

Medically Unexplained Physical Symptoms, Anxiety, and Depression: A Meta-Analytic Review

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Objective: Our objective was to review and compare, with meta-analytic methods, observational studies on the association of medically unexplained physical symptoms, anxiety, and depression with special emphasis on healthy and organically ill control groups and on different types of symptoms, measures, and illness behavior. **Methods:** A search of MEDLINE and PsycLIT/PsycINFO for abstracts from 1980 to April 2001 was performed; principal investigators in the field were contacted and article reference lists were used to retrieve additional relevant articles. Two hundred forty-four studies were included on the basis of consensus ratings if they fulfilled seven of eight inclusion criteria pertaining to diagnostic accuracy and statistical appropriateness. Five hundred twenty-two studies were deferred or excluded. We focused specifically on the four functional somatic syndromes for which there were sufficient numbers for meta-analytic integration: irritable bowel syndrome (IBS), nonulcer dyspepsia (NUD), fibromyalgia (FM), and chronic fatigue syndrome (CFS). Data were extracted independently by two authors according to a prespecified coding manual with up to 70 parameters per study. **Results:** Effect sizes for the association of the four functional somatic syndromes with depression and anxiety were of moderate magnitude but were highly significant statistically when compared with healthy persons and controls with medical disorders of known organic pathology. Moreover, this association was significant whether depression was measured with or without somatic items. Chronic fatigue syndrome is characterized by higher scores of depression, fibromyalgia by lower scores of anxiety than irritable bowel syndrome. Consulting behavior and severity of somatization is related to higher levels of anxiety and depression. **Conclusions:** Meta-analytic integration confirms that the four functional somatic syndromes (IBS, NUD, FM, CFS) are related to (but not fully dependent on) depression and anxiety. At present, there is only limited meta-analytic evidence for the same sort of association for medically unexplained physical symptoms in general. In view of the relative independence from depression and anxiety, classification and treatment of these symptoms and syndromes as “common mental disorders” does not seem fully appropriate. **Key words:** functional somatic syndromes, somatization, somatoform, anxiety, depression, meta-analysis.

CFS = chronic fatigue syndrome; FM = fibromyalgia; IBS = irritable bowel syndrome; MD = major depression; NUD = nonulcer dyspepsia; SD = somatization disorder.

INTRODUCTION

Medically unexplained symptoms of pain and bodily dysfunction are the single most prevalent class of symptoms in primary care. They also have a high prevalence in specialist care and are responsible for a significant proportion of disability in the workforce (1–3). They are a defining feature of the different functional somatic syndromes within somatic medicine and of the somatoform disorders within psychiatry. Patients with medically unexplained physical symptoms have been shown repeatedly to have increased rates of depression and anxiety (3–5). This correlation has not yet been reviewed systematically, and several possible explanations exist. The association might signify a reactive increase of depression and anxiety in patients suffering from chronic bodily symptoms (6). Alternatively, bodily and psychological symptoms may be related but have different expressions of common distress (7). Finally, these bodily symptoms or the heightened awareness for them could represent a primary psychological phenomenon, a consequence of depression and anxiety (8, 9). In the first case, medically unexplained physical symptoms might best be classified and treated as part of somatic medicine; if the second holds true, patients with medically unexplained bodily symptoms and coexisting anxiety and depression

would belong to a nosological borderland between somatic medicine and psychiatry. In the third case, it might be most appropriate to treat them as a primary psychiatric problem, as is currently the approach to somatization and somatoform disorders.

As a step toward clarification of these issues we performed a meta-analysis of observational studies which compared the extent of depression and anxiety in four key functional somatic syndromes and in somatization disorders with healthy controls and other different groups of patients on different levels of care. The four functional syndromes chosen are the ones with the best established and most widely used diagnostic criteria.

Our specific hypotheses were derived from the general assumption that medically unexplained physical symptoms are a measure of distress partially independent from depression and anxiety and with low relevance of (artificial) qualitative subdivision by type of symptom/functional syndrome (10–12). We therefore hypothesized that:

- Depression and anxiety are more severe and/or more prevalent in patients with irritable bowel syndrome (IBS), nonulcer dyspepsia (NUD), fibromyalgia (FM), and chronic fatigue syndrome (CFS) compared with healthy controls and phenomenologically similar medical diseases with known organic pathology (eg, IBS vs. inflammatory bowel diseases, FM vs. rheumatoid arthritis).
- Comparing, among patients with medically unexplained symptoms, the severity of depression and anxiety in those who seek health care with those who don't (groups we refer to as *consulters* and *nonconsulters*) yields significant effect sizes.

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- The psychometric profiles of the four functional syndromes are specific only in terms of the relative extent of depression and anxiety.
- Depression and anxiety are more prevalent in patients with more medically unexplained symptoms, ie, in patients with somatization disorder (SD) compared with its more frequent subsyndromal variants.

METHODS

Search Strategy

We restricted our search to literature from 1980 onwards (to April 2001) because operationalized diagnostic criteria for somatoform disorders became available only since 1980 with the introduction of the third edition of the Diagnostic and Statistical Manual (DSM-III), and relevant research criteria for the functional syndromes included in our analysis were published after that. Electronic databases MEDLINE, PsycINFO, and PSYINDEX were searched by the researchers without language restrictions. Thirty-seven authors who had published five or more papers identified in the search were contacted for unpublished material and their own references (13 replied); reference lists of selected studies were checked for further studies.

The string of search terms had two components that were combined with the Boolean operator AND: a) terms identifying medically unexplained symptoms, somatoform disorders, and functional disorders (13 syndromes specified according to Wessely et al. (11) – this broad search was necessary because pilot tests had revealed that keywords and abstracts did not always identify all functional syndromes investigated); and b) terms identifying depression and anxiety as psychometric distress measures and as diagnostic categories (interview-based). Terms of each component within a) and b) were linked with “OR.” We excluded studies in children and adolescents, pharmacotherapeutic trials, case reports, and books and book chapters (Boolean operator NOT). The terms included in our search were adapted according to the thesaurus of the respective database (string of search terms available on request).

Screening Procedure

After exclusion of reviews, other nonempirical studies, and studies with unsuitable topics, we identified 2726 primary studies with our search strategy. We could actually trace 2667 (97.8%) of these papers in full text, the remaining ones could not be traced even through distant loan; according to their abstracts, they were not directly related to the symptoms, syndromes, and disorders in question here.

Seven hundred sixty-six studies related to the hypotheses of our study and were screened for inclusion in the meta-analysis according to four main and four secondary criteria. The other studies related to other than primary empirical studies and less well-defined and infrequent functional and somatoform syndromes. Each inclusion criterion was rated as either fulfilled, questionable, or not fulfilled. The main criteria were:

- Patients conform to a diagnostic group defined for our meta-analysis.
- Second component (depression, anxiety categorized as disorder or measured psychometrically) is actually studied.
- Statistical parameters are given which can be integrated meta-analytically.
- In the definition of medically unexplained symptoms, medical diseases with known organic pathology have explicitly been controlled for.

By the first criterion, diagnoses based only on self-report measures of medically unexplained symptoms are excluded. The criterion also includes the requirement that the investigated group is not preselected for presence or absence of psychiatric symptoms/disorders (ie, patients with CFS with depression). Studies which only referred to the nondiagnostic entity “medically (or organically) unexplained symptoms” were included under the heading “subsyndromal somatization disorder” when symptom counts or thresholds were given. The fourth criterion is necessary because the concept of medically unexplained bodily symptoms rests on a thorough exclusion of organic causes and this is not always reported explicitly in the literature.

The secondary criteria were:

- Diagnostic assignment procedure clearcut (use of research diagnostic criteria/structured diagnostic interview)
- Diagnostic instrument and/or psychometric test valid
- Symptom lists and/or frequencies explicitly stated
- More than one sample studied

In order to be included in the meta-analysis straight away, a study had to fulfill all main criteria and at least three of the four secondary criteria. Inclusion of a study was deferred when one main or more than one secondary criterion was considered questionable, all other studies were excluded. Here we report the results on the studies of the first, nondeferred group only.

At the beginning of the screening procedure we tested its initial interrater-reliability on a subsample of 50 studies that were screened independently by two raters. There was an initial concordance on inclusion/exclusion in 87.3% of the studies. Throughout the ongoing screening, we obtained consensus group ratings (P.H., T.Z., H.S.) on discordant or questionable inclusions or exclusions.

All included studies were coded with a prespecified coding manual with up to 70 parameters per study pertaining to publication, sample, diagnostic procedures, tested constructs, and statistics (list of included studies available on request).

Statistical Procedures

The statistical parameters of the included studies were transformed into effect sizes. If more than one effect size was present in one study with regard to one outcome measure, the arithmetic mean of the effect sizes was used. If a primary study only noted “not significant,” a conservative assumption of a *p* value of .5 and an effect size of 0 was made.

All effect sizes were integrated using Meta-Analysis software version 5.3 by Schwarzer (13). The meta-analytic approach to these probably heterogeneous observational studies was comparative rather than synthetic, ie, we did not attempt to synthesize the effect sizes of all studies in one, potentially misleading single measure (14, 15). Weighted mean effect sizes (*d*⁺) were computed (16). Homogeneity of effect sizes was tested using the *Q* statistic; heterogeneity was assumed when the null hypothesis (study effect sizes are homogenous) had to be rejected with a likelihood of 90% or more. In cases where heterogeneity was present, effect size Δ was used under a random effects model. The significance levels and confidence intervals of the effect sizes were computed. To address the so-called “file drawer problem” or the extent to which nonsignificant results are more liable to remain unpublished, Orwin’s Fail-Safe *N* was computed in cases with significant effect sizes, giving the number of studies with effect size 0 necessary to reduce the effect size to *d*⁺ = 0.2 (17). We performed subgroup analyses according to the hypotheses set out in the introduction. Analysis of covariance (ANCOVA) was used for further explorations of heterogeneity (results not reported here).

Reporting of our review follows the recommendations by the MOOSE Group (18) but, due to the large number of studies included, we do not give details of design and estimates of individual studies (available on request).

RESULTS

Overview

Two hundred forty-four studies fulfilled all main and at least three secondary screening criteria and therefore were included in this analysis; in coding they yielded 1723 data sets (1412 on current, 311 on lifetime psychiatric disorders/symptoms). Two hundred eight studies were deferred and 314 were excluded, 31 of them because of redundant data sets.

Twenty-nine studies were conducted in primary care, 137 in specialized somatic care, 45 in psychiatric/psychosomatic care, and 20 were epidemiological population studies. The sample size of primary studies varied between *N* = 11 and *N* = 18,690 participants.

Apart from several diagnostic interviews, 39 standardized

instruments were included for the assessment of depression and anxiety, with the four most widely used instruments – Symptom Check List (SCL-90/R), State Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS) – accounting for 324 of 624 assessments.

In 44 studies, cognitive variables like causal attributions and illness perceptions, mostly under the heading of hypochondriasis, were studied and could be coded in addition to depressive and anxiety-related symptoms and disorders.

In the following we report only the results of the construct combinations extracted from the 244 included studies which were frequent enough for meta-analytic integration.

Depression and Anxiety in Functional Syndromes

Although most effect sizes are heterogenous, the overall pattern of the individual, independent results turns out to be highly consistent (Table 1).

Patients whose medically unexplained symptoms are diagnosed as one of the four functional syndromes (IBS, NUD, FM, or CFS) are suffering from current major depression or any current anxiety disorder at a higher rate than either healthy controls or patients with phenomenologically similar medical diseases of known organic pathology. The same applies for the amount of depression symptoms, be they measured with or without somatic items. The effects are highly significant, with one exception for the amount of depression symptoms without somatic items compared with healthy controls, which is only moderately significant. The magnitude of the effect sizes is small to moderate, as expected they are higher in comparisons with healthy controls. On the other hand, there is no significant difference in the rate of depressive disorder or degree of symptoms between patients with these functional syndromes and comparison groups with mixed psychiatric disorders.

The amount of self-reported depressive symptoms is not significantly higher in patients who seek medical care for their

gastrointestinal functional syndrome compared with those who do not consult. The degree of anxiety is higher in consulters than in nonconsulters, with a moderate effect size and significance level. There are insufficient primary data to analyze this question for patients with FM, CFS, or somatization disorder (Table 2).

In order to test the relative extent of psychiatric symptoms in single functional syndromes, only the effect sizes obtained against healthy controls were used, as the control groups with different disorders of known pathology do not allow meaningful comparisons (Table 3).

Patients with all functional syndromes are significantly more depressed and anxious than healthy controls, with the exception of patients with FM who are only insignificantly more anxious than healthy controls. Comparing the functional syndromes, patients with FM are significantly less anxious and patients with CFS are significantly more depressed than patients with IBS.

Depression and Anxiety in Somatization Disorder Compared With its Subsyndromal Variants

Somatization disorder (SD) is the extreme, but rare, variant of somatoform disorders with multiple, long-standing medically unexplained bodily symptoms. Subsyndromal variants are characterized by less and less long-standing similar symptoms (3). In the only comparison frequent enough for meta-analytic integration, patients with SD have a higher comorbidity rate of panic disorder than patients with subsyndromal SD (effect size $\Delta = 0.571$ (confidence interval = 0.133–1.009, $p < .006$; 3 studies with 2148 participants)). Comparing the cumulated frequencies of major depression (MD) in patients with SD and subsyndromal SD without meta-analytic techniques also yields a highly significant difference: MD was present in 58.9% (178 of 302) of patients with SD and in 40.9% (408 of 1003) of patients with subsyndromal SD ($\chi^2 = 31.3, p < .0001$).

TABLE 1. Psychiatric Disease and Psychiatric Symptoms in Four Aggregated Functional Syndromes (IBS, NUD, FM, CFS)

Psychiatric/ Psycho-metric Variable in FS4 ^a	Control Group	Number of Studies	Total Sample Size	Effect Size	Confidence interval 95%	Significance Level $p <$	Orwin's Fall Safe N ($d = +0.20$)
Major depression (current)	Healthy	3	10618	0.332 ^b	0.254–0.411	.0001	2
	Known path	8	629	0.287 ^b	0.119–0.454	.0001	4
	Psychiatric	3	269	–0.615	–1.535–0.304	NS	
Anxiety Dis. (any, curr.)	Healthy	5	453	0.524 ^b	0.328–0.720	.0001	9
	Known path	8	773	0.386	0.123–0.649	.002	8
Depression symptoms	Healthy	45	9629	0.881	0.699–1.063	.0001	154
	Known path	43	8008	0.328	0.226–0.430	.0001	28
	Psychiatric	4	2576	–0.117	–1.219–0.985	NS	
Depression symptoms (No somatic)	Healthy	5	2777	0.640	0.068–1.212	.02	11
	Known path	3	163	0.481	0.138–0.824	.002	5

^a FS4 = Four aggregated functional syndromes (IBS, NUD, FM, CFS). Curr = current. No somatic = no somatic items in instrument.

Known path = Medical diseases of known organic pathology; There were not enough studies for meta-analytic integration comparing FS4 with psychiatric controls other than for Major Depression.

^b Homogenous effect, effect size $d+$ was used. Remaining effects are heterogenous, in these cases effect size DELTA was used under a random effects model. Significance level and confidence interval refer to effect size $d+$ in homogenous effects and to effect size DELTA in heterogenous effects.

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TABLE 2. Depression Symptoms and Anxiety in Consulters Versus Nonconsulters With Two Aggregated Functional Syndromes (IBS, NUD)

Psycho-metric Variable in Consulters vs Non-consulters With FS2	Number of Studies	Total Sample Size	Effect Size ^a	Confidence Interval 95%	Significance Level <i>p</i> <	Orwin's Fail Safe N (d = +0.20)
Depr. Sympt.	5	371	0.331	-0.137-0.800	NS	
Anxiety	6	361	0.417	0.059-0.775	.02	7

^a Heterogenous effects; effect size DELTA was used under a random effects model; FS2 = Two aggregated functional syndromes (IBS, NUD); Depr. Sympt. = Depression symptoms.

TABLE 3. Depression Symptoms and Anxiety in Four Single Functional Syndromes (IBS, NUD, FM, CFS) Compared With Healthy Controls (HC)

Psycho-metric Variable	Functional Syndrome Versus Healthy Controls	Number of Studies	Total Sample Size	Effect Size	Confidence Interval 95%	Significance Level <i>p</i> <	Orwin's Fail Safe N (d = +0.20)
Depression symptoms	IBS	25	3675	0.801	0.564-1.038	.0001	76
	NUD	11	3138	0.828	0.453-1.202	.0001	35
	FM	3	947	0.619 ^a	0.465-0.773	.0001	8
	CFS	6	1869	1.354 ^b	0.789-1.919	.0001	35
Anxiety	IBS	23	3136	0.697	0.511-0.883	.0001	58
	NUD	9	871	0.828	0.325-1.331	.001	29
	FM	3	1144	0.182 ^c	-0.399-0.763	NS	
	CFS	5	3432	0.737	0.478-0.995	.0001	14

^a Homogenous effect, effect size *d*+ was used. Remaining effects are heterogenous, in these cases effect size DELTA was used under a random effects model. Significance level and confidence interval refer to effect size *d*+ in homogenous effects and to effect size DELTA in heterogenous effects.

^b Difference of effect size CFS vs HC-IBS vs HC significant at *p* < .0001 (*t*-Test).

^c Difference of effect size FM vs HC-IBS vs HC significant at *p* < .0001 (*t*-Test).

DISCUSSION

This meta-analytic review confirms our hypotheses. It extends, in a systematic way and for a range of functional somatic syndromes and disorders defined by medically unexplained physical symptoms, the repeated isolated observations that depression and anxiety are a regular, though not universal accompanying, feature of them. The review demonstrates that this association with depression and anxiety goes beyond the rate observed in healthy controls or in patients with similar diseases of known organic pathology. There is limited meta-analytic evidence for three further effects: a linear dose-effect-like relationship between the number of medically unexplained symptoms and psychiatric disorder, differences between types of medically unexplained symptom or syndrome in terms of the degree of association with depression and anxiety, and a higher degree of anxiety (but not of depression symptoms) in consulters compared with nonconsulters.

We assume that we have identified a subset of observational studies for meta-analytic integration with sufficient criterion validity concerning the quality of diagnostic criteria and of the diagnostic evaluation of psychological and bodily symptoms (15). More than 68% of all studies were deferred or excluded for want of one or more quality inclusion criteria. The effect was also apparent in subgroup analyses when only the cognitive rather than the somatic aspects of depression were measured. Therefore it is not likely that increased levels

of depression and anxiety in patients with medically unexplained physical symptoms merely reflect an artifactual confounding due to the bodily symptoms inherent in the concepts and measurement of anxiety and depression (19). The integration of so many primary studies allows for a broad overview of the research literature, but it necessarily hampers detailed reporting and analysis of single effects – although it has to be stressed that great care was taken to analyze the validity of the primary studies closely according to the prespecified coding manual. Many results of the meta-analytic integration remained heterogenous despite a design which controlled for some confounding variables. This makes it difficult to draw definitive conclusions concerning the extent of the observed correlations in relation to yet unknown moderators. But heterogeneity was expected as it is the rule rather than the exception in meta-analyses of observational studies (20) and it does not prevent us from interpreting the integrated effect size as an average measure (21). When interpreting this study it has to be borne in mind that it focused, due to the lack of other primary sources suitable for meta-analytic integration, on functional somatic syndromes; a generalization to all sorts of medically unexplained physical symptoms, particularly to various forms of somatization and somatoform disorders, therefore must be seen with caution.

Although cross-sectional in nature, the results obtained in our “overview design” help to interpret the consistent corre-

lation of medically unexplained physical symptoms with depression and anxiety in several ways. First of all, the finding that depression and anxiety are higher in patients with medically unexplained symptoms than with comparable but medically explained ones argues against the assumption that they are primarily a psychological consequence of the experience of pain and other bodily symptoms, irrespective of their cause (6). (For the comparison of depression in fibromyalgia vs. rheumatoid arthritis, another meta-analysis has recently confirmed this finding (22)).

Secondly, medically unexplained symptoms often arise without concurrent depression and anxiety, as the small-to-moderate effect sizes for the associations indicate. Therefore these symptoms cannot globally be seen as the bodily expression of depression and anxiety or as the consequence of the amplification of bodily sensations due to depression and anxiety (23). Thirdly, in patients with medically unexplained gastrointestinal symptoms, help-seeking is correlated with increased levels of anxiety only, but not depression symptoms, and bodily and psychological symptoms are correlated also in population studies of people with functional syndromes as well as with somatoform disorders (data not shown). However, our data do not allow interpretation whether help-seeking is causally related to increased levels of anxiety or to increased severity of bodily symptoms (24) or to other factors.

In our view, it is most parsimonious to interpret the findings as implying that medically unexplained physical symptoms are best described as constituting one dimension of common distress symptoms and disorders alongside depression and anxiety (7, 25), with each of these dimensions potentially being subdivided further (26–28). As our results do not imply a primacy of mental over physical symptoms, this description does not imply that medically unexplained symptoms belong primarily to the realm of mental disorders. It might therefore indeed be more appropriate to drop “mental” from the term “common mental disorders” (29). A designation as “common distress disorders” might be preferable as the word “distress” refers equally to bodily and mental suffering – although, from our data, we cannot exclude the possibility that some patients suffering only from bodily distress do so due to a yet undetected structural organ pathology. Our results provide limited evidence for the assumption that the degree of correlation between the three dimensions of common (mental) disorders varies according to the type of medically unexplained symptoms (ie, in the different functional syndromes) and according to the level of care. The evidence for a dose-response-like relationship between the severity of somatoform disorder and the degree of anxiety and depression fits with the assumption of dimensionality (as functional syndromes lack indicators of severity, this aspect of dimensionality cannot be investigated there). We suppose that cognitive-behavioral variables like causal attributions of the patient are additionally important for differentiation of clinical picture and outcome (30) but, even with our far-reaching literature search, there were far too few studies on these key phenomena to reach a conclusion.

In terms of etiology, one must assume that a certain degree of heterogeneity underlies more homogenous clinical descriptions (31). In particular, there might be different causal relations underlying the same cross-sectional association of bodily symptoms, depression and anxiety; eg, in some cases, anxiety and depression may be a reaction to bodily pain and distress, in others, depression and anxiety may lower the threshold for reporting bodily symptoms. There might also be potent common genetic and environmental causal factors underlying bodily as well as psychological dimensions of distress (8). Such a view of medically unexplained bodily symptoms as one dimension of distress does not imply a diminishing role of biological factors in general, but it favors a shift of emphasis from dysfunction of peripheral bodily organs toward seeing these symptoms and syndromes as functional disorders of body representations and emotions in the brain (32). It has to be determined empirically whether psychosocial or neurophysiological approaches are more valid for explaining the disposition, onset, and course of these common disorders (33, 34).

Clinically, recent reviews have shown that both pharmacological and nonpharmacological psychological treatments are effective across a variety of functional somatic and other unexplained physical syndromes (35, 36). A view of “common distress disorders” fits with these therapeutic approaches without implying a purely psychogenic frame of reference. It may therefore help to overcome the barriers against “nonorganic” treatment of people with medically unexplained bodily symptoms who feel stigmatized by overtly psychiatric descriptions. In terms of clinical research, our results imply that outcome has to be evaluated in the bodily as well as the psychological dimensions of distress rather than focusing on treatments and outcomes only in terms of isolated functional syndromes or specific somatoform disorders (37).

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