution of these experiences lost significance when other variables of interest such as negative affect and trait anxiety were included in the analyses.

A better understanding of the aetiological factors in health anxiety might help guide preventive approaches (e.g. during childhood) or develop better targeted interventions. Also, the above mentioned twin study³⁶ stressed that as genetic factors play some role in excessive health anxiety, it may be that pharmacotherapy can be improved in the future by tailoring medications to the person's genotype.

Onset and course

Health anxiety may arise at any age, although an early onset has been suggested⁴⁰. In respect to the natural course of health anxiety, a systematic review of the epidemiology of hypochondriasis found that there are inadequate longitudinal studies allowing for exact determination of these factors¹⁹. Still, a number of studies have found an increased risk of chronic course in severe cases of health anxiety left untreated^{5, 41-43}. Most studies have found no gender or age differences in the prevalence of health anxiety^{1, 15, 44-46}, whereas within other somatisation disorders women seem to be at higher risk¹⁹. In general, RCTs have found that patients with severe health anxiety are well-educated with approximately 2/3 of patient samples having attended further education⁴⁷⁻⁵¹. Furthermore, a chronic course of health anxiety has been associated with more severe symptoms, more impaired physical functioning, childhood punishment and a longer duration of health anxiety at baseline^{52, 53}.

Personal and socio-economic costs of health anxiety

Severe health anxiety can cause frustration in both GPs and patients. GPs may find it frustrating that they cannot offer the same treatment quality as they do to other patients⁵⁴. Also, some GPs may be less comfortable addressing health anxiety directly compared to offering information on physical health and therefore rarely diagnose health anxiety, and some may also be inclined to view health anxiety as non-responsive to therapy or even as not a genuine disorder. Besides struggling with substantial personal suffering, patients with severe health anxiety may experience a lack of sufficient help and that their problems are not taken seriously. Also, patients with severe health anxiety may be reluctant to be referred from a medical setting to a psychiatric setting⁵⁵.

A two-year follow-up study in primary care showed that health anxiety is a persistent condition and spontaneous remission is rare⁵. Furthermore, the study found that patients with severe health anxiety used about 41-78% more health care per year in total, both during the 3 years preceding inclusion and during follow-up, compared with patients with well-defined medical conditions⁵. Patients with severe health anxiety have a high use of health care services as they go through a wide range of examinations, assessments and treatment attempts without medical indication⁵⁶⁻⁵⁹. Earlier findings demonstrate that training GPs in management and treatment of patients with functional disorders can improve the treatment quality⁶⁰, yet this does not seem to be the case in the

management of patients with health anxiety. Results indicate that severe cases demand a more intensive and specialized treatment^{5, 61}.

Due to the numerous investigations made to rule out any medical condition as well as reassurance-consultations in primary care, health anxiety is expensive in terms of direct health care resource usage^{5, 62-64}. Yet, the high health care costs do not include time lost from work and reduced productivity. Studies on indirect costs such as morbidity-related sick leave or productivity losses are scarce, but they indicate that patients with severe health anxiety report more disability days compared with a medical outpatient group⁴² and the general population^{15, 62, 65} and have an increased risk of disability pension⁶⁶. A recent systematic review on the economics of medically unexplained symptoms, including health anxiety, stressed that more extensive research on indirect costs as well as long-term perspectives are needed⁶⁷.

Treatment of health anxiety

Until the late 1980s, treatment of health anxiety was largely considered unproductive, and in some cases extreme interventions such as prefrontal lobotomies were performed in attempt to reduce the disorder⁶⁸.

During the 1990s, theory-driven studies of the effectiveness of cognitive and behavioural therapies lead to major advances in the understanding of both nature and treatment of health anxiety⁶⁹. The emphasis on cognitive analyses and concepts helped therapists and researchers place the concept of health anxiety on more solid foundation and challenged the earlier predominant view of health anxiety as a treatment-resistant condition.

Patients with health anxiety may show a preference for psychological treatment over pharmacotherapy⁷⁰, yet only two studies^{47, 71} have examined the effect of pharmacotherapy in health anxiety in RCT. In both studies, pharmacotherapy (respectively Fluoxetine and Paroxetine) was found to be superior to placebo, still in one of the studies⁴⁷ including a psychotherapy comparison, no significant treatment effect was found between pharmacotherapy and psychotherapy. The long-term effects of pharmacotherapy on health anxiety remain to be investigated.

Psychoeducational approaches have also shown effectiveness in the treatment of health anxiety⁷²⁻⁷⁵, though this approach has been suggested adequate predominantly for mild and uncomplicated health anxiety⁷⁶. So far, the most studied and most effective treatment approach is different versions of cognitive behavioural therapy (CBT), and in the latest Cochrane review⁶⁹ and narrative review⁷⁷ of psychological treatments for health anxiety, CBT is recommended as the gold standard intervention for health anxiety. Still, the Cochrane review failed to find any superiority of CBT over non-specific therapies⁶⁹, which has been pointed out to be in contrast to reports in many anxiety disorders⁷⁸. Recently, a third-wave development of CBT combining traditional cognitive-behavioural strategies with mindfulness (Mindfulness-Based Cognitive Therapy) has been tested on severe health anxiety and likewise shown to be effective in improving severe health anxiety⁴⁹. Only, this recent Mindfulness-Based Cognitive Therapy study⁴⁹ has tested group therapy in an RCT, whereas earlier trials on health anxiety have focused on individual CBT as group-based approaches have been dismissed as counteractive⁷⁹.

Currently 12 RCTs on the treatment of health anxiety^{30, 33, 47, 49-51, 80-87} (see Table 2 below for overview of RCTs) have been pub-

lished and generally yield moderate to large effect sizes. However, earlier trials show methodological shortcomings^{69, 77}, which may question whether outcomes and discrepancies between studies reflect real effects or are biased by selection of sample (e.g. due to various definitions and diagnostic criteria for classification) or methods of analysis. Also, recent studies have drawn attention to the importance of transparent and easily identifiable diagnostic criteria, thus warranting a more homogeneous patient group^{48, 50}.

Reviews^{69, 77} have pointed out methodological issues with earlier trials such as; a large proportion of potentially eligible patients declining participation, no use of power calculations, limited use of standardised diagnostic instruments, limited independent assessor ratings, high drop out rates, and no or short follow-up periods.

Some patients with health anxiety do not respond to CBT interventions³⁴, and many who show improvement do not maintain their gains long-term³⁰. Two earlier follow-up studies on medical outpatients both found that 2/3 of patients still met at least some diagnostic criteria for hypochondriasis after a follow-up period of 1 and 4 to 5 years^{41, 42}. Newly published results from a 6-year follow up CBT study confirmed earlier findings of 2/3 of patients maintaining case status³⁰. In this way, alternatives to traditional (individual) CBT approaches need exploring in order to improve treatment results⁶⁹.

A new treatment approach for health anxiety - Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT)^{88, 89} is part of a new generation of behavioural therapies that combine well-known behaviour techniques from CBT with strategies that promote acceptance, that is intentionally allowing painful psychological events such as illness worry, to be present and felt in order to be able to move in a valued direction⁹⁰. In therapy, ACT combines acceptance- and mindfulness-based processes with behavioural strategies to increase the psychological flexibility of the individual. Psychological flexibility spans a wide range of human abilities and can be defined as the ability to recognize and adapt to various situational demands in the present moment and without needless defence, in the service of chosen values, even when difficult thoughts, feeling or sensations are present⁹¹. The opposite position - psychological inflexibility - is in ACT thought to emerge from experiential avoidance, which refers to rigid and in the long term fruitless attempts to avoid or gain control over private events such as aversive thoughts or bodily sensations. Behavioural patterns dominated by experiential avoidance may be problematic as they restrict behaviour and hence may result in lower quality of life due to dominance of rule-driven versus values-driven behaviour.

ACT has an emphasis on the function of inner experiences, that is how thoughts are experienced and regulated, rather than on testing the validity, form, intensity or frequency of such experiences. In this way, the ultimate goal of ACT is to increase psychological flexibility and hence strengthen the ability to act in accordance with personal values even in the presence of anxiety. To some extent, ACT uses techniques from CBT, but the goals may differ. For instance, when exposure is applied in ACT-G for health anxiety it is in order to increase behavioural flexibility in the presence of illness worry, that is expand the behavioural repertoire

Table 2. RCTs of treatment for health anxiety

Study	N	Patients recruited from	Treatment setting	Clinical case status	Treatment condition	Control condition(s)	Drop out of treatment condition	Primary outcome	Follow-up (months)	Results
Warwick et al. (1996)* [§] (84)	32	primary and secondary care	secondary care outpatients	DSM-III-R hypochondriasis	Individual cognitive behavioral therapy	Waitlist	6% in CBT	None stated (VAS)	3	CBT>WL
Clark et al. (1998)* [§] (83)	48	primary and secondary care	not stated	DSM-III-R hypochondriasis	Individual cognitive therapy	BSM; waitlist (subsequently treated with CT or BSM)	6% in CT	None stated (VAS)	3, 6, 12	CT> BSM >WL
Fava et al. (2000)* (87)	20	secondary care psychosomatic outpatients clinic	secondary care outpatients	DSM-IV hypochondriasis	Individual explanatory therapy	Waitlist (subsequently treated with ET)	20% in ET	None stated	6	ET> WL
Visser & Bouman (2001)* [§] (80)	78	None stated	University clinic and in several mental health institutes	DSM-IV hypochondriasis	Individual cognitive therapy	Exposure in vivo plus response prevention; waitlist	35% in CT	Health anxiety subscale of IAS	1, 7	(CT=exposure)> WL
Barsky & Ahern (2004)* [§] (82)	187	Primary care and self-referrals	Secondary care outpatient	Cut-off on a combined Whitely Index & Somatic Symptom Inventory	Individual cognitive behavioral therapy	treatment as usual from general practitioner	10% in CBT	Whiteley Index	6, 12	CBT> TAU
Greeven et al. (2007)* [§] , (2009) [§] , (2014) (30,33,47)	112	secondary care and self-referrals	secondary care outpatients (psychiatric outpt clinics)	DSM-IV hypochondriasis	Individual cognitive behavioral therapy	Paroxetine; placebo drug	25% in CBT 30% in paroxetine	Whiteley Index	4, 18 (naturalistic FU)	(CBT=Paroxetine)> placebo
Seivewright et al. (2008) [§] (85)	49	genitourinary outpatient clinic	genitourinary outpatient clinic	Cutoff on SHAI	Individual CBT+ BIB	care as usual	9% in CBT	HAI	3, 6, (12)	CBT+BIB> CAU
Hedman et al. (2011) [§] (47)	81	primary care, psychiatrist and self-referrals	Psychiatry clinic at a University hospital	DSM-IV hypochondriasis	Internet-delivered cognitive behavioral therapy	Discussion forum (subsequently treated with CBT after 12 weeks)	15% (6/40) non-completers in CBT	HAI	6	CBT> Discussion forum
Sorensen et al. (2010) [§] (78)	80	primary care, medical consultant and psychiatrists	Liason psychiatry unit and private clinic	ICD-10 reserach criteria for hypochondriasis,	Individual cognitive behavioral therapy	STPP; waitlist	3% in CBT; 10% in STPP	HAI	6, 12	CBT> (STPP=WL)
McManus et al. (2012) [§] (46)	74	Health professionals and self-referrals	University setting	DSM-IV hypochondriasis	Group Mindfulness-based cognitive therapy	usual services	3% in MBCT	SHAI	12	MBCT>US
Tyrer et al. (2014) (83)	444	Secondary care	Multicentre study in secondary care	DSM-IV hypochondriasis	Individual cognitive behavioral therapy	Standard care	Not stated (7% 15/219 allocated to CBT received no treatment)	HAI	6, 12, (24)	CBT> standard care
Hedman et al. (2014) (48)	158	primary care, psychiatrist and self-referrals	Not stated	DSM-IV hypochondriasis	Internet-delivered exposure-based CBT	Internet-delivered BSM	In CBT 9% completed less than 4 modules	HAI	6	CBT>BSM

Note 1: * included in Thomson & Pages Cochrane review ⁶⁹

Note 2: [§] included in Boumans narrative review ⁷⁷.

Note 3: BIB: Bibliotherapy/booklet; BSM: behavioural stress management; BT: Behavioural therapy; CAU: care as usual; CBT: cognitive behavioural therapy; CT: cognitive therapy; DSM: Diagnostic and Statistical Manual of Mental Disorders; ET: explanatory therapy; (S)HAI: (short) Health anxiety inventory; IAS: Illness Attitudes Scale; MBCT: Mindfulness-based cognitive therapy; STPP: short-term psychodynamic psychotherapy; TAU: treatment as usual; US: usual services (unrestricted services); VAS: visual analogue scales (designed by the authors to assess different aspects of health anxiety); WL: waitlist;

previously narrowed in the presence of worry, whereas in traditional CBT the goal may primarily be to reduce the arousal evoked by illness worry. In this way, CBT's focus on modification of the content of cognition, such as dysfunctional thoughts, in order to influence behaviour and emotion may differ from ACT's focus on increasing awareness of and changing the function of inner experiences⁹⁰.

Though there are fundamental differences between CBT and ACT as regards both view of psychopathology and focus in treatment, it has been argued that therapeutic techniques used in ACT are compatible with CBT, and that the added acceptance-based techniques may improve outcome in many disorders⁹².

The empirical support for ACT has increased substantially in recent years with positive results for an array of problems⁹³⁻¹⁰¹. Even so, a recent systematic review emphasises that methodologically rigorous trials of ACT are very much needed^{102, 103}. A literature search for ACT and health anxiety found no RCTs when initiating this study in 2009, and the status is today unchanged except for the trial of this thesis (the intervention is described in paper II). However, to date there are almost 100 RCTs on ACT with promising evidence for effectiveness in the treatment of both anxiety and depression¹⁰⁴.

Background at a glance

- The issues of classification have hampered research in health anxiety and hence have added a spurious complexity to our understanding of treatment.
- There is a need to establish meaningful boundaries of caseness for health anxiety.
- Severe health anxiety tends to show the highest prevalence in medical settings.
- Health anxiety may be moderately heritable yet more strongly influenced by environmental factors.
- Health anxiety may have an early onset and a chronic course in severe cases left untreated.
- Overall, persons with severe health anxiety are high users of health care.
- Ability to work is an additional outcome of clinical and societal significance, but the association between health anxiety and sick leave is scarcely investigated.
- Research has shown effectiveness of CBT, yet many studies have been affected by methodological problems
- Further development and improvement of treatment approaches may help enhance treatment results.

AIMS OF THE STUDY

The aims of the thesis were:

To develop, test the feasibility and effect of a new treatment approach, Acceptance and Commitment Therapy in groups (ACT-G), for patients with severe health anxiety:

- I. To test the feasibility and acceptance of ACT-G (Paper I)
- II. To evaluate the effect of ACT-G in a randomised controlled trial as well as the acceptance of the diagnostic research criteria for health anxiety (Paper II)

To explore the association between severe health anxiety and sick leave:

III. To assess

- a) the association between severe health anxiety and sickness-related benefits compared with a matched general population sample during a 5-year period before randomisation to ACT-G, and
- b) the treatment effect of ACT-G on sickness-related benefits in patients with severe health anxiety (Paper III).

GENERAL DISCUSSION OF METHODS

I will discuss methodological issues with regard to the design and data sources of the study. In the discussion section of the individual papers, general strengths and limitations of the study have been stated, and therefore, to avoid recapitulation of arguments provided, not all of these will be repeated in the present discussion of methods.

Reviews of earlier RCTs on health anxiety^{69, 77} have focused on a number of methodological shortcomings in existing trials. Based on these, a number of methodological topics have been chosen for discussion with the purpose of shedding further light on the contribution of the present results to the current body of knowledge as well as the generalisability of the results of the present study.

Design

Recruitment and treatment setting

The generalisability of findings from the present study to individuals in the general population with severe health anxiety can be affected by multiple factors. In the present study, we set up exclusion criteria in order to ensure that included patients were able to participate in the group therapy and that their symptoms were not better explained by another disorder, hence we only included patients of Scandinavian origin between 20 and 60 years of age, who did not have a drug or alcohol abuse, were not pregnant and did not have a history of severe psychiatric morbidity such as psychotic and bipolar disorders. For ethical reasons, i.e. to ensure we only included patients severely disabled by health anxiety and with strong treatment need, we only included patients reaching diagnostic criteria for severe health anxiety, which implies moderate to severe impairment¹.

In Denmark, almost all health care is free of charge for all citizens, including visits to GPs, and is therefore easily accessible for every citizen. Also, we had patients referred from both rural and urban parts of western Denmark (catchment area of approximately 2.5 million persons).

Up to and during the recruitment phase of the study, we sent thorough information material to all GPs in West Denmark in order to inform GPs on the health anxiety diagnosis and criteria for referral. In this way, we tried to reduce potential selection bias as all GPs received the same information and hence all patients with severe health anxiety had a theoretical chance for referral to the study. In this way, the representativeness of the study sample may be fair to good compared with the general population of Danish adults with severe health anxiety, with the exception of the gender representation. In the present study, as in all other RCTs on health anxiety, predominantly women were referred and included in the study. As earlier studies have found no gender differences in the prevalence of health anxiety^{1, 15, 44-46}, the inclusion of predominantly women in this and other stud-

ies may potentially affect the outcome and to some extent undermine the external validity. It may be that women respond differently to the treatment compared to men. We can not say why predominantly women were included in our trial. The reason may be that women in general consult their GP more often than men¹⁰⁵ and thus are overrepresented in general practice. Also, presentation of health anxiety could be gender-specific and perhaps more easily identifiable in women thus making GPs more aware of health anxiety in women. In order to correct for this bias and equally distribute the under-represented men, we stratified for gender in the block-randomisation.

Also, we can not know if ACT-G for instance has attracted especially well-educated patients as the large majority of patients in this study, as well as other RCTs on health anxiety, are well-educated. This may well be a characteristic for patients with severe health anxiety too. Moreover, it may be that patients in rural areas have been less likely to accept a referral due to transportation time to the clinic.

At large, differences in for instance recruitment procedure and setting complicates comparison of results across studies. In the present study, patients were recruited from mainly GPs, yet a very small proportion of patients were referred from secondary care. In the latter cases, the GP was informed of the referral. Accordingly, the study sample consisted of patients all consulted by a medical doctor, which, compared to other studies recruiting through self-referrals^{47, 49-51, 82}, may have ensured a certain amount of impairment present and segregation of primary physical diseases, and hence a more homogenous sample compared to self-referred samples. One may expect this to result in a more severely ill sample in the present study compared to other studies, although comparing this study's baseline scores on illness worry and illness duration with other RCTs does not seem to suggest this.

Furthermore, the present study was conducted at a specialised clinic for functional disorders, within a psychiatric specialty, yet located at a general hospital. In other RCTs on health anxiety treatment, the study was conducted at secondary care settings^{82, 84-87} and/or university clinics^{49, 80}. It may be that some patients have declined a referral from their GP because the study and treatment took place at a specialised clinic and in this way only patients who accepted the referral to this type of setting were included. Despite this, patients have generally accepted referral, and according to the feedback from patients and GPs, they have welcomed the treatment.

Decline of participation and dropout

In the present trial we experienced that very few (9%, 24 of 254) referred patients and only 5% (9 of 173) of the potentially eligible patients declined participation in the study. Furthermore, only 6% (4 of 63) dropped out of treatment. Compared to some other trials having been hampered by large decline (70-80%)^{82, 86} and dropout of up to 1/3 of patients⁴⁷, the present RCT shows low numbers of decline and dropout.

There can be different explanations for these findings, potential ones might be; 1) GPs have only referred a selected type of patients, 2) lack of available treatment alternatives 3) the specific treatment offered, or 4) the assessment procedure at the research clinic. Firstly, it is possible that GPs only referred specific cases, such as the most severe and troublesome, the most motivated, or only those open-minded towards psychotherapy. In this way, a predominantly motivated sample may have been referred. It seems unlikely that GPs would have intentionally made this selection as the information material specifically asked for refer-

als of all patients with severe illness worry according to in- and exclusion criteria, still some patients may have declined a referral. Also, we did experience some decline of participation among referred patients (9%, 24 of 254). A second possible explanation is that the low decline and dropout reflects the lack of alternative treatment offers. This may be the case, yet it may not explain the difference in decline and dropout seen in the present study compared to others as a lack of treatment alternative has been the same for other studies and still is the case in most countries. A third possible explanation may be that the specific treatment offered – a group therapy with an acceptance-based focus – has been very attractive and meaningful to the patients. This explanation might be supported by the fact that besides low dropout, a high adherence to treatment was found as patients in ACT-G had a median of attendance of nine sessions (interquartile range (IQR) 8-10). The only other group-based RCT⁴⁹ for health anxiety also found a very low dropout rate. Furthermore, this treatment, the same way as the present, was based on a further development (third-wave) of CBT.

Another explanation for the low decline and dropout may be that assessors at the research clinic were very motivating in getting patients to participate. As only 5% (9 of 173) declined participation after assessment, this could well be the case. Yet, this may not be the only explanation as one would expect only an immediate high-motivation effect and a later high dropout of treatment, but this was not seen. Based on our clinical experience, we think that the low decline and dropout may at large be caused by a high patient acceptance of the diagnosis, due to the easily identifiable and empirically validated diagnostic criteria, and a thorough assessment. At assessment, patients received psychoeducation on e.g. the nature and cause of health anxiety and received a diagnosis, which the large majority (97-98%) categorised as the right diagnosis to fit their ailment and agreed that the diagnosis helped them to better understand their symptoms⁴. Other studies^{47, 49-51, 80, 86, 87} have at large used the broadly defined DSM-IV hypochondriasis diagnostic criteria, and this may first of all have caused decline in participation as patients often find the diagnosis stigmatising and maybe can not identify with it. Secondly, it may have recruited a more heterogeneous sample, of which some might not have found the treatment focus on illness worry suitable for their condition and thus have dropped out.

Diagnostic criteria for inclusion

In this study, we used well-defined empirically established diagnostic criteria for health anxiety¹. Clinically, we experienced that these criteria were transparent, identifiable and easily understood by the patients and the referring GP compared with the more poorly defined DSM-IV or ICD-10 criteria¹. Also, the patients easily accepted the new diagnosis, which they contrarily to the DSM-IV and ICD-10 diagnostic labels did not find stigmatising. Furthermore, the DSM-IV and ICD-10 diagnoses have been criticised for being too broad and hence show difficulties in differentiating health anxiety from other somatoform disorders and resulting in heterogeneous samples^{1, 15}. Furthermore, in the diagnostic criteria for health anxiety, the DSM-IV B criterion regarding “appropriate medical evaluation and reassurance” has been omitted, which may generate a more homogeneous sample. According to the diagnostic criteria used for the present trial, patients with primary severe other somatoform disorders were excluded such as a patient for whom the primary concern and diagnosis was fibromyalgia and where severe illness worry presented secondary. The diagnostic criteria may thus have helped

specify a sample of patients that only represents a subgroup of the participants included in other trials. It may be that differences found between the current study and other studies as regards treatment effect might to some extent be explained by different samples due to use of different definitions and assessment methods.

Waitlist as a control condition

A waitlist control group can be defined as a group of patients who have been assigned to wait for treatment and are aware that they are currently not receiving the treatment they are waiting for. First of all, in that way, a waitlist control group is not untreated. In the present trial, patients were referred, assessed, measured, diagnosed, received psychoeducation, and were randomised. After the assessment, the GP and the patient received a preliminary discharge letter regarding diagnosis and illness history. In the present RCT, both groups improved statistically significantly in illness worry from pre-screening to randomisation, which may be due to the assessment. Patients on the waitlist sustained this improvement during the 10-month follow-up period, but they did not improve further on the primary outcome of illness worry (SRM randomisation to 10-month follow-up = -0.07, 95% CI 0.20-0.33)⁴.

Secondly, it has been suggested¹⁰⁶ that patients in waitlist control groups improve less or not at all as they know they are awaiting treatment and efforts at improving are interrupted. Also, the control group knows that they are not yet receiving active treatment and has no reason to expect positive change, also referred to as treatment expectancy effects. Thus, the waitlist design may have inflated the reported effects of ACT-G. Being assigned to the waitlist group may have reduced participation in other beneficial activities during the 10-month period, even though such participation was not discouraged.

On the other hand, it is possible that at least some patients allocated to waitlist, after having received a brief introduction to ACT and mindfulness as part of the assessment, may have acquired self-help books on ACT or have felt motivated to contact a therapist in the wait period. In this way, the control group may have been contaminated, and the effect of the intervention could be underestimated. In the present trial, patients on waitlist received usual care by their GP, and there were no restrictions applied to the psychological or pharmacological interventions or on referrals to secondary care or mental health services during this time period. We can not know what impact the waitlist design may have had on the effect size, yet we chose not to include the significant effect of the assessment in the calculated effect sizes, and therefore one may expect the effect of the intervention to be even larger in everyday clinical practice.

In a recent meta-analysis¹⁰⁷ of CBT treatment outcomes for health anxiety it was found that waitlist control conditions (4 studies) showed larger effect sizes than treatment as usual conditions (5 studies). In the review it was not possible to examine other control conditions (e.g. psychological or pill placebo control conditions) due to few available studies (3 studies). Considering the possibility that a waitlist design may overestimate treatment effects, as suggested in the recent meta-analysis on treatment of health anxiety¹⁰⁷ and in RCTs in general¹⁰⁶, this must be taken into consideration when comparing effect sizes with other trials, and the findings of the present study need replication in studies with an active control group.

The present study was a somewhat pragmatic trial, which is why we - for ethical reasons - decided on the waitlist design offering

the control group treatment after the follow-up period, which the large majority of the patients accepted (84% 53 of 63). We considered offering the control group weekly check-in sessions, which would serve as someone showing concern, but as many patients would have to spend up to two hours on transportation each way to the clinic, we found it unethical and unfeasible. We think that the waitlist design was the best choice as no other specialised treatment was available for this patient group in Denmark at that time, just like in most other countries. With no other specialised treatment available for health anxiety, it is difficult to set up a treatment as usual condition.

Data

Processing of questionnaire data

Questionnaires were designed and processed using the TELEform software program, which allows for optical reading and hence has showed low error rate¹⁰⁸. A research secretary, student and data manager scanned the questionnaires following thoroughly predefined guidelines on how to handle and document cases of doubt. Project head and statistician were responsible for the further collation of data.

Self-rated measures of health anxiety

In the area of health anxiety, predominantly three questionnaires have been used as self-rated measures of health anxiety; the Illness Attitudes Scales (IAS), the Health Anxiety Inventory (HAI) and the Whiteley Index (WI). The validity and reliability of measures are often based primarily on the discriminant validity such as the sensitivity to differentiate between for instance cases of health anxiety and other somatoform disorders and the sensitivity to changes of treatment. All questionnaires may be useful as screening instruments for preliminary case identification, but can not be used alone for the purpose of diagnosis¹⁰⁹.

The HAI short version consists of 16 items with each a group of 4 statements. In a validation study, the scale was found to have good discriminant validity, good test-retest reliabilities and also found to be sensitive to treatment effects¹¹⁰.

The IAS measures attitudes, belief and fears associated with health anxiety and consists of 27 items distributed within 9 scales, of which only the first 7 directly concern fears and beliefs of health anxiety^{111, 112}. The 9 scales are clinically-derived and show good test-retest reliabilities.

Both the IAS and HAI show good discriminant validity and sensitivity to changes of treatment, yet may be considered quite comprehensive instruments for screening purposes.

The WI¹¹³ was developed in order to clarify the symptom clusters that are seen in clinical health anxiety by using factor analysis.

The WI was developed by Pilowsky et al. almost 50 years ago and originally consisted of 14 items with dichotomous answer categories (true-false). Hiller et al.¹¹⁴ investigated the similarity between IAS and WI and found that the two instruments were highly correlated (0.80) both yielding high sensitivity/specificity (71-80%), yet the IAS showed superior discriminative validity. The authors stressed that the nine original scales of the IAS are not sufficiently empirically supported. Also, a recent qualitative review of the dimensional assessment of health anxiety¹¹⁵ concluded that the WI is one of the most validated and used instruments, but that it should be a second choice to the IAS as the IAS shows superiority over the WI in clinimetric properties, in particular sensitivity to treatment-related changes and content validity. However, it should be stressed that both the qualitative review and the study by Hiller et al. were based on assessing the 19-item version of the WI with a dichotomous response format.

The WI has since the introduction of the original version been refined and psychometrically rigorously tested compared to other instruments e.g. by means of a latent trait model (the Rasch model)¹¹⁶ to a 7-item version with a Likert-scoring from 1 to 5. Using a Likert scale provides a wider response range and may hence allow for a better representation of the continuum of health anxiety¹¹⁷. The WI-7 has been widely used and has demonstrated satisfactory psychometric properties in primary care samples, with high internal validity and impressive external validity for screening DSM-IV somatisation disorder and hypochondriasis/health anxiety^{116, 118}. Furthermore, the WI has been shown to have a satisfying responsiveness to changes over time¹¹⁹.

In the present study, the WI was chosen because of its sound psychometric properties and simplicity, which makes it attractive as a screening instrument, and the primary outcome was decided *a priori* as the mean change in the WI-7 score¹¹⁶ from baseline (randomisation) to the 10-month follow-up (6 months after treatment).

In all questionnaire data, there is the risk of recall bias as a possible confounder, though on the WI patients were asked to assess how much they had been bothered by illness worry within the last four weeks, which is a fairly short time period hopefully minimising recall bias. Still, assessing illness worry over a period of 4 weeks may serve as a potential bias as illness worry clinically is known to fluctuate over short time spans for some patients depending on how much or how little they are confronted with illness worry evoking information or sensations. Fluctuations may cause problems both in respect to validity and to estimation of effects.

It is up to future research to further refine the WI. It may be that the discriminant validity of WI could be heightened by taking out the two items in the 7-item version concerning complaints of general pain/aches and multiple symptoms, which may not underlie health anxiety specifically, but somatisation or somatoform disorders in general. A recent study¹²⁰ has used data from a large population-based study to conduct confirmatory factor analysis and item response theory analysis of WI and found evidence for a 6-item (item concerning different pains and aches taken out), single factor model of WI, yet these findings need to be replicated in other samples.

Cut-off for identification of case status

In this study we used the WI both as a dimensional measure (scale score 0-100) and as a categorical measure (dichotomization in regards to cut-off of <21.4) to establish potential case status at 10 months follow-up. The cut-off determining clinical case status was based on existing data on patients with severe health anxiety^{2, 5}. Still it may be said to be a somewhat arbitrary cut off and the validity of case status based on just a cut off is always questionable. Conradt et al.'s¹¹⁸ has suggested that for screening purposes, a cut-off score of ½ on the WI shows enough sensitivity, whereas a cut-off score of 2/3 (equalling a WI <33.33 on a 0-100 score scale) shows the best balance for sensitivity and specificity for identification of cases of health anxiety. If we had applied the 2/3 cut off to estimate case status at end point in the present study, 58% (30 of 52) of patients in ACT-G and 24% (13 of 55) in the waitlist were no longer clinical cases of health anxiety. Comparably, the more conservative cut-off chosen in our study proposed a considerably lower proportion of 27% (14 of 52) of non-cases in ACT-G and 9% (5 of 55) in the waitlist.

Using less restrictive criteria, such as a questionnaire, to assess caseness, poses a risk of under- or overestimating prevalence of a disorder and missing important symptom patterns. Furthermore, a questionnaire is often not capable of differentiating whether symptoms are better explained by another disorder, e.g. major depression or an anxiety disorder. Health anxiety may be seen on a continuum of severity ranging from transient and relatively mild symptoms that may be difficult to separate from normal physiological phenomena, and to conditions of severe, chronic and disabling health anxiety. In all cases, a diagnostic reassessment with a (semi-) structured interview would be preferable to a somewhat arbitrary cut-off on a questionnaire. A questionnaire can be used as a screening instrument, but can not be used to diagnose, and in studies where this is done, it might show a tendency to include many cases without clinical relevance¹⁰⁹. Creed & Barsky¹⁹ refer in a review of the epidemiology of somatisation disorders and hypochondriasis to researchers having lowered the threshold of a questionnaire cut-off and hereby increased the number of people reaching case status, but still the additional individuals were no less disabled than those fulfilling the criteria of full ICD-10 hypochondriasis. The authors conclude that future work is still needed to determine the optimal cut-off point in order to determine cases of illness worry that is associated with impairment.

The diagnostic assessment

To classify health anxiety, we used a modified version of the semi-structured psychiatric interview, Schedules for Clinical Assessment in Neuropsychiatry (SCAN) which includes the symptoms of health anxiety used in the research diagnostic criteria of health anxiety^{1, 121, 122}. SCAN is symptom-driven, contrary to diagnosis-driven, and uses a 'bottom-up' approach, which is why it is not limited to specific symptoms included in diagnostic criteria for various conditions, and therefore its' validity does not rely solely on a diagnostic system. Nearly any DSM-IV or ICD-10 diagnoses can be established based on the SCAN diagnostic algorithms. In our study, the SCAN assessments were carried out in a clinical context by six certified SCAN assessors who were all trained clinicians, implying that assessment at large is comparable to other diagnostic situations such as clinical consultations, which is considered a strength of the SCAN. In the study, we used SCAN for case identification, which we find is a strength of the study and may have increased the diagnostic consistency and validity of health anxiety, whereas others^{82, 85} assessed cases of health anxiety based on questionnaire data alone or layman interviews. Compared to questionnaires alone, this semi-structured interview allows for qualitative aspects such as impairment and well-being and assesses possible organic causes for symptoms. In this way, using SCAN may have allowed us to overcome some of the methodological problems in determining the origin of symptoms and whether severity is clinically significant.

In order to minimise potential problems of misclassification, the interviewers were: 1) instructed to consult relevant medical specialists in case of doubt of symptom origin, 2) instructed to go through all chapters in SCAN, including detailed symptom description, in case of the slightest doubt of the origin of the reported symptoms in order to rule out another primary diagnosis that may better account for the reported symptoms. Also, throughout the inclusion period, video-taped SCAN interviews were randomly selected to assess inter-rater agreement on diagnoses.

Register data

The Danish registers provide optimal conditions for conducting research into social consequences of a disorder as every Danish citizen is registered in a nationwide centralised register of personal information with a unique personal identification number. The registers have almost full population coverage, can be used in anonymous form without requiring informed consent and enable researchers to follow citizens on e.g. health-related information from birth to death. In the second part (paper III) of the present study, data were obtained retrospectively from the Danish DREAM register (Danish Register for Evaluation of Marginalization) to provide objective and complete data on the effects of health anxiety on sick leave measured by weeks of sickness-related benefits. We included data from a period five years prior to enrolment in the RCT and up to two years after on the 126 patients enrolled in the RCT. Also, we matched a randomly sampled population control group (n=12,600) on gender and age from the DREAM database (proportion of 100 to 1) in order to compare clinical cases of health anxiety with a general population control condition.

DREAM is a database administered by the Danish Labour Market Authority and contains weekly information on benefit payments for all citizens in Denmark since 1991. DREAM contains information regarding e.g. sickness benefits, flexible jobs (jobs created for persons with limited working capacity), disability pension and unemployment benefit. Individuals who are not included in DREAM are not supposed to have received any social benefits since July 1991 and are hence considered self-supporting. A major strength of the register-based data is that there is no missing data and no information-, recall- or response bias. DREAM data have shown superiority over self-reported data for follow-up of social and economic consequences of disease¹²³. A limitation with data from DREAM is missing information on short-term sick leave, that is sick leave with less than two weeks duration, and occasional sick leave is not registered in DREAM. For example, if an individual is absent from work one day a month due to illness, this will not be recorded in the database. Overall, DREAM may be said not to be sensitive towards short-term sick leave and hence may result in an underestimation of sick leave. Also, data on benefit payments from DREAM are estimated on a weekly basis, which means just one day of sick leave in a week counts as a week. For example, if a person is sick six weeks in a row, but in the seventh week sick only one day, that one day counts as a whole week. This may result in overestimation of the length of sick leave. Another limitation of the DREAM database is that a minor proportion of Danish citizens, such as individuals who are supported by their spouse and do not receive employer or benefit payments, are not registered in the database and will appear as being employed. Also, decrease in weeks of benefit payments due to time spent abroad or migration is not taken into account, which may present a small sampling bias. It may be that the validity of the data on sick leave could have been further heightened if it had been combined with self-reported outcomes providing further data on for example short-term sick leave or individuals supported by spouse or migrated.

Statistical considerations

In the present study, non-completion was only relevant regarding the questionnaire data as the register-based data ensured 100% follow-up. In the questionnaire data, we obtained full baseline data on the primary outcome and in general reasonably high completion at later follow-ups. We had data available for 116

patients (92%) at four months (end of treatment), 112 patients (89%) at seven months, and 107 patients (85%) at ten months respectively. Furthermore, the 52 (83%) patients in ACT-G completing the study were not statistically significantly different from the 55 (87%) completing in the waitlist group ($\chi^2(1) = 0.558$, $p=0.455$).

In the present study, a mixed model method was applied due to repeated measures data. The model does not require that all subjects provide data on all outcomes. As we had a reasonably high completion rate at all measure points, we made the decision to not apply imputation. Furthermore, in general authors have advised against the use of imputations in clinical trials as clinical trials usually do not collect sufficient data to allow good estimation¹²⁴. However, it can be argued, that applying imputations may have been a feasible improvement of the generalisability. As earlier RCTs and the pilot study found an overrepresentation of men, we decided to stratify for gender in the randomisation procedure in order to secure an equal distribution of males in the two groups.

All analyses were unadjusted, only post hoc analyses were performed to control for comorbidity effects. Overall, there seems to be a lacking consensus in the literature on how to handle the imbalance between study groups in analysis¹²⁵. Some studies adjust the outcome model for baseline differences between groups, whereas others consider baseline differences to be chance findings and therefore not to be adjusted for, and some argue against even checking for them¹²⁶. We decided not to adjust analyses in order to present data as raw as possible and make comparison between studies easier as adjustments may influence the interpretation of the study outcome.

Descriptive statistics were used to characterise the patients and to provide raw data of primary and secondary outcomes at pre-screening, at baseline and at the designated follow-up times. All other analyses were done on an intention-to-treat (ITT) basis and no subjects were excluded from the analysis. We choose the ITT analysis against completer/per-protocol analysis as there is a risk of overestimating the clinical effectiveness if an ITT analysis is not done¹²⁷. Also, ITT analysis has been found the most suitable for pragmatic trials¹²⁴. We found it was an advantage to use the ITT analysis as it may provide the best pragmatic, unbiased comparisons among ACT-G and the waitlist group. Still, applying the ITT analysis gives information on the potential effects of the treatment allocation compared to completer analysis estimating the potential effect of specific treatment received. Full application of ITT is only possible when complete outcome data are available for all randomised subjects¹²⁴. If dropout depends upon some other process which is related to outcome, for instance acceptance of treatment, the dropout process information is informative. The ITT allows for non-compliance and dropouts as would also be expected in routine practice. In this way, using the ITT or completer analyses may affect the generalisability of the results. In the present study, the dropout rate was very low and completion was high, and no statistically significant difference was found between completers and non-completers on baseline characteristics, for which reason it may not have affected the results substantially to have used a completer-analysis in the present study. Findings on treatment effect were presented as: within group effect sizes (the standardised response mean, SRM), between group comparison effect sizes (unadjusted Cohen's d), number needed to treat (NNT) and clinically significant differences. We defined a clinically significant difference as 0.5 SD as often defined in the literature^{128, 129}.

Methods at a glance

- The present study sample may be a somewhat selected group compared to earlier RCTs, but at large may be more representative for individuals in the general population with severe health anxiety as patients were referred from easily accessible, free of charge, and well-informed GPs and empirically-based diagnostic criteria for severe health anxiety were used for inclusion in trial.
- Patients were predominantly well-educated and female, which may not be representative for individuals in the general population with severe health anxiety.
- The study was conducted at a specialised clinic, which first of all had highly trained therapists available and secondly may have segregated patients not interested in treatment at a specialised clinic.
- A semi-structured psychiatric interview was used to identify clinical cases of health anxiety at baseline and may have increased the diagnostic consistency and validity compared to identification of cases based on questionnaire data.
- The diagnostic criteria were found easily identifiable, acceptable and useful to the patients and may have helped identify a treatable group.
- Decline of participation and dropout was low suggesting that a thorough assessment with psychoeducation may motivate patients to accept and adhere to psychological treatment.
- A group-based approach showed high acceptance and adherence.
- The waitlist control condition may have affected reported effects. In this trial, rather conservative measurement points were chosen not including the significant effect of the assessment in the calculated effect sizes.
- The Whiteley-7 Index was chosen a priori as primary outcome. Compared to other self-rated measures of health anxiety, WI has been tested with modern item response theory and demonstrated satisfactory psychometric properties.
- The long-term consequences of severe health anxiety on sick leave was assessed by observer-independent data from a national database ensuring full follow-up and allowing comparison with a large general population sample.
- ACT-G has shown effect in the treatment of young and middle-aged, predominantly female and well-educated Scandinavians suffering from severe health anxiety and who did not meet any of the study's exclusion criteria. It is up to future research to test if the findings are reproducible in less specialised settings and other samples.

GENERAL DISCUSSION OF RESULTS

I aim to discuss the findings of the present thesis from a broader perspective. Initially, primary findings will be briefly summed up as conclusions to the main aims of the thesis. In each of the three

papers of the thesis, respective findings are discussed in relation to strengths and limitations of the study in question and compared with other studies. Therefore, these discussions will not be repeated here. Instead, findings of the present thesis will be discussed in relation to selected topics that were beyond the scope of the discussion for the respective papers. Also, clinical implications will be stressed as well as how these findings may add new knowledge to the field of health anxiety.

Main conclusions in relation to aims

The primary aims of the thesis were to 1) develop and test the feasibility and 2) the effect of ACT-G for patients with severe health anxiety and the acceptance of the health anxiety diagnosis. Findings from the uncontrolled pilot study (paper I) indicate that ACT-G is an acceptable and feasible treatment for patients with severe health anxiety. This is an important finding since treatment adherence is reported to be problematic in this particular patient population⁶⁹ and also has been shown to significantly predict outcome of therapy in severe health anxiety¹³⁰.

In the randomised, controlled trial (paper II), ACT-G was compared to a waitlist control condition and showed statistically significant large and sustained improvements on the primary outcome of illness worry as well as clinically significant changes. Also, significant improvements were seen on most secondary outcomes, which is contrary to the only other group-based RCT for health anxiety⁴⁹. Patients on the waitlist showed no significant changes over the 10-month follow-up period, which is in line with the literature suggesting a poor prognosis for patients with severe cases of untreated health anxiety^{1, 5}.

Furthermore, the health anxiety diagnosis and the treatment were well accepted by patients. This may indicate that the health anxiety diagnosis, contrary to the DSM-IV hypochondriasis diagnosis⁵, is not only acceptable to patients, but also meaningful in the way that it helps patients to better understand their symptoms. Also, dropout rates were very low in ACT-G, and retention rates were high compared to other trials, e.g.^{47, 82, 86} further indicating a high acceptance of treatment.

The final aim of the thesis was to explore the association between severe health anxiety and sick leave compared with a matched general population sample during a 5-year period and the treatment effect on sick leave in patients with severe health anxiety (paper III).

Patients with severe health anxiety showed significantly more weeks on sickness-related benefits in the five years preceding enrolment to the RCT compared to a matched general population sample, with a significant increase the last year before enrolment. Thus, health anxiety seems to pose a substantial burden on society, which is in line with other studies where patients with health anxiety have shown more disability days than medical outpatients⁴² and the general population^{15, 62, 65}.

Results of the effect of ACT-G on sickness-related benefits are more difficult to interpret: A significant within-group reduction in weeks on sickness-related benefits was observed among participants in ACT-G from before enrolment to one year after. However, there was no significant difference in change of weeks on sickness-related benefits between ACT-G and the waitlist group from before to 1 year after enrolment to RCT (8 months after treatment completion). Uncontrolled post-hoc analyses showed a statistically significant reduction in weeks on sickness-related benefits in ACT-G also at 2-year follow-up (20 months after treatment completion). Potentially, treatment effects on sickness-related benefits may set in late compared to the primary effect on illness worry and other outcomes of psychosocial functioning.

Hence, the observed reductions in sickness-related benefits might continue and potentially show an effect of ACT-G on sickness-related benefits if a longer follow-up and a larger sample were available.

Implication of findings

Classification and management of health anxiety

Doctors have at large been reluctant to diagnose hypochondriasis^{8, 131}. One reason suggested is that the label of hypochondriasis has pejorative connotations that may be unacceptable to patients¹³². In the present study, we found preliminary evidence that the positive diagnostic criteria for health anxiety¹ may be widely acceptable and meaningful to patients as well as doctors and may identify a treatable group of patients suffering from severe health anxiety. The findings may suggest that when patients are presented with easily identifiable diagnostic criteria and thorough explanations on nature and course of the disorder, they are less likely to perceive the diagnosis as a stigmatising label. The impression of stigmatisation and reluctance to use the diagnosis among GPs might be a result of misunderstandings associated with the diagnosis partly due to the lack of empirically valid diagnostic criteria.

In the new diagnostic criteria for health anxiety, compared to the former DSM-IV hypochondriasis criteria, the reassurance criterion has been removed, and the 6-month duration criterion has been replaced by a symptom duration of at least two weeks¹. From a clinical point of view, this may allow for better discrimination of cases of health anxiety as not all patients with health anxiety seek reassurance and may guide early stage classification and hence early intervention. In the introduction of the thesis, the health anxiety diagnostic criteria have been described to be rather similar to the DSM-V illness anxiety disorder, the major differences being that the DSM-V diagnosis does not include the rumination symptom and excludes patients with moderate and severe somatic symptoms. In the present study, we did not exclude patients with somatic symptoms, still patients' mean score at baseline on the physical component of health-related quality of life (the physical component summary derived from z-scores from the eight SF-36 subscales, The MOS 36-item Short-Form Health Survey)¹³³ was very close to that of the Danish adult population, and this was the only outcome not showing a significant improvement. This may indicate that it might not be of importance to make the distinction whether patients, apart from illness anxiety disorder, have additional somatic complaints or not as is currently the issue in the DSM-V. Also, as the health anxiety diagnosis allows for discrimination between mild and severe cases (depending on impairment) and with only the severe cases showing a chronic course if left untreated⁵, this new diagnosis may have the potential to help doctors identify and address illness worries at an early stage and hence prevent development of a severe and chronic course accompanied by personal suffering and potentially high health care costs.

Medical settings deal with health care by offering medical services, treatment and tests among other things with the purpose of providing reassurance to the patient. Though, for patients with health anxiety, medical evaluations and reassurance often do not have this effect, or the reassurance only provides a temporary relief. The reassurance may even become counterproductive as the patient can get heavily dependent on easy access to reassurance. Thus, GPs may unintentionally become part of patients' vicious circle of health anxiety if they continue to provide immediate reassurance to them. Findings from the present study stress

the importance of assessing health anxiety and providing psychoeducation to the patient, even if treatment is not available, as significant and long-term sustained effect of a thorough assessment on illness worry was seen in the RCT. These results may indicate that treatment as usual may adequately sustain a potential effect of assessment, which may be an important first step towards a productive alliance and acceptance of diagnosis as well as treatment. Yet, in this study we do not have information on which concomitant treatments the patients potentially had alongside the protocol treatment.

Still, evidence-based treatment followed by assessment should be applied when possible given that in the present trial, the waitlist control group showed unchanged mean scores on outcomes from randomisation throughout the 10-month follow-up period, which is in line with the literature suggesting a chronic course in severe cases left untreated³¹.

Our results suggest that with easily identifiable diagnostic criteria, proper assessment, direct communication and psychoeducation about diagnosis, a high acceptance of diagnosis and psychological treatment can be seen in patients with severe health anxiety.

Treatment approach for health anxiety and mechanisms of change

In the present study, the treatment emphasised 1) behavioural analysis of the workability of attempts to control or eliminate illness worry, 2) developing an observing and accepting attitude towards illness worrying through mindfulness and defusion exercises, and 3) changing behaviour in valued directions. The target of the intervention was not the symptoms per se, such as eliminating ruminations about illness or bodily sensations, but the function of the symptoms, for instance ruminations causing continued reassurance-seeking. Hence, changing the function of the symptom, in this example having to seek reassurance continuously in order to control ruminations, became the focus of treatment. In this way, the patient's relationship with thoughts and behaviours was the target of intervention and hence a metacognitive approach was used. Earlier ACT models developed for anxiety disorders, for example generalised anxiety disorder⁹⁷, have emphasised the central role of experiential avoidance in the development and maintenance of ruminations and worry. It has been suggested that the inability to be in contact with anxiety might lead to worry functioning as an experiential avoidance strategy that would be negatively reinforced as it works to reduce anxiety in the short term. Furthermore, worry is thought to be positively reinforced as the person follows rules focused on eliminating and controlling anxiety¹³⁴. It may be possible that the same pattern of reinforcement is seen in health anxiety. One might then expect that interventions directly focused on contacting and opening up to distressing illness-related thoughts, sensations or emotions, like in ACT, might have increased illness worry. However, we observed a significant improvement in illness worry, which was sustained at end point, indicating that acceptance and mindfulness-based interventions may be effective in decreasing health anxiety, which has also been suggested elsewhere^{20, 78}.

A recent meta-analysis of CBT for health anxiety found that CBT outperformed control conditions on different primary outcomes of illness worry with large effect sizes (Hedges' $g=0.95$) at post-treatment, yet small effect sizes at follow-up (Hedges' $g=0.34$)¹⁰⁷, whereas a Cochrane review on the treatment of health anxiety failed to find superiority of CBT over non-specific therapies⁶⁹. Williams et al⁷⁸ suggest that failure to demonstrate superior efficacy of CBT in the treatment of health anxiety may partly be

due to patients with health anxiety, compared to anxiety disorders, are more difficult to disconfirm in their feared predictions via use of standard CBT methods.

In the present trial, we found a large effect size for ACT-G compared to waitlist, and the effect was sustained at 10-month follow-up on the primary outcome, illness worry. It may be speculated that components of ACT may result in different and potentially more stable changes compared to CBT.

A recent study¹³⁵ explored behavioural avoidance (as a potential behavioural indices of emotion dysregulation) as a predictor of respectively 12 individual sessions of ACT or CBT for anxiety disorders. The sample consisted predominantly of patients diagnosed with panic disorder and found preliminary evidence for high behavioural avoidance as a prescriptive indicator of superior outcome of ACT compared with CBT. Both CBT and ACT target emotional regulation, yet it may be that ACT's focus on staying in the present moment and openly "inviting" and exploring sensations and thoughts may be very beneficial to patients who show high levels of behavioural avoidance, for instance towards bodily sensations and illness-related thoughts as seen in health anxiety. It is suggested that patients who are highly behavioural avoidant may first need training in how to engage in interoceptive exposure, which may be learned by the general focus on acceptance and willingness in ACT¹³⁵.

Furthermore, ACT emphasises the importance of establishing treatment goals beyond a focus on symptom reduction by identifying and clarifying patients' values and hence goals and behaviour consistent with these values. An important part of ACT-G is for the patient to commit to values as a way of living a more meaningful and vital life compared with a life constrained with avoidance of and controlling anxiety as the main goal in life. Likewise, the use of mindfulness in ACT-G was not limited to formal mindfulness meditation, but was taught and practised as a general psychological approach to life and hence a way of coping with challenges in life at large, as suggested elsewhere¹³⁶. In this way, the focus in ACT on acceptance, generic skills of attentional control and values-based behaviour may produce widespread benefits and help patients to further adapt their lifestyle, for instance a more open and accepting attitude to life in general and increased ability to manage obstacles while continuing to move forward in life. Finally, some authors have speculated that acceptance-based psychotherapies are especially well suited to more severe, treatment-resistant patients¹³⁷⁻¹³⁹. The active components of ACT-G for health anxiety may not be easily defined, but finding out for whom and under what conditions a specific treatment may be most effective may guide treatment-matching attempts. Hopefully, we will be able to address some of these questions in the future as research initiatives have been planned in order to identify which treatment components of ACT-G may be crucial for positive treatment outcome.

ACT as an evidence-based treatment

Findings from the present study suggest that ACT-G may be an effective treatment approach for severe health anxiety. As this is the first study to test ACT on health anxiety and the design did not include an active treatment comparison group, the findings need to be confirmed in other samples and settings. Although CBT is found effective in the treatment of health anxiety, some patients still do not respond to treatment or experience a relapse of symptoms at later follow-up^{34, 69, 77}. In this way, examination

of the effect of other psychological treatments than CBT for health anxiety might shed further light on possible prescriptive variables and thereby help tailor individually-oriented treatments. ACT may be a viable second option in treatment of health anxiety in cases where CBT is ineffective or refused as stressed within research in anxiety disorders¹⁰⁴.

On the homepage of the Society of Clinical Psychology, American Psychological Association, Division 12 Task Force¹⁴⁰, ACT is defined as a treatment with modest to strong research support. Still, RCTs on ACT may have room for methodological improvements and hence the status of ACT as an empirically supported treatment can be discussed. A systematic review and meta-analysis of the efficacy of ACT by Öst, currently in press¹⁰³, presents a very critical methodological evaluation of ACT compared to CBT and concludes that ACT is not yet well-established for any disorders and may be "possibly efficacious" for depression and anxiety disorders¹⁰³. The above-mentioned meta-analysis and review is an update of a six-year-old meta-analysis and review, also made by Öst¹⁴¹, with a specific focus on methodological stringency based on modified criteria for evidence-based treatments developed by the American Psychological Association Division 12 Task Force. Comparison of RCT effect sizes from the 2008 review with the current review, including RCTs up to November 2013, suggests a decrease in effect size from 0.96 to 0.63 in ACT RCTs with a waitlist design and an overall decrease across all RCTs from 0.68 to 0.42. In this respect, the between groups effect size of 0.89 at 10 months found in the RCT of this thesis may seem promising. Öst lists 15 recommendations for future research in ACT in order for ACT to be evaluated as an evidence-based treatment. Due to the waitlist control design of the RCT of this thesis, it is only possible for this study to obtain a total score of 11. Cautiously evaluating the methodological stringency of the study suggests an acceptable methodological quality score of 8, with the study failing to reach criteria on the recommendations of; using three or more therapists, independent ratings of treatment adherence and therapist competence, and procedures to control for concomitant treatment obtained alongside the protocol treatment. We therefore recommend for future studies testing the effect of ACT-G for severe health anxiety to include these recommendations in the design as well as use an active treatment as comparison, for instance CBT.

Health anxiety and sick leave

Overall, the findings from paper III on the association between health anxiety and sick leave suggest that severe health anxiety may not only be a burden for patients and society in terms of personal suffering and expensive and unproductive tests and examinations; it also seems that severe health anxiety is associated with more sick leave compared to the general population. To our knowledge, no previous studies have used observer-independent prospective registration of sickness-related benefits in order to explore the societal consequences associated with diagnosed severe health anxiety as well as the long-term effects of psychological treatment for this condition. In this way, especially analysis on the treatment effect of ACT-G on sick leave, in this case measured by weeks on sickness-related benefits, had an exploratory nature. We found a significant decrease among patients in ACT-G in weeks on sickness-related benefits from before enrolment to 1- and 2-year follow-up, yet we found no significant difference in change of weeks between the waitlist and ACT-G at 1-year follow-up. Thus, we can not say that ACT-G has a direct effect on weeks on sickness-related benefits. As suggested in

paper III, the non-significant treatment effect of ACT-G on sickness-related benefits may be due to the random difference at randomisation between the two groups in number of patients on sickness-related benefits or due to methodological issues, such as the sensitivity of the data source or sample size. Analyses (results not shown) testing for individual positive or negative change in occupational status from before randomisation to 1-year follow-up found no statistically difference in change of occupational status between ACT-G and the waitlist (respectively, $p=0.097$, $p=0.544$). Individual positive change was defined as a person changing status from being on sickness-related benefits to unemployment benefits or self-support, or maintaining self-support status. Negative change was defined as a person changing status from being on unemployment benefits or self-supporting to being on sickness-related benefits. Very few patients made a change in occupational status, that is neither a positive nor a negative change, during the 1-year follow-up. Only 5 patients in ACT-G and 7 in the waitlist made a negative change. It may be that data from the DREAM database are not sensitive enough to detect potential changes in sick leave as it does not register occasional sporadic short-term sick leave, and/or the sample not being large enough to measure a change.

Only one other RCT⁶⁴ on health anxiety conducted by Hedman et al. has, as far as we are aware, reported effects of treatment on sick leave. Yet, as discussed in paper III, the study focused on cost-effectiveness, and costs of sick leave was only one item of an aggregated variable of indirect costs. Also, no statistical analyses were available on the between groups change from before to after treatment or within-group change in the primary treatment group at follow-up times. Despite this, contrary to the present study, Hedman et al. report a rather large increase in costs of sick leave from pre-treatment to 1-year follow-up (mean (sd) cost of sick leave in £; from £159 (603) to £968 (908)). In the present study, we found that the waitlist group was very stable on all outcomes, be it the primary outcome of self-reported illness worry in paper II or the observer-independent outcome on sickness-related benefits in paper III, and hence the results are in line with the literature suggesting a chronic course in untreated health anxiety¹⁻⁵. Hedman et al. found that their control group, which was an internet discussion forum, showed a substantial increase in sick leave costs from pre- to post-treatment (mean (sd) cost of sick leave in £; from £236 (749) to £600 (1363)). A discussion forum may serve as an attention control and precautionously, these results may be interpreted in the way that a certain increase in sick leave could be caused by an augmented awareness or attention to the disorder, derived from being part of a discussion forum, and not necessarily a negative treatment effect. Still, this is mere speculation that needs empirical testing. Other explanations for differences between Hedman et al.'s findings and those of the present study's may be specific factors of the treatments such as different mechanisms of change between ACT and CBT, as discussed in the former section, or due to one treatment being an on-line treatment and the other a face-to-face group setting. It will be up to future studies to determine the contribution of specific treatment factors on outcomes such as sick leave.

As emphasised throughout the thesis, differences in findings may also be due to methodological differences such as assessment of health anxiety case status. In Hedman et al.'s study, case status was based on the broad DSM-IV hypochondriasis criteria, which may identify a heterogeneous sample of patients with somatoform disorders^{20, 48, 51} and not only patients with predominantly

severe health anxiety. Findings from an RCT¹⁴² conducted at The Research Clinic for Functional Disorders and Psychosomatics on patients with somatisation disorder and functional somatic syndromes may suggest that a broader group of somatoform disorders may have a more negative impact on sick leave, unemployment and disability pension than severe health anxiety. It can be speculated that patients suffering primarily from severe health anxiety classified according to the diagnostic criteria used in the present study¹ may show more sick leave compared to the general population, yet the impact of the disorder on sick leave, unemployment and disability may be less severe when compared to a broader group of somatoform disorders. It will be up to future research to find empirical evidence in support of this hypothesis.

Overall, findings from the present trial on the effect of untreated and treated health anxiety on sick leave need to be replicated in other and larger samples and other settings. Also, we recommend for future studies to combine subjective measures of sick leave with observer-independent measures in order to better estimate the total impact of health anxiety on sick-leave.

PERSPECTIVES FOR FUTURE RESEARCH

I will briefly discuss some perspectives for further research in the treatment of health anxiety based on the findings of this thesis. Knowing that a large majority of potentially eligible patients with severe health anxiety decline participation in CBT and some patients participating in CBT do not recover⁶⁹, we find the need for researchers and clinicians to further develop treatment approaches. Individual CBT might not fit every patient, thus having more treatment options is an advantage. Further studies are needed to replicate the promising findings of the current study in large-scale multicenter trials as well as to add another active treatment arm to the design, use several therapists, and rate treatment adherence and therapist competence.

The present study was conducted at a highly specialised clinic for functional disorders with highly trained therapists with substantial experience in group treatment, ACT and functional disorders. Also, many patients had to travel 2 hours to attend assessment and treatment. Comparable expertises are seldom available in medical settings. Patients with health anxiety are frequent in medical settings¹⁷, and it may be appropriate for treatment to be delivered in this setting by less specialised hospital staff. Recently, Tyrer et al.⁸⁶ for the first time tested this in a multicentre RCT and found a significant reduction in case status in patients allocated to CBT compared with standard care, yet effects of the study have been discussed, for one thing because the majority of potentially eligible patients declined participation¹⁴³.

When treating patients with health anxiety in medical settings, it is recommended to ensure proper identification of case status by thorough diagnostic assessment, which is not achieved by a questionnaire alone. In this context, the empirically established positive diagnostic criteria for health anxiety may prove useful as they seem acceptable to patients and may serve as a frame within which symptoms can be discussed and interpreted in a non-stigmatising and meaningful manner. Further studies are needed to test how the empirically-based diagnostic criteria for health anxiety and treatment may be implemented in medical settings in order to make treatment potentially easier accessible to patients compared to treatment offered in highly specialised settings and at times with poorly defined diagnostic criteria.

In a previous study by Wattar et al.⁷⁹ on health anxiety, the group format was dropped in favour of individual CBT, because the therapists found that their continual attempts to control and reduce anxiety due to illness worry contamination in the group made it difficult to focus on treatment strategies. In the present trial, we did not experience these problems, which may be explained by the ACT approach. In ACT, therapists deliberately do not focus on directly controlling or eliminating anxiety. Contrarily, experiencing and evoking illness worry in the group through experiential exercises and practising willingness in the presence of severe and persistent worry was a deliberate focus in the treatment, and clinically we experienced this type of exposure as important for improvement. In line with findings from the other group study⁷⁸, we clinically experienced that at large patients derived benefit from the group format as it may serve as a validating and normalising experience regarding their excessive illness worry. Still, as only two studies have tested this format, it needs further exploration. There may be a potential for a more cost-effective approach compared with resource demanding individual therapy. Also, comparing the effect and mediators of outcome in individual treatment compared with a group-based approach may provide evidence for pros and cons of the two approaches and help guide individually-tailored treatments.

ACT-G may be said to be a rather comprehensive treatment programme as it consists of ten group-sessions with a total of 30 hrs group treatment. Earlier RCTs on health anxiety have predominantly tested individual CBT with sessions ranging from 6-22. The only other group-based study offered eight 2-hour sessions (Table 2). A recent meta-analysis of CBT treatment outcome and moderators for health anxiety¹⁰⁷ has furthermore found that more sessions were associated with larger effect sizes post-treatment, yet this association was not significant at follow-up. Further research needs to investigate the relationship between session length / number of sessions and treatment outcome. Along the same lines, studies comparing the effect between the different evidence-based available treatments are needed. It may be that not all patients with severe health anxiety need intensive treatment or benefit from the same treatment, and further research related to the stepped care potential of the available treatments (treatment in medical settings, individual or group treatment, traditional or further developments of CBT, internet-based treatment) await attention.

The group therapy in the present study did not incorporate specific work-related components and was not focused on improving work ability or sick leave, and therefore the therapists did not directly intervene as regards the patients' work status. It is plausible that having targeted specific components of sickness-related work disability or employment might have resulted in a treatment effect on these outcomes as this has been suggested in research on cognitive-behavioural training¹⁴⁴.

It is up to future research to test the incorporation of these specific components in existing treatment manuals. Also, findings from the present study may suggest that a longer timeframe might be necessary to demonstrate effect on sick leave, and it may be recommended to combine observer-independent outcomes with self-reported outcomes.

Currently an RCT on internet-based ACT for severe health anxiety is being set up at the Research Clinic for Functional Disorders in order to test if ACT may also show effect in reducing illness worry when delivered online, which may be less resource-demanding

and hence potentially more cost-effective than face-to-face therapy.

Future follow-up studies and secondary analysis of the present RCT have been planned in order to investigate cost-effectiveness of ACT-G, mechanisms of change, predictors of treatment outcome and long-term (2-4 years) follow-up on outcomes of health care use, sick leave, self-reported symptoms and clinical case status assessed by diagnostic interview.

SUMMARY

Health anxiety is prevalent (5-9%) in all health care settings and in the general population, may have an early onset, and a poor prognosis is seen in severe cases if untreated. Research shows that health anxiety is rarely diagnosed though it causes great suffering for the individual and constitutes a substantial socio-economic burden. Studies have shown that individual cognitive behavioural therapy can relieve health anxiety, but these studies are affected by methodological problems, among others, struggling with patients declining participation, high dropout rates, and some patients not responding to the treatment. Moreover, the impact of health anxiety on sick leave is only scarcely examined. This thesis examines the effect of a new treatment approach, group-based Acceptance & Commitment Therapy (ACT-G) for patients with severe health anxiety in an uncontrolled pilot study and a randomised controlled study (RCT) on ACT-G compared with a 10-month waitlist control condition (paper I and II). Also, the thesis comprises a study on sick leave in patients with health anxiety compared with the general population during a 5-year period and the effect of ACT-G on sick leave. The findings from this study are described in paper III.

Patients (age 20-60 years) consecutively referred from general practitioners from Jutland and Funen in the period of March 2010 - April 2012 (approx. 2.5 million citizens) to the Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, were included. The pilot study included 34 patients, the RCT on ACT-G included 126 patients. In the RCT, patients were block-randomised to either ACT-G and received treatment in 7 groups of each 9 patients in the period of December 2010 - October 2012, or to a 10-month waitlist control group. The primary outcome measure was the Whiteley-7 paper and pencil index for illness worrying. The last paper is based on data on sickness-related benefits from the DREAM social register of transfer benefits and also includes a matched general population register control cohort (n=12,600).

In this thesis, we wish to answer the following questions:

- 1) Is ACT-G an acceptable, feasible and effective treatment approach for patients with severe health anxiety?
- 2) Can ACT-G improve severe illness worry compared with a waitlist control condition, and are the recently introduced diagnostic criteria for health anxiety acceptable for the patients?
- 3) Do patients with health anxiety show more sick leave than the general population during a 5-year period, and can ACT-G reduce sick leave measured by transfer benefits (weeks on sickness-related benefits) at one-year follow-up?

As ACT has not previously been examined as treatment approach for health anxiety, we initially conducted an uncontrolled pilot study to test the newly developed manualised program (ACT-G). The study included 34 patients with severe health anxiety and showed very low dropout and high treatment satisfaction. Significant improvements in self-reported illness worry were demonstrated post-treatment, and the results were sustained and fur-

ther improved at 3- and 6-months follow-up compared to baseline.

The subsequent RCT found high acceptance of the diagnosis of health anxiety. All patients (except one) accepted the diagnosis as the right diagnosis to fit their ailment, and the majority of the patients found that the diagnosis helped them to better understand their symptoms. In an intention-to-treat analysis, ACT-G showed significant effect in the improvement of self-reported illness worry and other secondary measures compared with a waitlist control condition, both post-treatment and at 10-month follow-up (6 months post-treatment). The results were considered clinically significant as 2/3 of the patients in ACT-G at follow-up had demonstrated a pre-defined treatment response, and ¼ of the patients were considered to no longer have clinical case status. Furthermore, the number needed to treat was found to be 2.4.

Patients with severe health anxiety showed significantly more weeks on sickness-related benefits than matched individuals from the general population during the five years prior to entering the RCT. This difference was stable until an estimated cut-point at 1 year before enrolment, where patients with health anxiety showed further increase in sickness-related-benefits. At one-year follow-up (8 months post-treatment), we did not find a significant difference between ACT-G and the waitlist group in weeks on sickness-related benefits. Post-hoc analysis, however, revealed a significant decrease in weeks on sickness-related benefits for ACT-G during the two years after randomisation.

In conclusion, the thesis suggests that ACT-G is both an acceptable and effective treatment approach for patients with severe health anxiety. Hopefully, these findings can contribute to the future research and identification of which treatment approaches are the most effective and for which patients and contribute to tailored, early interventions. This may possibly prevent development of otherwise chronic symptoms, increase the quality of life for the patients, and potentially reduce socio-economic costs.

REFERENCES

- (1) Fink P, Ørnbøl E, Toft T, Sparle KC, Frostholm L, Olesen F. A new, empirically established hypochondriasis diagnosis. *Am J Psychiatry* 2004 September;161(9):1680-91.
- (2) Eilenberg T, Kronstrand L, Fink P, Frostholm L. Acceptance and commitment group therapy for health anxiety - Results from a pilot study. *J Anxiety Disord* 2013 June 19;27(5):461-8.
- (3) Eilenberg T, Frostholm L, Schroder A, Jensen JS, Fink P. Long-term consequences of severe health anxiety on sick leave in treated and untreated patients: Analysis alongside a randomised controlled trial. *J Anxiety Disord* 2015 May;32:95-102.
- (4) Eilenberg T, Fink P, Jensen JS, Rief W, Frostholm L. Acceptance and commitment group therapy (ACT-G) for health anxiety: a randomized controlled trial. *Psychological med* 2015 August 18;46(01):103-15.
- (5) Fink P, Ørnbøl E, Christensen KS. The Outcome of Health Anxiety in Primary Care. A Two-Year Follow-up Study on Health Care Costs and Self-Rated Health. *PLoS ONE* 2010 March 24;5(3):e9873.
- (6) Salkovskis PM, Warwick HM. Morbid preoccupations, health anxiety and reassurance: a cognitive-behavioural approach to hypochondriasis. *Behav Res Ther* 1986;24(5):597-602.
- (7) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*. Fifth ed. Arlington, VA: American Psychiatric Association; 2013.
- (8) Kellner R, Schneider-Braus K. Distress and attitudes in patients perceived as hypochondriacal by medical staff. *Gen Hosp Psychiatry* 1988;May;10(3):157-62.
- (9) Hansen EB. *Paranoia Hypochondriaca*. København: Rigshospitalet, Psykiatrisk afd. O; 1976.
- (10) Kenyon FE. Hypochondriasis: a survey of some historical, clinical and social aspects. *Br J Med Psychol* 1965;38:117-33.
- (11) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-II)*. 2nd ed. Washington DC: American Psychiatric Association; 1968.
- (12) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. 3 ed. Washington DC: American Psychiatric Association; 1980.
- (13) American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-III-R)*. 3rd ed. Washington DC: American Psychiatric Association; 1987.
- (14) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4 ed. Washington DC: American Psychiatric Association; 1994.
- (15) Gureje O, Ustun TB, Simon GE. The syndrome of hypochondriasis: a cross-national study in primary care. *Psychological med* 1997 September;27(5):1001-10.
- (16) Longley S, Calamari JE, Noyes R, Meyers K, McDowell E. Health Anxiety (Hypochondriasis): An Emotional Disorder in an Alternative Taxonomy. *Current Psychiatry Reviews* 2014;10(1):3-13.
- (17) Weck F, Richtberg S, Neng JM. Epidemiology of Hypochondriasis and Health Anxiety: Comparison of Different Diagnostic Criteria. *Current Psychiatry Reviews* 2014;10(1):14-23.
- (18) Barsky AJ, Wyshak G, Klerman LG. Transient hypochondriasis. *Arch Gen Psychiatry* 1990 August;47(8):746-52.
- (19) Creed F, Barsky A. A systematic review of the epidemiology of somatisation disorder and hypochondriasis. *J Psychosom Res* 2004 April;56(4):391-408.
- (20) Hedman E, Andersson E, Andersson G et al. Mediators in internet-based cognitive behavior therapy for severe health anxiety. *PLoS ONE* 2013;8(10):e77752.
- (21) Allen LA, Woolfolk RL. Cognitive behavioral therapy for somatoform disorders. *Psychiatr Clin North Am* 2010 September;33(3):579-93.
- (22) Collimore CC, Asmundson GJG, Taylor S, Abramowitz JS. Classification of hypochondriasis and other somatoform disorders. In: McKay D, Abramowitz JS, Taylor S, Asmundson GJG, editors. Springer Publishing Company, LLC; 2009.
- (23) Noyes R, Jr. The relationship of hypochondriasis to anxiety disorders. *Gen Hosp Psychiatry* 1999 January;21(1):8-17.
- (24) Barsky AJ, Barnett MC, Cleary PD. Hypochondriasis and panic disorder. Boundary and overlap. *Arch Gen Psychiatry* 1994 November;51(11):918-25.
- (25) Olatunji BO, Deacon BJ, Abramowitz JS. Is hypochondriasis an anxiety disorder? *Br J Psychiatry* 2009 June;194(6):481-2.

- (26) Gropalis M, Bleichhardt G, Witthoft M, Hiller W. Hypochondriasis, somatoform disorders, and anxiety disorders: sociodemographic variables, general psychopathology, and naturalistic treatment effects. *J Nerv Ment Dis* 2012 May;200(5):406-12.
- (27) Tyrer P, Fowler-Dixon R, Ferguson B, Kelemen A. A plea for the diagnosis of hypochondriacal personality disorder. *J Psychosom Res* 1990;34(6):637-42.
- (28) Ferguson E. Hypochondriacal concerns and the five factor model of personality. *J Pers* 2000 August;68(4):705-24.
- (29) Noyes R, Happel RL, Yagla SJ. Correlates of hypochondriasis in a nonclinical population. *Psychosomatics* 1999 November;40(6):461-9.
- (30) Greeven A, van Balkom AJ, Spinhoven P. Personality predicts time to remission and clinical status in hypochondriasis during a 6-year follow-up. *J Nerv Ment Dis* 2014 May;202(5):402-7.
- (31) Barsky AJ, Wyshak G, Klerman LG. Hypochondriasis. An evaluation of the DSM-III criteria in Medical Outpatients. *Arch Gen Psychiatry* 1986;May;43(5):493-200.
- (32) Barsky AJ, Wyshak G, Klerman LG. Psychiatric comorbidity in DSM-III-R hypochondriasis. *Arch Gen Psychiatry* 1992;49:101-8.
- (33) Greeven A, van Balkom AJ, van der LR, Merkelbach JW, van den Heuvel OA, Spinhoven P. Cognitive behavioral therapy versus paroxetine in the treatment of hypochondriasis: an 18-month naturalistic follow-up. *J Behav Ther Exp Psychiatry* 2009 September;40(3):487-96.
- (34) Olde Hartman TC, Borghuis MS, Lucassen PL, van de Laar FA, Speckens AE, van WC. Medically unexplained symptoms, somatisation disorder and hypochondriasis: course and prognosis. A systematic review. *J Psychosom Res* 2009 May;66(5):363-77.
- (35) Taylor S, Lang KL, Stein MB, Asmundson GJG. A behavioral-genetic analysis of health anxiety: Implications for the cognitive-behavioral model of hypochondriasis. *J Cogn Psychother* 2008;22(2):143-53.
- (36) Taylor S, Thordarson DS, Jang KL, Asmundson GJ. Genetic and environmental origins of health anxiety: a twin study. *World Psychiatry* 2006 February;5(1):47-50.
- (37) Fiddler M, Jackson J, Kapur N, Wells A, Creed F. Childhood adversity and frequent medical consultations. *Gen Hosp Psychiatry* 2004 September;26(5):367-77.
- (38) Reiser SJ, McMillan KA, Wright KD, Asmundson GJ. Adverse childhood experiences and health anxiety in adulthood. *Child Abuse Negl* 2014 March;38(3):407-13.
- (39) Noyes R, Jr., Stuart S, Langbehn DR, Happel RL, Longley SL, Yagla SJ. Childhood antecedents of hypochondriasis. *Psychosomatics* 2002 July;43(4):282-9.
- (40) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. 4 ed. Washington DC: American Psychiatric Association; 2000.
- (41) Noyes Jr R, Kathol RG, Fisher MM, Phillips BM, Suelzer MT, Woodman CL. One-year follow-up of medical outpatients with hypochondriasis. *Psychosomatics* 1994 November;35(6):533-45.
- (42) Barsky AJ, Fama JM, Bailey ED, Ahern DK. A prospective 4- to 5-year study of DSM-III-R hypochondriasis. *Arch Gen Psychiatry* 1998 August;55(8):737-44.
- (43) Simon GE, Gureje O, Fullerton C. Course of hypochondriasis in an international primary care study. *Gen Hosp Psychiatry* 2001 March;23(2):51-5.
- (44) Noyes R, Stuart S, Watson DB, Langbehn DR. Distinguishing between Hypochondriasis and Somatization Disorder: A Review of the Existing Literature. *Psychother Psychosom* 2006;75(5):270-81.
- (45) Barsky AJ, Wyshak G, Klerman LG, Latham KS. The prevalence of hypochondriasis in medical outpatients. *Soc Psychiatry Psychiatr* 1990 March;25(2):89-94.
- (46) Barsky AJ, Frank CB, Cleary PD, Wyshak G, Klerman LG. The relation between hypochondriasis and age. *Am J Psychiatry* 1991;148:923-8.
- (47) Greeven A, van Balkom AJ, Visser S et al. Cognitive behavior therapy and paroxetine in the treatment of hypochondriasis: a randomized controlled trial. *Am J Psychiatry* 2007 January;164(1):91-9.
- (48) Barsky AJ, Ahern DK, Bauer MR, Nolino N, Orav EJ. A Randomized Trial of Treatments for High-Utilizing Somatizing Patients. *J Gen Intern Med* 2013 March 14.
- (49) McManus F, Surawy C, Muse K, Vazquez-Montes M, Williams JM. A Randomized Clinical Trial of Mindfulness-Based Cognitive Therapy Versus Unrestricted Services for Health Anxiety (Hypochondriasis). *J Consult Clin Psychol* 2012 June 18.
- (50) Hedman E, Andersson G, Andersson E et al. Internet-based cognitive-behavioural therapy for severe health anxiety: randomised controlled trial. *Br J Psychiatry* 2011 March;198:230-6.
- (51) Hedman E, Axelsson E, Gorling A et al. Internet-delivered exposure-based cognitive-behavioural therapy and behavioural stress management for severe health anxiety: randomised controlled trial. *Br J Psychiatry* 2014 August 7.
- (52) Hiller W, Leibbrand R, Rief W, Fichter MM. Predictors of Course and Outcome in Hypochondriasis after Cognitive-Behavioral Treatment. *Psychother Psychosom* 2002 November;71(6):318-25.
- (53) Kellner R. Prognosis of treated hypochondriasis. A clinical study. *Acta Psychiatr Scand* 1983;67:69-79.
- (54) Rosendal M, Fink P, Olesen F. Managing medically unexplained symptoms. *BMJ* 2005;330:4-5.
- (55) Dowrick CF, Ring A, Humphris GM, Salmon P. Normalisation of unexplained symptoms by general practitioners: a functional typology. *Br J Gen Pract* 2004 March;54(500):165-70.
- (56) Gerson CD, Gerson MJ. A collaborative health care model for the treatment of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003 November;1(6):446-52.
- (57) Hansen MS, Fink P, Frydenberg M, Oxhøj ML. Use of health services, mental illness, and self-rated disability and health in medical inpatients. *Psychosom Med* 2002 July;64(4):668-75.
- (58) Hansen MS, Fink P, Sondergaard L, Frydenberg M. Mental illness and health care use: a study among new neurological patients. *Gen Hosp Psychiatry* 2005 March;27(2):119-24.
- (59) Fink P. *Persistent Somatization*. Thesis; Faculty of Health Sciences, University of Aarhus, Denmark 1997.
- (60) Fink P, Rosendal M, Toft T. *Assessment and Treatment of Functional Disorders in General Practice: The Extended Reattribution and Management Model - An Advanced Educational Program for Nonpsychiatric Doctors*. *Psychosomatics* 2002;43(2):93-131.
- (61) Fink P, Burton C, de Bie J, Söllner W, Fritzsche K. Current state of management and organisation of care. In:

- Creed F, Henningsen P, Fink P, editors. Medically unexplained symptoms, somatisation and bodily distress: Developing better clinical services. Cambridge University Press; 2011. p. 97-123.
- (62) Sutherland M, Newby JM, Andrews G. Health anxiety in Australia: prevalence, comorbidity, disability and service use. *Br J Psychiatry* 2012 April 12.
- (63) Barsky AJ, Ettner SL, Horsky J, Bates DW. Resource utilization of patients with hypochondriacal health anxiety and somatization. *Med Care* 2001 July;39(7):705-15.
- (64) Hedman E, Andersson E, Lindfors N, Andersson G, Ruck C, Ljotsson B. Cost-effectiveness and long-term effectiveness of Internet-based cognitive behaviour therapy for severe health anxiety. *Psychological med* 2012 May 21;1-12.
- (65) Martin A, Jacobi F. Features of hypochondriasis and illness worry in the general population in Germany. *Psychosom Med* 2006 September;68(5):770-7.
- (66) Mykletun A, Heradstveit O, Eriksen K et al. Health anxiety and disability pension award: The HUSK Study. *Psychosomatic Med* 2009 April;71(3):353-60.
- (67) Konnopka A, Schaefer R, Heinrich S et al. Economics of medically unexplained symptoms: a systematic review of the literature. *Psychother Psychosom* 2012;81(5):265-75.
- (68) Kenyon FE. Hypochondriasis: a clinical study. *Br J Psychiatry* 1964;110:478-88.
- (69) Thomson AB, Page LA. Psychotherapies for hypochondriasis. *Cochrane Database Syst Rev* 2007;(4):CD006520.
- (70) Walker J, Vincent N, Furer P, Cox B, Kjernisted K. Treatment preference in hypochondriasis. *J Behav Ther Exp Psychiatry* 1999 December;30(4):251-8.
- (71) Fallon BA, Petkova E, Skritskaya N et al. A double-masked, placebo-controlled study of fluoxetine for hypochondriasis. *J Clin Psychopharmacol* 2008 December;28(6):638-45.
- (72) Barsky AJ, Geringer E, Wool CA. A cognitive-educational treatment for hypochondriasis. *Gen Hosp Psychiatry* 1988;Sep;10(5):322-7.
- (73) Avia MD, Ruiz MA, Olivares ME et al. The meaning of psychological symptoms: effectiveness of a group intervention with hypochondriacal patients. *Behav Res Ther* 1996 January;34(1):23-31.
- (74) Bouman TK, Buwalda FM. A Psychoeducational Approach to Hypochondriasis: Background, Content, and Practice Guidelines. *Cogn Behav Pract* 2008;15(3):231-43.
- (75) Buwalda FM, Bouman TK, van Duijn MA. Psychoeducation for hypochondriasis: a comparison of a cognitive-behavioural approach and a problem-solving approach. *Behav Res Ther* 2007 May;45(5):887-99.
- (76) Taylor S, Asmundson GJG. Treating health anxiety. A cognitive-behavioral approach. The Guilford press; 2004.
- (77) Bouman TK. Psychological Treatments for Hypochondriasis. A Narrative Review. *Current Psychiatry Reviews* 2014;10(1):58-69.
- (78) Williams MJ, McManus F, Muse K, Williams JM. Mindfulness-based cognitive therapy for severe health anxiety (hypochondriasis): an interpretative phenomenological analysis of patients' experiences. *Br J Clin Psychol* 2011 November;50(4):379-97.
- (79) Wattar U, Sorensen P, Buemann I et al. Outcome of Cognitive-Behavioural Treatment for Health Anxiety (Hypochondriasis) in a Routine Clinical Setting. *Behavioural and Cognitive Psychotherapy* 2005;33(02):165-75.
- (80) Visser S, Bouman TK. The treatment of hypochondriasis: exposure plus response prevention vs cognitive therapy. *Behav Res Ther* 2001 April;39(4):423-42.
- (81) Sorensen P, Birket-Smith M, Wattar U, Buemann I, Salkovskis P. A randomized clinical trial of cognitive behavioural therapy versus short-term psychodynamic psychotherapy versus no intervention for patients with hypochondriasis. X 2010;(1469-8978 (Electronic)).
- (82) Barsky AJ, Ahern DK. Cognitive behavior therapy for hypochondriasis: a randomized controlled trial. *JAMA* 2004 March 24;291(12):1464-70.
- (83) Clark DM, Salkovskis PM, Hackmann A et al. Two psychological treatments for hypochondriasis. A randomized controlled trial. *Br J Psychiatry* 1998 September;173:218-25.
- (84) Warwick HM, Clarke DM, Cobb AM, Salkovskis PM. A controlled trial of cognitive-behavioural treatment of hypochondriasis. *Br J Psychiatry* 1996 August;169(2):189-95.
- (85) Seivewright H, Green J, Salkovskis P, Barrett B, Nur U, Tyrer P. Cognitive-behavioural therapy for health anxiety in a genitourinary medicine clinic: randomised controlled trial. *Br J Psychiatry* 2008 October;193(4):332-7.
- (86) Tyrer P, Cooper S, Salkovskis P et al. Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: a multicentre randomised controlled trial. *Lancet* 2014 January 18;383(9913):219-25.
- (87) Fava GA, Grandi S, Rafanelli C, Fabbri S, Cazzaro M. Explanatory therapy in hypochondriasis. *J Clin Psychiatry* 2000 April;61(4):317-22.
- (88) Hayes SC, Strosahl KD, Wilson KG. Acceptance and Commitment Therapy, An experiential approach to behavior change. New York: The Guilford Press; 1999.
- (89) Hayes SC, Strosahl KD, Wilson KG. Acceptance and Commitment Therapy. The Process and Practice of Mindful Change. 2nd ed. New York: The Guilford Press; 2012.
- (90) Hayes SC, Villatte M, Levin M, Hildebrandt M. Open, aware, and active: contextual approaches as an emerging trend in the behavioral and cognitive therapies. *Annu Rev Clin Psychol* 2011 April;7:141-68.
- (91) Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther* 2006 January;44(1):1-25.
- (92) Hofmann SG, Asmundson GJ. Acceptance and mindfulness-based therapy: new wave or old hat? *Clin Psychol Rev* 2008 January;28(1):1-16.
- (93) Twohig MP, Hayes SC, Plumb JC et al. A randomized clinical trial of acceptance and commitment therapy versus progressive relaxation training for obsessive-compulsive disorder. *J Consult Clin Psychol* 2010 October;78(5):705-16.
- (94) Forman EM, Herbert JD, Moitra E, Yeomans PD, Geller PA. A randomized controlled effectiveness trial of acceptance and commitment therapy and cognitive therapy for anxiety and depression. *Behav Modif* 2007 November;31(6):772-99.
- (95) Forman EM, Shaw JA, Goetter EM, Herbert JD, Park JA, Yuen EK. Long-term follow-up of a randomized con-

- trolled trial comparing acceptance and commitment therapy and standard cognitive behavior therapy for anxiety and depression. *Behav Ther* 2012 December;43(4):801-11.
- (96) Arch JJ, Eifert GH, Davies C, Vilardaga JC, Rose RD, Craske MG. Randomized Clinical Trial of Cognitive Behavioral Therapy (CBT) Versus Acceptance and Commitment Therapy (ACT) for Mixed Anxiety Disorders. *J Consult Clin Psychol* 2012 May 7;80(5):750-65.
- (97) Roemer L, Orsillo SM, Salters-Pedneault K. Efficacy of an acceptance-based behavior therapy for generalized anxiety disorder: evaluation in a randomized controlled trial. *J Consult Clin Psychol* 2008 December;76(6):1083-9.
- (98) Hayes-Skelton SA, Roemer L, Orsillo SM. A Randomized Clinical Trial Comparing an Acceptance-Based Behavior Therapy to Applied Relaxation for Generalized Anxiety Disorder. *J Consult Clin Psychol* 2013 May 6.
- (99) Bach P, Hayes SC. The use of acceptance and commitment therapy to prevent the rehospitalization of psychotic patients: a randomized controlled trial. *J Consult Clin Psychol* 2002 October;70(5):1129-39.
- (100) Bach P, Hayes SC, Gallop R. Long-term effects of brief acceptance and commitment therapy for psychosis. *Behav Modif* 2012 March;36(2):165-81.
- (101) Wetherell JL, Afari N, Rutledge T et al. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain* 2011 September;152(9):2098-107.
- (102) Swain J, Hancock K, Hainsworth C, Bowman J. Acceptance and Commitment Therapy in the treatment of anxiety: A systematic review. *Clin Psychol Rev* 2013 July 16;33(8):965-78.
- (103) Ost LG. The efficacy of Acceptance and Commitment Therapy: An updated systematic review and meta-analysis. *Behav Res Ther* 2014 Oct;61:105-21
- (104) Bluett EJ, Homan KJ, Morrison KL, Levin ME, Twohig MP. Acceptance and commitment therapy for anxiety and OCD spectrum disorders: An empirical review. *J Anxiety Disord* 2014 June 23;28(6):612-24.
- (105) Vedsted P. Kønssforskelle i brug af sundhedsvæsenet. *Ugeskr laeger* 2007;169(25):2403-8.
- (106) Cunningham JA, Kypri K, McCambridge J. Exploratory randomized controlled trial evaluating the impact of a waiting list control design. *BMC Med Res Methodol* 2013;13:150.
- (107) Olatunji BO, Kauffman BY, Meltzer S, Davis ML, Smits JA, Powers MB. Cognitive-behavioral therapy for hypochondriasis/health anxiety: A meta-analysis of treatment outcome and moderators. *Behav Res Ther* 2014 July;58:65-74.
- (108) Jorgensen CK, Karlsmose B. Validation of automated forms processing. A comparison of Teleform with manual data entry. *Comput Biol Med* 1998 November;28(6):659-67.
- (109) Kellner R, Abbott P, Winslow WW, Pathak D. Fears, beliefs, and attitudes in DSM-III hypochondriasis. *J Nerv Ment Dis* 1987;Jan;175(1):20-5.
- (110) Salkovskis PM, Rimes KA, Warwick HM, Clarke DM. The Health Anxiety Inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychol Med* 2002 July;32(5):843-53.
- (111) Kellner R. Somatization and hypochondriasis. New York: Praeger Publishers; 1986.
- (112) Kellner R. Abridged manual of the Illness Attitudes Scale. University of New Mexico; 1987.
- (113) Pilowsky I. Dimensions of hypochondriasis. *Br J Psychiatry* 1967;113:89-93.
- (114) Hiller W, Rief W, Fichter MM. Dimensional and categorical approaches to hypochondriasis. *Psychol Med* 2002 May;32(4):707-18.
- (115) Sirri L. Dimensional Assessment of Hypochondriacal Fears and Beliefs. *Current Psychiatry Reviews* 2014;10(1):50-7.
- (116) Fink P, Ewald H, Jensen J et al. Screening for somatization and hypochondriasis in primary care and neurological in-patients: a seven-item scale for hypochondriasis and somatization. *J Psychosom Res* 1999 March;46(3):261-73.
- (117) Asmundson GJG, Carleton RN, Bovell CV, Taylor S. Comparison of unitary and multidimensional models of the whiteley index in a nonclinical sample: Implications for understanding and assessing health anxiety. *J Cogn Psychother* 2008;22(2):87-96.
- (118) Conradt M, Cavanagh M, Franklin J, Rief W. Dimensionality of the Whiteley Index: assessment of hypochondriasis in an Australian sample of primary care patients. *J Psychosom Res* 2006 February;60(2):137-43.
- (119) Christensen KS, Bech P, Fink P. Measuring mental health by questionnaires in primary care - Unidimensionality, responsiveness and compliance. *European Psychiatric Review* 2010;3(1):9-12.
- (120) Veddegjaerde KE, Sivertsen B, Wilhelmsen I, Skogen JC. Confirmatory factor analysis and item response theory analysis of the Whiteley Index. Results from a large population based study in Norway. The Hordaland Health Study (HUSK). *J Psychosom Res* 2014 September;77(3):213-8.
- (121) WHO. SCAN. Schedules for Clinical Assessment in Neuropsychiatry, version 2.1. Geneva: World Health Organization, Division of Mental Health; 1998.
- (122) SCAN I-Shell. Computer assisted personal interviewing application for SCAN ver 2.1 [computer program]. Geneva: World Health Organization; 1999.
- (123) Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health* 2007;35(5):497-502.
- (124) Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999 September 11;319(7211):670-4.
- (125) Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med* 2002 October 15;21(19):2917-30.
- (126) Altman DG, Schulz KF, Moher D et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001 April 17;134(8):663-94.
- (127) Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. *Br J Psychiatry* 1999 April;174:297-303.
- (128) de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal changes in health status ques-

- tionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes* 2006;4:54.
- (129) Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003 May;41(5):582-92.
- (130) Hedman E, Lindfors N, Andersson G et al. Predictors of outcome in Internet-based cognitive behavior therapy for severe health anxiety. *Behav Res Ther* 2013 August 11;51(10):711-7.
- (131) Beaber RJ, MacMillan, Rodney W. Underdiagnosis of hypochondriasis in family practice. *Psychosomatics* 1984;25:39-46.
- (132) Mayou R, Kirmayer LJ, Simon G, Kroenke K, Sharpe M. Somatoform Disorders: Time for a New Approach in DSM-V. *Am J Psychiatry* 2005 May;162(5):847-55.
- (133) Ware JE, Kosinski M. SF-36 Physical and Mental Health Summary Scales: A Manual for Users of Version 1, Second Edition. Lincoln, RI: Quality Metric Inc.; 2001.
- (134) Ruiz FJ. Psychological inflexibility mediates the effects of self-efficacy and anxiety sensitivity on worry. *Span J Psychol* 2014 January;17:E3.
- (135) Davies CD, Niles AN, Pittig A, Arch JJ, Craske MG. Physiological and behavioral indices of emotion dysregulation as predictors of outcome from cognitive behavioral therapy and acceptance and commitment therapy for anxiety. *J Behav Ther Exp Psychiatry* 2014 August 23;46C:35-43.
- (136) Kabat-Zinn J. *Wherever you go, there you are: Mindfulness Meditation i everyday life*. New York: Hyperion; 1994.
- (137) Kenny MA, Williams JM. Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy. *Behav Res Ther* 2007 March;45(3):617-25.
- (138) Twohig MP. Acceptance and Commitment Therapy for Treatment-Resistant Posttraumatic Stress Disorder: A Case Study. *Cogn Behav Pract* 2009 August;16(3):243-52.
- (139) Masuda A, Hayes SC, Fletcher LB et al. Impact of acceptance and commitment therapy versus education on stigma toward people with psychological disorders. *Behav Res Ther* 2007 November;45(11):2764-72.
- (140) <http://www.div12.org/PsychologicalTreatments/treatments.html>. 2014. Internet Communication
- (141) Ost LG. Efficacy of the third wave of behavioral therapies: a systematic review and meta-analysis. *Behav Res Ther* 2008 March;46(3):296-321.
- (142) Fjorback LO, Carstensen T, Arendt M et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: analysis of economic consequences alongside a randomized trial. *J Psychosom Res* 2013 January;74(1):41-8.
- (143) Wise J. Short course of cognitive behavioural therapy may reduce health anxiety, say researchers. *BMJ* 2013;347:f6308.
- (144) Lagerveld SE, Blonk RW, Brenninkmeijer V, Wijngaards-de ML, Schaufeli WB. Work-focused treatment of common mental disorders and return to work: a comparative outcome study. *J Occup Health Psychol* 2012 April;17(2):220-34.