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Title: Long-term follow-up of Patients with Hypochondriasis

A. Study Purpose and Rationale

Hypochondriasis is generally considered to be a chronic condition with a relatively low spontaneous remission rate (1-3). However, our knowledge is lacking on the course of Hypochondriasis over intervals longer than 5 years. Such research is important in assessing the long-term predictive value and validity of the Hypochondriasis diagnosis, as well as in determining what factors are predictive of outcome. Current literature suggests that a better prognosis may be observed in patients with less Axis I and Axis II co-morbidity, and in those whose Hypochondriasis is more recent in onset and less severe, with fewer somatic symptoms and less functional impairment (4,5). However, these associations have been inconsistent, especially with regard to the significance of psychiatric co-morbidity. Furthermore, there are other potential predictors of outcome that remain to be characterized, such as history of childhood trauma and childhood medical illness, which are both known to occur more commonly in patients with Hypochondriasis (6).

Two studies by Barsky et al. have added to our understanding of long-term outcome in patients with Hypochondriasis (7, 8). In a prospective, case controlled study of 122 hypochondriacal patients, Barsky et al. found that after 4 to 5 years, 63.5% of patients still met diagnostic criteria for DSM-III-R Hypochondriasis. As compared to patients who no longer met criteria for Hypochondriasis, the non-remitters had significantly greater disease conviction ($P<.05$) and somatization ($P<.01$) at baseline, and their incidence of major medical illness during the follow-up period was significantly ($P<.05$) less. The two groups did not differ significantly with respect to psychiatric co-morbidity at inception, however, the authors note that statistical power for these analyses was low. In a second prospective study of 38 hypochondriacal patients, Barsky et al. found that 66% of patients continued to meet criteria for Hypochondriasis at 4 year follow-up, and that remission status could be correctly predicted in 82% of patients by a 3-way interaction term composed of the tendency to amplify bodily sensations, tendency to attribute common symptoms to disease, and somatization (all as measured at baseline). The authors emphasize the combinatorial effect of these three factors, as they found that remitters and non-remitters did not differ significantly with respect to any one of these characteristics alone. How these various factors may influence outcome of treatment remains to be seen.

The aim of our study will be to address the following questions:

1. What is the long-term course of Hypochondriasis?
2. What is the predictive value of various standard and widely used
3. Are any patient factors correlated with outcome?

Hypotheses to be tested:
Persistence of hypochondriasis at follow-up will be associated with the following characteristics (all of which were assessed at the time of initial study participation):

1. Clinical History:
    a) Age of Hypochondriasis onset
    b) Greater severity of Hypochondriasis at baseline
2. Psychiatric Co-morbidity at Baseline
    a) OCD Spectrum Disorder (OCD, Tourette's, Trichotillomania, BDD)
    b) Axis II personality disorder
3. Family history of OCD Spectrum disorder in 1st degree relative
4. History of childhood trauma (physical with bruising or sexual penetration)

B. Methods

Study Design

This will be a follow-up study of patients who were diagnosed with DSM-III-R (later DSM-IV) hypochondriasis at the Psychiatric Institute of Columbia University as part of enrollment in one of four treatment studies that were conducted between 11 and 20 years ago. Subjects will be recruited from a cohort of 74 patients, 16 of whom participated in an open trial and 44 in a double blind study of Fluoxetine, and 14 of whom participated in an open trial of Fluvoxamine. Patients will be interviewed to assess their current status in a 45-60 minute telephone interview. We will compare our findings to data collected on patients during their initial participation in the aforementioned studies.

To address our first question regarding the long-term course of hypochondriasis, we will evaluate patients for persistence of disease and range of severity with the following widely used and validated psychiatric research scales (9):

- Heightened Illness Concern (HIC) Severity Scale: a clinician administered Hypochondriasis specific assessment that uses a 7-point scale where 1 is healthy, 2 is sub-threshold Hypochondriasis, 3 is mild Hypochondriasis, 4 is diagnosable Hypochondriasis of moderate severity, 5 is Hypochondriasis with marked impairment, 6 is Hypochondriasis with severe impairment, and 7 is among the most extreme cases
- The Columbia Heightened Illness Concern Obsessive Compulsive Scale (CHIC-OCS): a clinician administered assessment based on the gold standard scale for OCD that is modified for Hypochondriasis. It is based on a 10 category scoring system.
- Clinical Global Impression (CGI) Scale: a clinician-rated general assessment of mental health and global functioning using a 7 point scale similar to the one described above for HIC
- Whiteley Index: a self-report 15-item questionnaire with possible scores from 0-75, with numbers above 45 indicative of Hypochondriasis.

Our primary outcome measure will be improvement on the HIC Severity Scale from baseline to follow up, with anything greater than a 10% improvement considered clinically significant (6). We will apply an unpaired t-test to detect the difference in

Hypochondriasis severity from baseline to follow-up. For further analysis, we will also categorize patients into a group with "persistent Hypochondriasis," and a second group with "remitted Hypochondriasis. These categories will be based on the information that we collect, and based on the criteria of the DSM-IV.

Statistical Analysis

To assess what factors are associated with long-term outcome, patients will be compared on various dimensions based on their categorization of "persistent" or "remitted" Hypochondriasis. We will use chi-square tests to examine the association between current disease status and co-morbid axis II personality diagnoses, and history of childhood trauma, as outlined in our hypothesis. We will consider using a Bonferroni adjustment for multiple comparisons, statistically significant results will be those with p values less than (alpha/#hypotheses) = .05/5= .01

To assess the predictive power of various baseline measures on current disease status, we will use regression analyses to study the effect of baseline severity measures on the previously described dichotomous outcome of "persistent" or "remitted" hypochondriasis . We will also use a multiple linear regression with change (from baseline to follow-up) in the CGI Rating Scale, HIC Severity Scale, CHIC-OCS, and Whiteley as outcomes measuring current disease status. Variables chosen as predictors of outcome will include age of onset of illness, baseline CGI/HIC/CHIC-OCS and Whiteley Severity scores. We will also look at the effect of the categorical variables of axis II or OCD Spectrum disorder co-morbidity and history of abuse.

Power Calculations

The sample size is determined by the need for adequate power, and the power calculation in a paired t test is dependent on the amount of effect which can be considered both reasonable to attain and clinically meaningful, as well as a standard deviation which is realistic. Given a set sample size, as in a follow-up study, and an estimate of standard deviation, the detectable effect size can be calculated. The cohort of patients from whom we will recruit subjects numbers 74 in total. Based on previous follow-up studies of similar length done in patients with Obsessive Compulsive Disorder, which is a group similar to hypochondriacal patients, we expect at least a 70% participation rate. This will give us approximately 50 subjects for our study. The standard deviation in baseline severity scores was approximately 0.2. Based on these numbers, our study will thus be powered (alpha= .05, 80% power) to detect an effect size of ~5% (http://www.biomath.info/crc/index.html). Since, 10% improvement in HIC severity scale is generally accepted to be clinically meaningful (7), our study will thus be powered to detect such a result.

As far as detecting differences between the “persistent” and remitted” Hypochondriasis patients, we can estimate the level of detectable difference by knowing the number of patients in each group and estimating the proportion in one group. We predict that the 50 patients will be evenly split between the two groups. This will allow us to detect effect sizes of 25-30% (with alpha= 0.05 and power=80%). So for example, if 5% of patients in the remitted group have an OCD Spectrum disorder, we will be able

to detect a significant difference between the groups if 30% or greater of the persistent group have an OCD Spectrum disorder.

C. Study Procedures

All patients who chose to participate will be administered a follow-up interview that will last between 45-60 minutes. This interview can be administered by phone or in person. The interview will consist of the aforementioned clinician administered scales CGI/HIC/CHIC-OCS Scales. We will also collect data regarding intervening and current biological and psychological treatments for Hypochondriasis.

D. Study Drugs or Devices

There are no drugs or devices involved in this study.

E. Study Questionnaires

All patients who chose to participate will be asked to complete the Whiteley self-report questionnaire, as well as an Employment and Marriage Status questionnaire, and Medical questionnaire that asks about history of illness, as well as history of treatments sought and received.

F. Study Subjects

Inclusion Criteria: All patients (completers and non-completers) who participated in the open and double blind study of Fluoxetine studies, and all those who participated in the open trial of Fluvoxamine are included.

Exclusion Criteria: Patients who do not wish to participate are excluded.

G. Recruitment

1. All Patients who previously participated in the open and double blind studies using fluoxetine or fluvoxamine at our facility will be sent a recruitment letter asking them to participate in a follow-up study in order to assess their current status and stability over time.
2. The letter will briefly mention the nature of the study.
3. Interested participants will be asked to contact Pernilla Schweitzer by calling or returning the self-addressed postcard.
4. All patients participating in the follow-up study will be asked to sign a consent form. The form will explain the nature of the study in detail. It will also explain the risks and benefits and alternatives to study participation. The consent form will also describe the research standards and participation rights to the patient.

H. Confidentiality of Study Data

All study data will be coded so as to eliminate any personal identifiers and all data will be stored in a secure location, accessible only to the investigators.

I. Potential Risks

There are no expected medical risks to the subjects. Violation of confidentiality and privacy, however, are possible risks, especially as patients are initially contacted. In addition, there is a risk of becoming emotionally upset by questions asked during the

interview.

J. Potential Benefits

There are no direct benefits to subjects. However, this study may enhance scientific knowledge about hypochondriasis, and our findings may yield insight that could lead to the design of better treatment strategies.

K. Alternatives

There is no therapy involved in this study.

L. Compensation and Costs to subjects

Patients will be paid an honorarium of $20 for completion of the interview and questionnaires.

References

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