Hypochondriasis. diagnostic issues and treatment.

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Summary and Discussion

Chapter 8

Outline

The present thesis has three main objectives. Chapter 2 to 4 can be grouped among the objective of diagnostics. In chapter 2 and 3 the boundaries between hypochondriasis and obsessive compulsive disorder (OCD) were assessed in order to gather more information about diagnostic overlap between both disorders and extending the evidence for placing hypochondriasis among the OCD spectrum disorders. In chapter 4, the extent of overlap between hypochondriasis and non cardiac chest pain (NCCP) was investigated and it was examined whether a diagnosis of hypochondriasis could be predicted by the presence of certain personality characteristics, like harm avoidance, self-directedness and uncooperativeness.

The second objective concerned treatment of hypochondriasis (chapter 5 and 6). In chapter 5, the short term treatment effect of open Cognitive Behavioral Therapy (CBT) and double-blinded Paroxetine and a placebo was investigated. The outcome of the naturalistic follow-up of this trial is reported in chapter 6.

Finally, because assessor-ratings are still lacking in the assessment of hypochondriasis the third objective was to adapt the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for hypochondriasis and examine its psychometric qualities (e.g. validity and reliability) (chapter 7).

In the following, the objectives will shortly be summarized and discussed first. Subsequently, some methodological issues about the studies will be considered and the theoretical implications of the studies will be

addressed. The discussion ends which some implications for clinical practice and suggestions for future research.

Summary

Diagnostics

Since hypochondriasis is, just like OCD, characterized by obsessive thoughts and repetitive stereotyped behaviours, it has been suggested that this disorder belongs to the OCD-spectrum (Hollander, 1993). A study on diagnosis-specific symptoms of hypochondriacs, OCD patients and healthy controls, however, revealed that the extent of symptomatic overlap between both disorders is rather small.

Nevertheless, hypochondriasis appeared to share several features with OCD patients: OCD patients, also those of the contamination/cleaning OCD subtype, had as much (feared) physical symptoms as hypochondriacs and the types of physical symptoms reported by both groups were approximately the same.

Furthermore, it was found that OCD patients suffering from illness-related obsessions, and patients with hypochondriasis shared the presence of fears of having an illness next to fears of acquiring an illness, reported flashes and evaluated their health-related thoughts as unreasonable. Besides, it was found that both groups used the same types of safety-seeking behaviours to avert or neutralize the obsessions.

A parallel discussion is about whether non cardiac chest pain (NCCP) is a veiled form of hypochondriasis. NCCP subjects are, just like

hypochondriacs, characterized by fearful attributions about their health and resort to anxiety-reducing behaviours in order to prevent or avert the feared catastrophe (Eifert, 1992). The results of a study comparing both groups demonstrated, however, that hypochondriacs were far more anxious about their health than NCCP subjects. Moreover, hypochondriacs appeared to be more harm-avoidant, less cooperative and less self-directed than NCCP subjects, but none of these personality characteristics predicted a diagnosis of hypochondriasis. Instead, hypochondriasis was primarily predicted by the presence of substantial health anxiety and a younger age. These findings are not in accordance with the assertion that hypochondriasis can be conceptualized as a personality disorder instead of a somatoform disorder (Tyrer et al., 1991).

Objective 2, treatment

Although several randomized controlled trial (RCT's) demonstrated that CBT was significantly more effective than a waiting list control group in the treatment of hypochondriasis, both directly after treatment and during naturalistic follow-up periods of approximately one year (Warwick, Clark, Cobb, & Salkovskis, 1996; Clark et al., 1998; Visser & Bouman, 2001; Barsky & Ahern, 2004), well-conducted placebo-controlled pharmacological treatment studies were still missing. The results of open-label studies mostly lacking a placebo group and with a short follow-up period with antidepressants, however, were promising (Fallon, Liebowitz, & Salman, 1993; Oosterbaan, van Balkom, van Boeijen, de Meij, & van Dyck, 2001). In

this thesis the first RCT comparing the efficacy of CBT, Paroxetine and a placebo is presented.

This RCT showed that after 16 weeks of treatment patients in the CBT, Paroxetine and placebo group had significantly less hypochondriacal, psychoneurotic, anxious and depressive symptoms compared to the pre-test assessment. In addition, patients in the CBT and the Paroxetine group had significantly less hypochondriacal symptoms than patients in the placebo group and did not differ significantly from each other.

After this 16-week treatment period, patients treated with placebo were offered active antidepressants or CBT, according to their preference. In addition, patients in both active treatment groups who were not sufficiently improved during the RCT were treated tailored to their individual needs.

From the results of the naturalistic follow-up period it could be concluded that after 1-month of follow-up, patients in the CBT and Paroxetine group still appeared to have less hypochondriacal complaints than patients in the former placebo condition. CBT, however, appeared to have a slight advantage above the former placebo group, because only this form of treatment predicted a significant decrease in depressive and psychoneurotic symptoms.

During the remaining follow-up period of 13-months the difference between active treatment and placebo gradually disappeared because the patients in the former placebo condition were treated with CBT or Paroxetine and therefore caught up with the former CBT and Paroxetine groups. Only duration of hypochondriasis significantly predicted deceleration of speed of recovery of hypochondriacal complaints, independent of treatment group, during the follow-up period. The presence

of comorbid diagnoses predicted slowing down of amelioration of the comorbid anxious and depressive symptoms.

Up to six years of the conclusion of the RCT patients were interviewed about the course of their hypochondriacal symptoms during the follow-up period. Fifty-three of all patients scored above the pre-determined cut-off score, which meant that they did still suffer from hypochondriacal complaints. Furthermore, it appeared that 6 years after conclusion of the RCT the presence of hypochondriacal complaints did not differ between the 3 original groups, but that the first year after conclusion of the RCT, 67% of the former placebo group had received treatment for their hypochondriacal complaints compared to 77% in the former paroxetine group and only 29% in the former CBT group. Six years after concluding the RCT these percentages were respectively 61%, 46% and 18%. Additional treatment during the follow-up period might therefore explain the fading out of differential treatment effects.

It is concluded that hypochondriacal complaints ameliorate after treatment, but that a subgroup of patients does not benefit fully from treatment.

Objective 3, assessment

The psychometric properties of the first clinician-administered semi-structured interview for assessing the presence and severity of hypochondriacal symptoms were investigated in chapter 6. The 16-item hypochondriasis Y-BOCS consisted of three *a priori* dimensions:

hypochondriacal obsessions (including insight) (6 items), compulsions (5 items), and avoidance (5 items).

The hypochondriasis Y-BOCS appeared to be a (factorially) valid and coherent interview with a high level of homogeneity across different raters. Moreover, the sensitivity to change was good as assessed in a subgroup of patients from the RCT. The relatively low convergent validity could be explained by the fact that the Y-BOCS for hypochondriasis has been developed for assessing the severity of hypochondriacal fears and behaviors in terms of time spent on thoughts and behaviors, interference with daily functioning, distress, resistance and control, while the convergent measures were content-related. The low discriminant validity could be due to co-morbid anxiety and depressive disorders and to the content of the divergent measures, all of which contained items for non-specific complaints.

Methodological issues

In the following paragraphs several methodological issues concerning the RCT will be discussed. First a short definition of internal and external validity will be given, since both play a central role in evaluating the methodological strengths and weaknesses of a particular study (Kazdin, 1986). According to Kazdin (1986) internal validity addresses the following question 'To what extent can the intervention, rather than extraneous influences, be considered to account for the results, change or group differences?' (p. 22). External validity, by contrast questions 'To what extent can the results be generalized or extended to persons, settings, times,

measures and characteristics other than those in this particular experimental arrangement?' (p. 22).

Internal validity is maximized when the efficacy of interventions is assessed with minimization of bias based on unknown factors to avoid false conclusions and is determined by homogeneity of a sample of adequate size meeting highly restricted eligibility criteria. Furthermore, patients are randomly allocated to a treatment arm. When possible, treatment takes place double-blinded and treatment conditions are clearly defined, standardized, manual-based and conducted by highly skilled, rigorously trained, and closely monitored therapist who will be supervised during the treatment. In addition, the outcome measure is based on a clearly defined and validated primary outcome measure (Nash, Andrasik, McCrory, & Nicholson, 2005).

Although the merits of trials with maximum internal validity are beyond doubt in investigating the efficacy of new treatments, there has been a lot of criticism of clinicians about generalizibility of these in 'laboratory' situations generated results to daily practice. The effect of interventions in an ideal research setting (efficacy) may well differ from its effect in the real world (effectiveness) (Stephenson & Imrie, 1998).

Because controlling for a potential threat to internal validity has direct implications for the external validity and vice versa (Kazdin, 1986), it may be clear that the relation between internal validity and external validity is strained and difficult. Besides, even when at first sight the conditions for an efficacy trial are met; internal validity is not automatically guaranteed. To what extent this applies to the studies in the present thesis will be clarified in the following paragraphs.

Recruitment

Hundred and twelve subjects were randomized to the three arms of the RCT. Subjects were not recruited from the same source: seventy-four (66%) had been referred by their general practitioner (GP) and 38 (34%) responded on articles in newspapers. Referral by a GP or self-referral did not result in any differences on demographic and psychiatric status variables at pretest. Furthermore, referral did not predict responder status. So, there was no differential effect of source of referral on treatment outcome, although it could be argued that self-referred patients will be more motivated for a treatment from a psychological point of view than those referred by their GP.

Nevertheless, one major problem concerning the external validity of the results remains. There is a considerable chance that only a subgroup of hypochondriacs has been reached for two reasons: not only must patients be willing to be treated for hypochondriasis in stead of a somatic disorder, but also the general practitioner must recognize the nature of the problems to be able to diagnose and refer adequately. It is unknown to what extent these factors have influenced the external validity of the findings.

Inclusion and exclusion criteria

There were some criteria which led to exclusion from the trial. Subjects with comorbid psychotic disorders, substance-use disorders and organic mental disorders, pregnant and lactating women and subjects with severe medical illnesses were excluded. Concomitant use of antidepressants,

mood stabilizers, antipsychotics and anticoagulants, an allergy for SSRI's and being in psychotherapy for hypochondriasis elsewhere were also exclusion criteria.

At the same time less rigorous criteria were applied in case of a comorbid mood disorder, anxiety disorder, and other somatoform disorders and concomitant benzodiazepine use. Patients suffering from one of these disorders in addition to hypochondriasis were included when they indicated hypochondriasis to be the psychiatric disorder they suffered the most. This decision was based on results of two studies which examined in detail the prevalence of psychiatric disorder of subjects with DSM-III-R hypochondriasis. Both studies demonstrated that a substantial proportion of subjects with hypochondriasis also suffers from a comorbid depressive disorder (from 44% to 55%) or a comorbid anxiety disorder (from 22% to 86%) (Barsky, Wyshak & Klerman, 1992; Noyes, Kathol, Fisher & Phillips, 1994). Refusing patients with a comorbid diagnosis would therefore severely restrict the external validity. The comorbidity rate in the RCT reported in this thesis was high: 75% evenly distributed among the three treatment groups. Hypochondriacal patients with a comorbid mood or anxiety disorder had not more severe symptoms at pretest than those without comorbidity. Furthermore, comorbidity did not predict responder status, so increasing the external validity was not at the expense of internal validity.

Concomitant use of benzodiazepines was also permitted to a maximum of the equivalent of 30mg oxazepam, but only if subjects had been taking benzodiazepines for more than 3 months and were willing to keep use at a constant dosage for the duration of the trial.

The rationale for including patients using benzodiazepines was that this medication is in general prescribed for the comorbid disorders, like generalized anxiety disorder and panic disorder (Shader & Greenblatt, 1993). Furthermore, its use is substantial in a hypochondriacal population (Barsky, 2001).

Although the rationale to allow benzodiazepine use was understandable, it is also an example of the strained relationship between internal and external validity, because of the following. First, although it is well-known that patients using benzodiazepine have less anxiety symptoms (a positive effect), they also have a decreased tolerance towards anxiety symptoms compared to when not using benzodiazepines (a negative effect) (Fava et al., 1994). Possibly, benzodiazepine use interfered negatively with exposure during CBT, because one of the main targets of exposure, namely habituation to anxiety, has been compromised. During exposure patients need to tolerate a certain amount of anxiety in order to learn that nothing terrible is going to happen which helps them to adjust their catastrophic cognitions. Studies on the effect of CBT for panic disorder showed indeed that long-term benzodiazepine use was associated with smaller treatment gains (van Balkom, Lange, van Dyck, de Beurs, & Koele, 1996). Second, general arguments against long-term benzodiazepine are its side effects, like feelings of depression or sedation, falls and traffic accidents, which makes it an ineffective treatment in case of a comorbid depression. Furthermore, there is a growing risk of physical dependence and withdrawal symptoms after stopping the drugs (Shader & Greenblatt, 1993; Ashton, 2005).

In the present population 19% of the sample used benzodiazepines, evenly distributed over the three treatment groups. In order to rule out that

changing the benzodiazepine dosage would influence outcome, subjects were asked to keep their use at a constant level during the trial, which was checked at all visits. The policy with respect to concomitant benzodiazepine use was liberal. Therefore, it seems unlikely that subjects surreptitiously used extra benzodiazepines. Benzodiazepine users did not differ in symptom severity at pretest from not-benzodiazepine users. At post-test, however, subjects using concomitant benzodiazepines responded significantly less than those who were not. When analyzing the predictive role of benzodiazepine use in change of hypochondriacal symptoms from pretest to one-month follow-up and from one month follow up to 18-months follow-up, however, no significant effect of benzodiazepine use was found. These contradictory results with regard to benzodiazepine use can probably largely be explained by differences in methods, like (i) data-analysis (independent sample t-test versus regression models) and (ii) number of assessments (two versus three). In summary, although there are some strong arguments against the use of benzodiazepine during treatment, more definitive conclusions can only be drawn when more treatment studies have investigated its role, using similar data-analytic approaches.

Setting, clinicians and treatment

Diagnosis and treatment took place at three psychiatric outpatient clinics in the Western region of the Netherlands. All were specialized in treating patients with hypochondriacal complaints.

Behavioral therapists as well as psychiatrists were trained to use the treatment protocol, and were supervised by senior cognitive behavior

therapists during treatment provision. CBT and both pharmacological treatment arms were completely delivered according to a protocol in order to minimize the contribution of unwanted treatment ingredients (like cognitive restructuring in the Paroxetine condition). Standardization was ensured by the use of detailed treatment manuals for all conditions. In order to monitor treatment integrity Paroxetine blood samples were taken in week 16 to verify subject compliance.

Unfortunately, however, the standardization of CBT is liable to at least two weaknesses. At first, the level of experience and the competence of the different therapist differed: some of them were relatively inexperienced. Second, treatment integrity was not formally and completely assessed. This meant that neither all sessions were audiotaped nor monitored. When present, audiotapes of the sessions were mainly used in supervision.

Randomization

The way randomization was conducted guaranteed as good as possible internal validity. Participating subjects were randomly assigned, by site, to receive CBT, paroxetine or a placebo (1:1:1). The randomization code was developed by a statistician not involved in this study. Random permuted blocks with a length of 6 were selected, and the details of the series were unknown to any of the researchers. The subject numbers were put in sequentially numbered, opaque, sealed envelopes by the independent statistician, bearing only a number on the outside. When a subject was included, the envelope with the appropriate number was opened. The card inside indicated the group to which the subject was assigned.

Blinding

Nowadays, pill-placebo comparisons are the golden standard to examine the efficacy of pharmacological treatment. They enable researchers to discern specific from non-specific pharmacotherapeutic effects of treatment since the placebo has the same physical properties as the active medication, like color, size, taste, smell, label and information, but lacks the active ingredients (Kirsch, 2005).

In the placebo and Paroxetine group, patients, psychiatrists and researchers remained blinded throughout the entire duration of the study. As a part of the present discussion the success of the blinding procedure was investigated. In the mid-session of medication provision patients and psychiatrists had to indicate to which treatment patients had been allocated. Results of analysis on this data showed that patients ($\chi 2 = 5.867$, $df = 1$, $p < 0.05$) and doctors ($\chi 2 = 24.441$, $df = 1$, $p < 0.001$) were both capable to recognize antidepressants as actual treatment, with respectively 65% and 78% correct classifications. When placebo was administered these percentages were respectively 74% and 95%. These results indicate that the double-blindness procedure did not mask the giving of active treatment.

Inspection of the adverse events supports this finding: patients in the Paroxetine group reported sexual problems, fatigue and perspiration problems significantly more often, while patients in the placebo group reported significantly more palpitations.

The idea, however, that one takes respectively Paroxetine or placebo could lead to adjusted expectancies of both therapists and patients and

therefore compromise the function of the placebo. By means of a $\chi 2$-test it was tested whether correctness of guess of treatment group was related to clinical significant change in both the Paroxetine and the placebo group. These results were interesting because they showed that:

1. Correctness of guess was unrelated to clinical significant change in the Paroxetine group. So, those patients in the Paroxetine group who incorrectly assumed they received placebo responded to the active medication to the same extent as those patients who correctly guessed they received active medication..
2. Incorrectness of guess was related to clinical significant change in the placebo group ($\chi 2 = 4.421$, $df = 1$, $p < 0.05$). So, those in the placebo group who supposed they received Paroxetine significantly more often responded to placebo than those patients who correctly guessed they received placebo.

These results underscore the efficacy of a SSRI, independent of correctness of classification, and the existence of a placebo effect. Unfortunately, however, considering that a substantial group of patients in the placebo group correctly guessed the treatment arm they were allocated to, the placebo effect was possibly limited, resulting in an artificially inflated difference between Paroxetine and placebo and impairment of internal validity.

Furthermore, recently a letter to the editor was published in the American Journal of Psychiatry (2006), warning for the possibility of a favorable response for psychotherapy compared to pharmacology resulting from a blinding procedure (pill-placebo) for the latter in RCT comparing psychotherapy, pharmacology and a placebo. The authors point out to the problem of 'two trials within one trial': an open-label effectiveness trial for

psychotherapy and double-blind efficacy trial for the pharmacological arm (Smith & Mathur, 2006).

The foregoing illustrates that even well conducted randomization and a double-blindness procedure, both important aspects of efficacy trials, do not completely guarantee internal validity.

Lack of a control group for CBT

In addition to the foregoing paragraph we could have overcome the problem of 'two trials within one trial' by including placebo psychotherapy. Just like pill-placebo comparisons, placebo psychotherapy enables researchers to make the contribution of the cognitive behavioral interventions more explicit over non-specific psychotherapeutic factors like attention, expectancy and the development of a psychotherapeutic relationship. The construction of a placebo condition for psychotherapy is, however, a difficult enterprise since most psychological treatments are based upon a theoretical framework, making the difference between specific and non-specific ingredients ambiguous: what is defined specific for one treatment is non-specific for another one. The difficulty of demonstrating the surplus value of a treatment with specific interventions and established efficacy for hypochondriasis, with a 'non-specific' placebo treatment for hypochondriasis can be demonstrated by the following two studies.

Clark et al., (1998) investigated the efficacy of cognitive therapy by comparing it to an equally credible alternative treatment, namely stress management, to assess among others the role of non-specific factors in therapy outcome. Both treatments comprised up to 16 weekly one-hour

sessions in the first 4 months and up to 3 booster sessions in the next three months. CBT was based on the model of Warwick and Salkovskis (1990) which consisted of cognitive components like identifying, challenging and modifying automatic thoughts and basic assumptions and restructuring images. The following behavioral interventions were used to aid reattribution: (gradual) in vivo and imaginary exposure and response prevention. Stress management was based on the rationale that some people react to stress by worrying about their health. Such worries can best be targeted by acquiring a comprehensive set of stress management techniques. These techniques focused on helping to identify stressors and to examine the physical and psychological reactions associated with stress by means of progressive relaxation, problem-solving, time-management skills and assertion training and stimulus control procedures. Although the cognitive therapy was more effective than behavioral stress management in decreasing hypochondriacal symptoms at mid- and post-treatment, at one year follow-up the two therapies did not differ from each other on almost all measures. Contrary to expectations, the authors had to conclude that both CBT and stress management are effective interventions in reducing hypochondriacal complaints, but that the specificity of stress management needs to be investigated (Clark et al., 1998).

Buwalda, Bouman and van Duijn (2006), also aimed to study the construct validity of a well-established intervention for hypochondriasis, namely a behavioral psycho educational group course by comparing this intervention to an equally credible problem-solving group course. Both groups were similar in duration (six 2-hour sessions and one booster session after a month). The behavioral psycho educational group course

departed explicitly from the cognitive-behavioral model for hypochondriasis (Warwick & Salkovskis, 1990). First, the different components of the cognitive behavioral model and their mutual relationships were explained, after which participants were asked to construct their own idiosyncratic vicious circle and deduct personal interventions. The problem-solving course had a two-fold aim: 1) to provide insight into how everyday problems can elicit or maintain hypochondriacal complaints, and 2) to help participants in identifying, defining and solving problems, using a structured procedure. Directly after treatment, participants of the behavioral psycho educational group course appeared to have less trait anxiety and to experience fewer problems in daily life than participants of the problem solving course. After six moths follow-up the results showed, however, that the differential treatment effects had disappeared (Buwalda et al., 2006).

Another and easier method to determine the efficacy of a specific intervention is to compare it to a no-treatment, waiting-list or natural history control group, which controls for regression to the mean, history or spontaneous remission (Kirsch, 2005). The time-frame and the difficulty of recruiting a sufficient number of hypochondriacal patients fulfilling all inclusion criteria was, however, a practical restriction, while at the same time several randomized controlled trials already demonstrated the efficacy of CBT compared to a waiting list control which makes such a comparison unnecessary.

Sample size and dropouts

According to a power analysis the sample size was only adequate to detect a large effect size between the three groups. Furthermore, approximately one fourth of all subjects dropped out of treatment prematurely, a number in accordance with most previous studies on the treatment of hypochondriasis. It appeared that dropouts suffered from more severe symptoms on pre-test than completers. The number of dropouts did not differ significantly between the groups, which implicates that all treatment arms were equally acceptable. Nevertheless, the risk of randomization being compromised by dropouts can not be neglected. First, because treatment effect could be biased; second, statistical power to detect differences is reduced and; thirdly, generalizibility is decreased.

The problem of external validity also applies to the patients who consented to be interviewed several years after the original RCT. Only 68 patients (CBT, N = 28; Paroxetine, N = 22; placebo. N = 18) were interviewed up to six years of the conclusion of the RCT. The other patients could not be traced or were unwilling to participate for various reasons (including severe hypochondriacal symptoms). It can not be ruled out that the course of their hypochondriacal symptoms would differ from those who consented to be interviewed, which compromises the generalizibility of the results.

Statistical analyses

Because of the relatively small sample size we were obliged to test our hypotheses by means of a limited number of planned orthogonal

contrasts because of two connected reasons, namely protection against type I errors and at the same time maximum statistical power to detect possible differences between means, which is especially important in smaller sample sizes (Kirk, 1982).

Although this method is valid, it makes it impossible to analyze the differences between both treatment groups separately to the placebo. We tried to solve this problem by calculating effect sizes of the different treatments to evaluate their relative efficacy, and a responder analysis was conducted to examine clinical significant change. The percentages of responders of all groups were directly compared to each other.

Furthermore, the problem of the dropouts was solved by conducting intent to treat analyses. In case no post-test data of the dropouts was available, pre-test data was carried forward to serve as post-test scores (last observation carried forward procedure (LOCF)).

In the follow-up study presented in this thesis, data were analyzed by means of Random coefficient regression models (RCRMs), which takes into count the hierarchical structure of a dataset and the dropouts. CBT and Paroxetine were incorporated in the model and separately compared to the placebo group in a trajectory from pre-treatment to 1-month FU and from 1-month FU to 18-month FU. In brief, an attempt was made to be as clear and complete as possible despite the above mentioned limitations.

Outcome measures

All outcome measures included in the present studies have well established psychometric properties; with two exceptions. The first is the

interview that was used to assess the course of hypochondriacal symptoms during the follow-up period. Although the method of a life chart interview is well-validated, the threshold we defined to assess whether patients were still suffering from hypochondriacal fears is rather arbitrary, since it was based on the mean of the responders in the RCT. Consequently, these results should be interpreted with care.

Another exception is that the questions asked to assess disease conviction; disease fear, experience and evaluation of health-related thoughts and safety-seeking and avoidance behaviours in the study on (meta) cognitions in hypochondriacs and OCD subjects have only face validity. Sample recruitment and validity of the results could have been compromised. OCD subjects with somatic obsessions were recruited by asking them the following questions:

1. How often are you afraid that you are currently suffering from a serious disease? And;
2. How often are you afraid that you will become seriously ill in the future?

This question is probably not specific enough to obtain the necessary representative reflection of the subgroup of OCD subjects who suffer from somatic or contamination obsessions and cleaning or washing compulsions. Second, a more general limitation is that the explorative questions might lack content validity. In sum, it would have been better to use validated assessment material.

Finally, it might have been interesting and important to administer an additional questionnaire assessing 'quality of life'. In the thesis only data on hypochondriacal and comorbid complaints are available. Although the outcomes on this assessments could be translated to daily life (e.g. those

with severe complaints probably also have a less 'quality of life'), this conclusion remains speculative. Since a substantial part of the population still reported hypochondriacal complaints approximately 6 years after conclusion of the RCT information about their quality of life compared to the period before the RCT would have been very valuable.

Treatment

Choice of treatments

Since the efficacy of Selective Seronine Reuptake Inhibitors (SSRI's) in OCD has been demonstrated by some well-conducted randomized-controlled trials (van Balkom et al., 1994), it was suggested that SSRI's might as well be beneficial in treating hypochondriacal complaints since these two disorders resemble each other in terms of obsessive thoughts followed by anxiety-reducing repetitive actions. Furthermore, clinicians have longer been aware that hypochondriacal symptoms resolve when co-existing disorders which are responsive to pharmacotherapy, like depression or generalized anxiety disorder, are treated adequately (Barsky, 2001; Fallon, 2004). The last decade, several uncontrolled open-labeled trials generated some optimistic results on the efficacy of SSRI's in the treatment of hypochondriasis (Fallon et al., 1993; Fallon, 2004), which motivated this research project to compare the efficacy of a pharmacological treatment of hypochondriasis with a placebo and CBT. However, since the market of SSRI's is extensive the choice to administer patients in the trial Paroxetine needs to be explicated. The choice is based on a study of Oosterbaan et al. (2001), in which the

efficacy, tolerance and safety of paroxetine in a small sample (11 patients) with a primary diagnosis of DSM-III-R hypochondriasis appeared to be good.

The choice of CBT, representing the evidence-based treatment needs more clarification, since not only CBT has proven to be effective but also a cognitive-educational treatment (Barsky, Geringer, & Wool, 1988; Avia, Ruiz, Olivares, & Crespo, 1996; Bouman, 2002; Buwalda et al., 2006) and stress management (Clark et al., 1998). This latter therapy was excluded as reference category, because although effective in reducing hypochondriacal complaints, its specificity still needs to be established. Cognitive-educational treatment, however, could have been a serious option. The choice for CBT was primarily made, because there was more evidence available that this treatment was effective in treating hypochondriacal complaints than there was for a cognitive-educational treatment.

The active ingredients and mechanisms producing effect of CBT

The RCT presented in this thesis did not investigate the relative contribution of specific interventions. On basis of the reported results it remains unknown which components of the CBT were effective: was the cognitive restructuring or were the behavioral interventions like exposure and response prevention more appropriate and effective in symptom reduction?

Bouman and Visser (1998) and Visser and Bouman (2002), compared the efficacy of the cognitive (identification, challenge and modification of dysfunctional automatic thoughts about bodily sensations and illnesses)

and the behavioral components (exposure and response prevention) and found that both were equally effective in reducing hypochondriacal complaints until the last 7-months follow-up assessment. Furer and Walker (2005), however, encourage exposure over cognitive interventions, because of the straightforward and easy to teach procedures for extinction of anxiety. Besides, according to these authors, exposure to a wide range of cues and contexts, including exposure to external triggers and to thoughts and images related to death (e.g. making a will), have some advantage in reducing relapse rates in the long run compared to cognitive interventions.

Until now, there is still a debate going on about the precise working of the different interventions in CBT. The early behavioral theory for example suggested that exposure led to habituation, the decrement in self-reported anxiety and in anxiety-related autonomic responses during confrontation with feared stimuli (Paunovic & Ost, 2001). Marks, Livanou, Thrasher, Lovell and Noshirvani (1998) stated that "exposure gradually alters behavior; physiology and cognitions by habituation and that cognitive restructuring might distance sufferers from strident feelings and facilitate dealing with them by changing perspectives" (Marks et al., p. 324). On the other hand, the authors of an up-to-date and comprehensive textbook of hypochondriasis stated that: “The distinction between cognitive and behavioral interventions is arbitrary (…). Cognitive and behavioral interventions both provide patients with corrective information, and so both are vehicles of belief change (Taylor and Asmundson, 2004, p. 141).” According to these authors cognitive interventions pave the way for behavioral exercises and are both treatment ingredients are intrinsically linked to each other.

In sum, the fight about the way specific interventions lead to change is not over yet, but for the time being it can be stated that a broad range of interventions is effective as long as these interventions are focused on breaking the vicious circle of symptoms – cognition – emotions and behaviors maintaining hypochondriacal concerns.

The choice of interventions should be based on the specific problem presentation of the patient and the skills to understand the rationale and conduct the interventions. This also gives room for development of therapies for hypochondriasis based on the ideas of the so-called third generation of behavior therapy, which emphasize the importance of a focus on function and context instead of solely on form (Hayes, 2004). An exponent of the third generation of behavior therapy is mindfulness-based cognitive therapy, which incorporates elements of cognitive therapy, but instead of active challenge and change of content of thoughts, aims to facilitate a detached, non-judgmentally but acceptant view on one's thoughts in the present (Kabat-Zinn, 1994).

Theoretical implications

In the following the theoretical implications of the results will be discussed. First the diagnostic implications will be brought up, subdivided in paragraphs about the place of hypochondriasis within the diagnostic categorization of the DSM. The question whether hypochondriasis should be categorized as an OCD spectrum disorder will also be mentioned. Finally, some theoretical issues related to treatment will be discussed.

Chapter 8

Hypochondriasis in the DSM

The nosological boundaries of hypochondriasis have been questioned earlier. Criterion A of the DSM-III-R "Preoccupation with fears of having, or the idea that one has a serious disease based on the person's interpretation of physical signs or sensations as evidence of physical illness" suggests that illness fears and illness convictions are two separate constructs within hypochondriasis (Kellner, 1987, Pilowsky, 1967). Cote et al., (1996), however, noticed that this definition made it difficult to differentiate between hypochondriasis and illness phobia.

Another problem concerning the definition consisted of the assumption of the necessity of physical symptoms. In the successor of the DSM-III-R, the DSM-IV, the presence and importance of bodily sensations is still supposed. Until now, no systematic studies have investigated what kind of physical symptoms and sensations are reported and feared by hypochondriacs (Cote et al., 1996).

The present thesis extends the knowledge on these two issues. First, preliminary evidence was found that fear of acquiring a disease is positively associated with fear of having a disease: in other words both types of fears represent no distinct subtypes, but can be present in the same patient. Second, it was found that OCD-patients and hypochondriacs have approximately the same number and type of physical sensations, which are often normal physiological sensations or benign self-limited ailments. This finding questions the justification of categorizing hypochondriasis among the somatoform disorders, since it seems that not the presence of bodily symptoms in itself is invalidating, but merely the interpretation of these

particular symptoms, which makes it more similar to an anxiety disorder. This suggestion is supported by another study in this thesis comparing hypochondriacs with subjects with another somatoform disorder, non cardiac chest pain (NCCP). Hypochondriacs appeared to be more fearful about their health than NCCP subjects.

Another objective of the same study was to investigate whether a diagnosis of hypochondriasis could be predicted by the presence of certain personality characteristics, like harm avoidance and uncooperativeness. The rationale of this topic was largely based on the plea of Tyer, Keleman, Fowler-Dixon, and Ferguson (1991) for the diagnosis of a hypochondriacal personality disorder when: "hypochondriasis begins early in life, shows characteristics patterns of behavior that are socially handicapping and distressing to others, and persists throughout life". It was found, however, that although hypochondriacs display these characteristics to a larger extent than healthy controls and subjects with NCCP, the presence of hypochondriasis could not be predicted by personality characteristics over and above level of health anxiety. Moreover, viewing hypochondriacal complaints from the perspective of a personality disorder, implicates that hypochondriacs have a constellation of health-related attitudes, beliefs and a perceptual style which may be interpreted as ego-syntonic and an integral part of the individual's personality (Barsky, Wyshak, & Klerman, 1992). It was found in this thesis, however, that hypochondriacs view their health-related thoughts often as strange and unreasonable and feel ashamed of them. These findings implicate that categorization of hypochondriasis among the clinical Axis-II disorders is as yet premature at least.

The current diagnostic categorization of hypochondriasis by the DSM-IV and the ICD-10 has also been criticized by Creed and Barsky (2004) in an extensive review on hypochondriasis and somatoform disorders. Their criticism was among others based on research of Guruje et al. (1997), who investigated which symptoms best defined hypochondriasis and concluded that the current criteria are not sufficient. Especially criterion B 'The preoccupation persists despite appropriate medical evaluation and reassurance' (American Psychiatric Association, 1994), might constitute a serious bottleneck in the diagnosis of hypochondriasis. They suspected that accepting reassurance was not exclusively dependent on the level of illness worry of a patient, but that also personality, attitudes and expectations of both the patient and the physician might play an important role. Furthermore, this criterion is sensitive to cultural differences, since not in all countries patients have easy access to health care services which might bias prevalence rates (Gureje et al., 1997). Interestingly, they found that patients meeting the inclusion criteria for abridged hypochondriasis (a triad of disease conviction, associated distress or interference with functioning, and medical help seeking) were no less disabled than patients meeting the full ICD-10 criteria for hypochondriasis (Gureje et al., 1997).

Another problem concerning the nosological criteria of hypochondriasis is the extensive diagnostic comorbidity of hypochondriasis with anxiety disorders (varying between 22% and 86%) and affective disorders (varying between 44% and 55%) (Barsky et al., 1992; Noyes, Kathol, Fisher, & Philips, 1994). The high comorbidity rates dispute the independent diagnostic status of hypochondriasis: some authors consider it to be a secondary phenomenon of other psychiatric disorders (Barsky et al.,

1992), despite that factor analytic research demonstrated hypochondriasis to be a valid and reliable diagnosis (Pilowsky, 1967) with correlating features (Barsky, Wyshak, & Klerman, 1986).

However, not only the existence of hypochondriasis is under debate, but also the validity of the procedure through which the diagnosis is obtained. There is a risk that comorbidity within one patient may be an artefact of the procedure, because most DSM-IV criteria which have to be fulfilled in order to obtain a diagnosis are rather arbitrarily and not unique for one disorder (van Balkom, 2004; Widiger & Samuel, 2005).

Creed and Barsky (2004) proposed that the current categorical approach should be replaced by a dimensional approach, since such a model would probably more completely describe the nature and the extent of hypochondriacal complaints, without producing unpleasant side-effects like large comorbidity rates. Besides, more patients with clinical significant health anxiety but who do not meet all criteria of the DSM-IV and ICD-10 will be reached. Possible dimensions for hypochondriasis could be: bodily symptoms, disease fear, disease conviction, reassurance seeking, checking, avoidance, impairment and duration and insight.

However, these are just preliminary suggestions. For the time being, therapists confronted with a patient suffering from different mental disorders, have to make a decision based on the story of the patient, a case conceptualization of the problems and clinical evidence for efficacy of treatments. Important questions are for example: what is the primary diagnosis (in term of suffering); what is the centrality of the diagnosis in relation to other problems and which disorder can easily be treated (to

generate a positive success experience facilitating further effective treatment).

Hypochondriasis in the obsessive compulsive disorder spectrum

Not only has hypochondriasis been characterized as a diagnostic category in the DSM-IV, it has also been placed among the so-called OCD spectrum disorders, because of overlap in symptom profile (intrusive obsessive thoughts or repetitive behaviours) and response to the same kind of treatments (CBT and a pharmacological treatment) (Hollander & Wong, 2000). This phenomenological overlap raises the possibility that hypochondriasis shares diagnosis-specific symptoms with OCD and vice versa. This suggestion, however, was not confirmed by the results of the present thesis: although hypochondriasis and OCD shared some similarities, the differences were far more substantial. When elaborating on the implications of the findings for the OCD spectrum, it should be stressed, however, that the validity of psychiatric diagnoses does not rely solely on differences in clinical features; it also depends on biological markers, etiology, associated features, like course of illness, demographics and family history (Hollander & Wong, 2000). A serious discussion about the place of hypochondriasis within this spectrum cannot be conducted before all important aspects have been investigated. To date, the literature provides information dismissing and supporting the hypothesis that hypochondriasis belongs to the OCD spectrum. Support for placing hypochondriasis within the OCD spectrum can be found in the phenomenological overlap with OCD and amelioration after treatment with CBT or SSRI. On the other hand,

hypochondriasis and OCD differ neurobiologically (van den Heuvel et al., 2005), share little diagnosis-specific symptoms and the percentages of co-morbid hypochondriasis in OCD patients and of co-morbid OCD in hypochondriasis are relatively low (Barsky et al., 1992; Noyes et al., 1994).

Summarizing, these results show that the OCD-spectrum and the DSM-IV share the same Achilles Heel: the categorization is largely based on descriptions of overt behavior, while little, at least for hypochondriasis, is known about etiology and pathophysiology. Furthermore, when overlap is found between hypochondriasis and OCD it can be questioned if this would increase the evidence of hypochondriasis being an OCD-spectrum disorder. Because not only knowledge about shared similarities between the OCD-spectrum disorders is needed, but also the differences with *not* OCD-spectrum disorders must be made clear. Since a large variety of psychiatric disorders can be treated effectively by means of CBT or pharmacological treatment (Butler, Beck, Chapman, & Forman, 2005), this particular feature is little specific for OCD-spectrum disorders.

Which treatment, CBT or Paroxetine?

Although CBT and Paroxetine are both effective and accessible treatments for subjects with hypochondriasis in the long-term, the results show a slight advantage of CBT above Paroxetine. CBT seems not only to have a stronger specific effect than Paroxetine in targeting hypochondriacal complaints, but is also very effective in decreasing comorbid psychoneurotic and depressive symptoms. These results are not isolated, but are congruent with results of studies comparing CBT and pharmacological treatment in

OCD, panic disorder and depression (Mitte, 2005a; Mitte, 2005b; Butler et al., 2005; O'Connor et al., 2006). Nevertheless, these findings are contrary to expectations because not CBT but SSRI's are known for their general effects on symptoms of anxiety and depression. How then to explain this effect? One explanation could be that CBT interventions like cognitive restructuring and exposure are successfully generalized by the patient to the depressive and not-hypochondriacal related anxious thoughts. Another explanation could be that exposure to feared situations aimed at disconfirmation of catastrophic thoughts generates a success experience which diminishes depressive symptoms.

Moreover, fewer patients from the former CBT group received additional medical or psychological treatment during the follow-up period than patients from the former placebo group, while the former Paroxetine group did not differ from the former placebo group. Therefore, CBT could be a more cost-effective intervention than Paroxetine.

The optimistic results of both types of treatments in reducing hypochondriacal complaints raise the question whether a combined therapy of both CBT and medication will be even more advantageous in decreasing hypochondriacal symptoms than receiving only one of the treatment modalities. Until now, most studies on various anxiety disorders found no evidence for the surplus value of combined treatment. According to Otto, Smits and Jasper (2005) an important drawback pertaining to combination treatment is the possible function of medication as a safety-cue. On basis of animal models of extinction of conditioned fears, they stated that that when the anxiety-attenuating effect of medication is removed a context shift will be brought about, resulting in a compromised effect of exposure (Otto et al.,

2005). Hence, they suggest that combination treatments should not be adapted as the treatment of first choice, but in case, medication treatment is selected as the initial therapy, exposure exercises should be added to the treatment to extend treatment gains.

In case patients need treatment for their hypochondriacal complaints full information, including advantages and disadvantages about treatments has to be given, so in dialogue with the therapist an informed choice, can be made. Based on all foregoing issues, however, CBT should be preferred over Paroxetine. CBT also seems to better fit the personal preferences of hypochondriacs. A study investigating the treatment preference of hypochondriacs found that acceptability and estimated short and long term effectiveness was rated higher for CBT than for a pharmacological treatment. When asked to indicate their first choice of treatment 74% chose psychological treatment while only 4% selected pharmacological treatment. Twenty-two percent indicated an equal preference (Walker, Vincent, Furer, Cox, & Kjernisted, 1999). Unfortunately however, this study did not ask patients their considerations influencing their choice. Possible, fear of side effects of medication plays an important role.

Suggestions for clinical practice

Recently an alarming message appeared in a Dutch newspaper that the Dutch government has no more money available for institutions for mental health care, resulting in incapacity to accept new patients and subsequent growing waiting lists (Volkskrant. June, 21, 2006). This problem

is caused because health care supply is overcharged by health care demand, which increases the pressure on budget. Looking at the expenses of total health care revealed that in 2003 approximately 22 percent of total health care costs was spent on care for mental disorders, exceeding the costs all other forms of medical care. A substantial part, 25 %, was spent on disorders like anxiety, depression, schizophrenia and substance-related disorders (Slobbe et al., 2006).

The prognoses are that this percentage will further accrue, since general practitioners are becoming better able to recognize psychological problems because of extensive training, while at the same time patients will also be better able to recognize symptoms themselves because of increased knowledge bases on information programs. Furthermore, population growth and the aging process with its accompanying mental problems like dementia and depression will also raise the pressure on the budget.

One of the possible solutions for these financial problems is the market effect. The present Dutch government stimulates a 'healthy' competition between different health care providers about the best and cheapest evidence-based treatments, and hopes also for related benefits like increased efficiency and enduring stimulation to innovate health care programs. Notwithstanding these possible advantages, there might also be some important disadvantages. First, competition between different institutions could obstruct constructive cooperation; second, an undesirable distribution of welfare: those with less money can not pay for expensive health care; and third disappointed patients, because they were given high and may be sometimes unrealistic expectations about treatment success.

The following are other, less risky (but more expensive) solutions for the growing waiting lists. At first, more vocational training places to increase the number of qualified health care professionals should be created; second, professionals should be retrained in order to offer patients the best possible, state-of-the-art evidence-based treatment; third, in order to decrease pressure on secondary care and general practitioners, this latter group should be supported by a nurse health care practitioner to treat uncomplicated mental problems by means of a protocol; fourth, because 'prevention is better than cure', a substantial amount of money should be utilized for prevention programs

In prolongation of the foregoing and in relation to hypochondriacal complaints the development of a stepped care program could be stimulated. Recently, a suggestion was made towards a stepped care program for patients with OCD depending on severity of complaints (Mataix-Cols & Marks, 2006). The format of this model might also, in adjusted form, be implemented for hypochondriasis. To begin with could less complex cases (i.e. less chronic and severe symptoms and comorbidity and better insight) be treated by means of self-help approaches within primary care. Bibiotherapy and self-help groups are well-established for several anxiety and mood disorders (den Boer, Wiersma, & van den Bosch, 2004). More complex cases could be referred to a psycho educational group as proposed by Bouman (2002). Such a group has a low threshold, a high cost-effectiveness and is acceptable and effective (Bouman, 2002). The next step could be to offer patients brief face-to-face cognitive behavioural therapy sessions with a therapist in an ambulatory setting. Finally, severe or

treatment resistant cases can be offered intensive face-to-face guidance in a specialized setting.

Notwithstanding the promising results of the treatment studies presented, a substantial subgroup of patients does not benefit from single or combined treatment. In the present thesis even 53% of all patients who could be contacted approximately 6 years after finishing the RCT still scored above the pre-determined cut-off score (at most thrice a month hypochondriacal complaints which gave a considerable amount of trouble). Although caution is warranted when interpreting this percentage because of the arbitrary cut-off point, it nevertheless makes clear that measures should be taken for those who do not benefit enough from treatment. What to do with them? Since treatment is no longer indicated for these patients, they have to learn to live with their 'handicap'. These patients could join a self-help group which can be practical and emotional supportive. Furthermore, they should be referred back to their GP, who in line with treatment suggestions for chronic somatizing (van der Horst & Feltz-Cornelis, 2003) should plan appointments, regularly scheduled and not contingent on the presence of physical complaints. The GP should be aware that these patients have a history of extensive, but also unsatisfying and frustrating medical care. They often felt ignored and not comprehended which resulted in a difficult and sometimes distrustful or even hostile attitude towards GP's. Physicians should therefore try to be understanding and acknowledge that what the patient feels is real. Tests and examinations should not be performed for the purpose of reassurance, but a GP must remain alert to the possibility of an organic basis of physical symptoms: just like non-hypochondriacs they run a risk for a medical illness (Barsky, 2001).

Suggestions for future research

The foregoing discussion generates some suggestions for future research. First a possible dimensional approach in the DSM-V needs to be further explored. Important issues are the descriptions of these dimensions, which need to have construct validity and a reliable cut-off score distinguishing 'healthy' from 'invalidating hypochondriacal complaints'. Although a lot of knowledge about the construct 'hypochondriasis' is available an important instrument as the DSM needs refined and well validated dimensions reflecting hypochondriacal complaints. Possible dimensions could be: bodily symptoms, disease fear, disease conviction, reassurance seeking, checking, avoidance, impairment and duration and insight

Second, until now, no specific pathophysiological substrate of hypochondriasis is identified, but the development of neuroimaging techniques makes such research possible. It would help clinicians to be able to diagnose in a more objective way since they will be less dependent on history taking, and could make psychiatric or psychological treatment more evidence-based. A recent review on functional neuroimaging aiming to detect neural correlates of psychotherapy or pharmacotherapy in OCD and specific phobia found similar effects in the CBT and the SSRI-treated group. Although preliminary, these results point to a common final pathway for the neural changes underlying the clinical effects of both types of interventions (Linden, 2006). It would be interesting to replicate such research in a hypochondriacal population.

Third, the RCT did not offer patients treatment consisting of both CBT and Paroxetine. Although both treatments are effective, a subgroup does not benefit from one of these options. This automatically leads to the question *which* patients (do not) benefit from treatment. The RCT reported in this trial found no characteristics, demographic as well as clinical, relating to non-response to treatment. But it could be that some important moderators of treatment success have been neglected. It is conceivable that attitude towards treatment plays an important predictive role instead of clinical and demographic variables. In continuation of this a variant of the consort statement should be developed and applied to prediction studies to help researchers design and conduct their studies according to a standardized format.

Fourth, more research should be conducted directed to those patients who cannot successfully be treated by either antidepressant medication or CBT. Although it has been suggested that these patients should be treated according to the model for chronic somatizing patients it remains unclear to what extent this indeed happens and what the effects of such scheduled, unspecific therapeutic sessions, might be. In other words, more attention should be given to those who have been 'given up' by regular mental health care.

Fifth, it would be interesting to study the efficacy and the mechanisms of change of promising new therapies for hypochondriasis to find out whether they could be applicable. Examples are mindfulness and attention training. Next to investigating new therapies, it would also be important and interesting to further disentangle the working mechanisms of

the current second generation cognitive behavioral therapy (e.g. is exposure: habituation or cognitive restructuring?).

Sixth, although one study of the present thesis found some preliminary evidence that patients with hypochondriasis have as much insight in their health-related thoughts as OCD patients, more information is needed with regard to the experience and the evaluation of cognitions and safety-seeking behaviours of patients suffering from hypochondriasis. Therefore, it would be advisable to replicate our study with validated measures, like for example an adapted version of the Meta-Cognitive Beliefs Questionnaire of Clark, Purdon and Wang (2003) in order to further examine whether indeed the common picture of hypochondriacs lacking insight in the irrationality of their thoughts and behaviours needs to be revised.

Finally, although in the past, researchers were reluctant to study hypochondriasis because they thought that 'le maladie imaginaire' would not be treatable, the present thesis is further proof of the groundlessness of this hypothesis. Not only can hypochondriasis be successfully treated by means of CBT, the treatment arsenal has been extended by another empirically-based intervention, namely an SSRI (Paroxetine). Further, the studies in this thesis add some empirical support to the diagnosis of hypochondriasis and more clearly defines its boundaries with OCD. Still, however, a lot of works need to be done in the field of hypochondriasis and it is hoped that the present thesis will inspire other researchers to extend the scientific knowledge on this interesting and long neglected condition.