The Infrequency of "Pure Culture" Diagnoses Among the Anxiety Disorders

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Background: Anxiety disorders are known to commonly coexist in individuals, both with other anxiety disorders and with mental disorders from other groupings, such as affective disorders. We questioned how frequently anxiety disorders actually occur in isolation, as "pure cultures."

Method: We examined diagnostic patterns among the 711 subjects entered into a large, multicenter study of anxiety disorders, the Harvard/Brown Anxiety Disorders Research Program (HARP), which focused on panic, agoraphobia, generalized anxiety disorder, and social phobias as "index disorders" required for intake.

Results: We used various definitions for "pure culture." By all definitions, subjects with "pure culture" represented a minority, especially in cases of generalized anxiety disorder and social phobia, where comorbidity was virtually ubiquitous. "Pure culture" status was associated with later onset of illness and less chronicity.

Conclusion: Future studies of anxiety disorders should aim to document the extensive comorbidity, rather than eliminate it by restrictive diagnostic exclusion criteria, lest they yield atypical or even misrepresented groups of patients. Clinicians should not stop at identifying only the "main" diagnosis but look for other, comorbid diagnoses that are often present.

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Research protocols, especially those for controlled clinical trials of psychotherapeutic medications, often specify criteria to exclude subjects who carry additional diagnoses besides that of interest. For example, a study of drug treatment for generalized anxiety disorder might prohibit inclusion of subjects with comorbid panic disorder or depression. This practice stems partly from the policies of regulatory agencies such as the Food and Drug Administration.[1] There is concern that, without such exclusions, therapeutic effects on generalized anxiety disorder might be confounded with antipanic or antidepressant effects. Underlying this approach is the assumption that such disorders as generalized anxiety disorder and panic disorder are fundamentally separate and, with sufficient effort, can be isolated. However, the isolation of such "pure cultures" of specific disorders may depart from clinical reality, in which patients often or even usually present with a mix of symptoms justifying more than one diagnosis, i.e., they commonly present with comorbid disorders. In fact, such a concatenation of disorders may represent a factor that impels people into treatment.

The clinical reality of comorbidity has been obscured by earlier diagnostic systems (e.g., the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, or DSM-III) which made extensive use of hierarchical exclusion criteria that eliminated the possibility of one diag-

nosis in the presence of another.[2] The revised version of DSM-III (DSM-III-R) retreated from this practice, altering criteria to make comorbidity more possible in principle by allowing an individual who meets criteria for several different diagnoses to receive them all. Furthermore, structured diagnostic interviews that routinely assess a wide range of symptoms may make comorbidity more apparent than clinical interviews that focus on what seems to be the "main" problem.

The anxiety disorders, with their characteristically high degree of chronicity, may offer especially fertile ground for the development of other mental disorders in the same individual. Their broad array of criterion symptoms—with extensive overlap between, for example, generalized anxiety disorder, panic disorder, depression, and somatoform disorders—may also place patients in multiple diagnostic categories. Extensive comorbidity within this group of disorders has been documented in various studies.[3–10] A separate report of the comorbidities among the anxiety disorders in the Harvard/Brown Anxiety Disorders Research Program (HARP) study group also found a high degree of comorbidity.[11] Generalized anxiety disorder was most often a comorbid diagnosis, while panic disorder without agoraphobia was the disorder most often found as the sole diagnosis, when both lifetime and active cases at intake were considered. Panic disorder with agoraphobia and agoraphobia without history of panic disorder were frequently comorbid with three specific diagnoses: social phobia, simple phobia, and generalized anxiety disorder. Agoraphobia without history of panic disorder, social phobia, and generalized anxiety disorder were frequently found in the presence of each other. Several family studies[12–16] have indicated moderate familial aggregation of phobic disorders but differing results regarding the specificity or distinctness of the heritability of these disorders.

Classification methods clearly determine the likelihood and rates of comorbidity observed. Frances and colleagues[17] enumerated several ways in which assumptions and definitions applied in interpreting diagnoses impact these rates. Issues of methodology that increase the likelihood of detecting comorbidity include (1) increasing the variety of disorders included in a diagnostic system; (2) creating narrow categories that are associated with each other; (3) establishing rules of diagnosis that encourage multiple diagnoses; (4) providing clearly specified criteria that lead to systematic and equivalent attention paid to the less predominant symptoms; (5) allowing disorders to share items within their definitional criteria sets; (6) setting low thresholds for expected severity, frequency, and duration of symptoms; and (7) creating bias by the belief that two disorders are related.

Here we focus on the converse of comorbidity—the isolation of patients with a single diagnosis—which we term *pure culture* for a given disorder. We were interested in what proportion of patients with an anxiety disorder have one diagnosis only and therefore fall into the category of "pure culture" as defined below. The hypothesis was that such patients are uncommon and atypical of a clinical study group such as that in the HARP study. We were also interested in whether pure culture status was less common in certain anxiety disorders than others and whether other characteristics (degree of chronicity, age, sex, level of impairment) would differentiate pure culture patients from those with mixed diagnoses. In particular, greater duration of chronic illness might lead to development of other disorders, and a combination of disorders might be expected to result in more symptoms and greater impairment than a single disorder.

METHOD

The HARP is a prospective, naturalistic, longitudinal, multicenter study of adults with a current or past history of the following: panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without panic disorder, social phobia, or generalized anxiety disorder (GAD). Insufficient for inclusion, but frequently seen as comorbid conditions, are DSM-III-R diagnoses of simple phobia, posttraumatic stress disorder, obsessive-compulsive disorder, or anxiety disorder not otherwise specified. Subjects are at least 18 years of age and willing to voluntarily participate in the study and sign a written consent form. Exclusion criteria are the presence of an organic brain syndrome, a history of schizophrenia, or current psychosis; otherwise, any comorbidity was allowed. Subjects entered this study from over 30 clinicians' practices at 11 different clinical treatment facilities. The methods are described in detail elsewhere.[18]

The present data derive from the structured diagnostic interview administered at intake. The initial comprehensive evaluation assesses lifetime history using the Structured Clinical Interview for DSM-III-R Non-Affective Disorders, Patient Version (SCID-P)[19] and the Research Diagnostic Criteria (RDC) Schedule for Affective Disorders-Lifetime (SADS-L).[20] Items of the SCID-P and SADS-L were combined to create the SCALUP, a structured interview used to assess diagnoses at intake (available from M. B. Keller, upon request). The instrument thus yielded both present and past RDC diagnoses for affective disorders[21] and DSM-III-R diagnoses for nonaffective (including anxiety) disorders.[22] Interviews, conducted by trained research assistants, usually took place in single sessions lasting 2 to 4 hours, but varied widely in duration from 1 to 10 hours (depending largely on the number of diagnoses). If lengthy, the interview could be conducted in two sessions. There was thus ample time for interviewers to explore as much varied psychopathology as subjects presented, which interviewers were encouraged to do. To enhance reliability, after each inter-

view the interviewer wrote a "narrative summary" describing the symptoms and course of each diagnosed disorder for a given subject as well as diagnoses that were considered but not made; this summary was reviewed by and often discussed with a protocol monitor before the diagnoses were made final.

Three sub-studies were conducted using subjects already enrolled in HARP to assess interrater reliability, subject recall, and validity of the Longitudinal Interval Follow-up Evaluation-Upjohn (LIFE-UP) psychiatric status ratings (PSRs), used to assess the course of all disorders.[23] The study to assess interrater reliability of the anxiety disorder PSRs and the other instruments found good-to-excellent reliability. The long-term test-retest sub-study conducted to assess the reliability of using subjects' retrospective recall to assess PSRs over 1 year found acceptable reliability for panic and very good-to-excellent reliability for all other index disorders and for major depressive disorder. The separate external validity assessment comparing PSRs with other psychosocial measures found good concurrent and discriminant validity.

Data Analysis

The group examined here derives from the 711 subjects entered into HARP. Of these, 670 were actively in an episode of an anxiety disorder at intake; they are the focus of our analyses. We then put these 670 subjects through progressively finer filters of comorbidity in order to yield a group we labeled "pure by history of any disorder."

The first filter removed all those who had more than one anxiety disorder of any kind active at intake, yielding a group we labeled "pure in episode within the anxiety disorders." The next level of refinement removed from the group of subjects "pure in episode within the anxiety disorders" those who had any other nonanxiety disorder (e.g., depression, substance abuse) actively in episode at intake. We termed the group that resulted "pure in episode for any disorder." The last level of refinement removed subjects who had a past history of any other psychiatric diagnosis besides the one active at intake. We termed this group "pure by history of any disorder."

The resultant groups are described in terms of the frequency of occurrence and percentage of the original group. We report on the index disorders necessary for entry into HARP, namely panic disorder, panic disorder with agoraphobia, agoraphobia without panic disorder, general anxiety disorder, and social phobia. The rationale for focusing on the index disorders is that, due to the inclusion criteria of HARP, disorders other than the index disorders necessitated comorbidity for entry to the study and thus would artificially inflate the observed level of comorbidities.

We then investigated whether certain clinically relevant variables might be associated with purity for each of these index diagnoses. These variables were sex, age at intake, age at onset of the specific anxiety disorder, duration of current episode of illness, and level of impairment as measured by Global Assessment Scores at intake.[24] To compare the means of pure and mixed-diagnoses groups for these variables, t tests were computed. Sex ratios were compared by one degree of freedom chi-square tests. Data were analyzed using SAS software (SAS Institute, Cary, N.C.).

Table 1. Frequency of HARP Subjects Categorized as "Pure Culture" by Different Criteria as a Proportion of Total HARP Subjects in Episode of an Anxiety Disorder at Intake (N = 711)

Index Diagnosis	All HARP Subjects in Episode of Anxiety Disorder at Intake	"Pure" in Episode Within Anxiety Disorders		"Pure" in Episode for Any Disorder		"Pure" by History of Any Disorder	
		N	%	N	%	N	%
Panic disorder	81	43	53	17	21	8	10
Panic with agoraphobia	357	158	44	54	15	29	8
Agoraphobia without panic	30	13	43	6	20	6	20
Social phobia	176	38	22	12	7	2	1
Generalized anxiety disorder	180	30	17	8	4	1	1
Totals	670[a]	329[b]	49	112[b]	17	56[b]	8

[a]670 is the total number of subjects with any anxiety disorder in episode at intake; this is smaller than the sum of the rows above because it is possible for subjects to have more than one diagnosis.
[b]These totals are larger than the sum of the columns above because they include some subjects "pure" for non-index anxiety disorders not listed in this table.

RESULTS

Of the 670 subjects with an anxiety disorder active at intake, 440 (66%) were female and 230 (34%) were male. The mean ± SD age was 40.4 ± 12.7 years. Specific patterns of comorbidity of the index diagnoses are detailed in a separate report[11]; however, Appendix 1 reports the proportions of the total group of 711 who were affected in either the past or present by each of the disorders assessed with the intake protocol.

The frequencies of the index anxiety disorder diagnoses (panic disorder, panic disorder with agoraphobia, agoraphobia without panic disorder, GAD, and social phobia) in this study group are shown in Table 1. There were substantial numbers in all categories except for agoraphobia without panic disorder (N = 30). The group labeled "pure in episode within the anxiety disorders" totaled 329, representing 49% of the group of 670 with anxiety disorders active at intake from which they were derived. As can be seen in Table 1, by the "pure" classification, the index diagnoses were reduced by a maximum of 53% to a minimum of 17% of each of the original diagnostic groups. At the next level of refinement, subjects who were "pure in episode for any disorder" totaled 112, representing 17% of the original group of 670 subjects.

Table 2. Comparison of Characteristics of Subjects "Pure in Episode for Any Diagnosis" With Subjects of "Mixed Diagnoses"

Characteristic	"Pure" (N = 112)	"Mixed" (N = 599)
Age at intake		
Mean	42.3	40.3
(SD)	(14.3)	(12.3)
Male %	31.3%	34.2%
Illness onset age[a]		
Mean	28.0	17.8
(SD)	(15.5)	(11.5)
Global Assessment Scores		
Mean	61.1	59.8
(SD)	(11.9)	(11.3)

[a]t = –6.65, p = .0001.

Table 3. Comparison of Duration of Episode of Index Disorders of Subjects "Pure in Episode for Any Diagnosis" With Subjects of "Mixed Diagnoses"

Index Diagnosis	"Pure" N	"Pure" Years Mean	"Pure" Years SD	"Mixed" N	"Mixed" Years Mean	"Mixed" Years SD
Panic disorder[a]	17	2.94	3.4	64	13.29	13.0
Panic disorder with agoraphobia[b]	54	11.10	10.9	303	17.69	14.0
Agoraphobia without history of panic disorder	6	16.51	17.8	24	20.74	19.0
Social phobia	12	21.61	31.1	164	18.98	12.7
Generalized anxiety disorder	8	24.70	17.7	172	17.80	13.9

[a]t = 5.68, p = .0001.
[b]t = 3.28, p = .0011.

Diagnostic groups were reduced dramatically from 4% to 21% of their initial group. At the last level of refinement, the group "pure by history of any disorder" totaled only 56 subjects (8% of the original group). At this most stringent level of "filtering," only 1% to 20% of the original index diagnoses are represented.

The group "pure in episode for any diagnosis" at intake was examined more closely. Table 2 compares these 112 subjects with the remaining 599 mixed-diagnosis cases. The two groups had equivalent ages at intake, sex ratios, and levels of impairment as measured by Global Assessment Scores at intake. However, the mixed-diagnosis cases had overall onset of illness earlier in life (mixed, mean ± SD years = 17.79 ± 11.5 vs. pure, mean ± SD years = 28.0 ± 15.5; t = –6.65, df = 135.1, p = .0001). Furthermore, mixed-diagnosis subjects had significantly longer duration of current episode of illness for panic disorder (mixed, mean years = 13.29 ± 13.0 vs. pure, mean years = 2.94 ± 3.4; t = 5.68, df = 79, p = .0001) and panic disorder with agoraphobia (mixed, mean years = 17.69 ± 14.0 vs. pure, mean years = 11.10 ± 10.9; t = 3.28, df = 355, p = .0011), but not for agoraphobia without panic disorder, social phobia, or generalized anxiety disorder (Table 3).

DISCUSSION

The widespread occurrence of comorbidity among patients with psychiatric disorders in general and anxiety disorders in particular has already been well documented.[3–11] HARP provides a notably large clinical study group in which this is demonstrated. What may not have been sufficiently emphasized previously, as this report attempts, is the existence of comorbidity so extensive that "pure culture" forms of these disorders in clinical samples are atypical, if not rare or even in some cases virtually nonexistent. This point is important because treatment studies continue to seek such subjects through diagnostic exclusion criteria in their protocols. Homogeneity of subject samples has become an ideal of good clinical research but unfortunately, when efforts to accomplish this ideal succeed, they may yield patient samples quite unlike what clinicians have to treat. Unrealistic exclusion criteria may also yield distorted impressions of the kind of patients being studied, by discouraging thorough diagnostic assessment and frank appraisal of the results or by forcing patients to be "pigeon-holed" into single categories even though multiple categories are applicable.[1]

These data also have implications for clinicians who may satisfy themselves with assessing the patient enough to make one definite diagnosis. Treatment plans should take into account the usual occurrence of comorbidity. This may be especially applicable to certain disorders such as social phobia and generalized anxiety disorder since both of these diagnoses were observed as the sole lifetime diagnosis in only 1% of our study group.

It is, of course, likely that in nonclinical (e.g., epidemiologic) studies, "pure culture" subjects will be more prevalent, because many diagnosable subjects not in treatment will presumably be less ill than those who do seek treatment. This represents the phenomenon known as "Berkson's bias," which is the tendency of people with greater numbers and/or severity of symptoms to be more likely to seek treatment and thereby to enter into clinical studies. To clinicians, the diagnostic status of those who seek treatment is generally most relevant—though the characteristics of treatment-seekers may change as public awareness of these disorders and of their potential for treatment is raised. Nevertheless, even in a community survey, Sturt[25] described it as a "very robust finding" that "a subject who exhibits any given symptoms or syndrome is more likely to show other symptoms or syndromes as well."

"Pure culture'' subjects did exist in the HARP sample. At least in the case of panic disorder and panic disorder with agoraphobia, they may represent less chronically and severely ill patients in earlier phases of their illness. However, even by the most liberal definition of "pure culture,"

such subjects constituted, at most, half (17%–53%) of any diagnostic group examined. Defined more stringently, so that only subjects with a solitary diagnosis of any kind active at intake could be called "pure," their proportions diminished drastically, to 4% to 21% of the original sample. At the most stringent level, demanding "virginal" subjects who had never had any diagnosis other than the solitary one active at intake, their proportions (1%–20%) were reduced to the vanishing point. Because we were concerned that inclusion of a common and sometimes "minor" diagnosis such as simple phobia in our analysis might result in misleadingly high levels of comorbidity, we investigated whether removal of simple phobia as a possible comorbid diagnosis altered the "purity" rates for each of these definitions. Removal of this diagnosis did not change the rates, so we included simple phobia as a possible comorbid diagnosis.

Lest these definitions of "pure culture" seem overly stringent, consider this condensation from the narrative summary of a case of generalized anxiety disorder defined as "pure culture in episode for any disorder" because at intake he was diagnosed with generalized anxiety disorder as his only active disorder:

> This 45-year-old man was diagnosed with ongoing GAD since age 6 on the basis of his having been a "chronic worrier" with associated symptoms of muscle tension, restlessness, light-headedness, lump in throat, feeling on edge, exaggerated startle response, difficulty concentrating, and irritability. In addition, he was given a past history diagnosis of Anxiety Disorder Not Otherwise Specified from ages 43 to 45 on the basis of acute anxiety attacks with light-headedness, racing heart, sweating, flushing, and fear of loss of control which occurred predictably at work for 2 years, immediately following a stroke that affected his facial musculature. Developing concurrently, but lasting only 6 months, was a past diagnosis of Social Phobia based on a fear that he might choke while eating in front of others. At that time, also lasting 6 months, he had a Major Depressive Disorder with loss of appetite and weight, hypersomnia, lack of energy, psychomotor retardation, pervasive loss of interest, and feelings of worthlessness and guilt. Two months after recovery from this, he underwent a 2-month Hypomanic Episode; for 10 years previous to this he had been having brief periods of feeling "super-high" for less than a day at a time about once a week, but these episodes did not meet criteria for diagnosis. He had previously had a Minor Depressive Disorder for 1 month at age 37.

Clearly, while he met criteria only for generalized anxiety disorder at intake, the complexity of his history would leave one hesitant to call him a "pure" generalized anxiety disorder patient. Consider also the case of our only generalized anxiety disorder subject to be classified as "pure by history of any disorder":

> This 63-year-old man had been a chronic worrier with 12 associated symptoms of GAD since age 17. Although he met criteria for no other diagnosis, he failed to meet criteria for panic disorder with agoraphobia only because his otherwise typical panic attacks were associated with only three somatic anxiety symptoms (hot flashes, tightness in chest, and sweating) instead of the requisite four. Also, he was a World War II veteran "tailgunner" who reported ongoing intrusive recollections and dreams about his war experiences, intense distress at reminders of the war, and efforts to avoid such reminders and to avoid thinking about the war, but lacked the requisite third criterion under category "C" for the DSM-III-R diagnosis of Posttraumatic Stress Disorder.

Examples such as these lead us to believe that, if anything, our diagnostic practices and definitions of "pure culture" could potentially lead to underestimation of the ubiquity of comorbidity. Note, for example, that the diagnostic convention of HARP omitted a potential bipolar diagnosis in the first case because *at intake* the subject did not meet criteria for a current episode for major depressive disorder, hypomania, or minor depression, even though all of these had occurred in his past.

In our study group, generalized anxiety disorder simply did not exist in forms that most clinicians would comfortably label "pure culture." In another study, which excluded from its sample subjects with current major depression (represented by 27% of our sample) and omitted some of the diagnoses our intake instrument made, Brawman-Mintzer and associates[26] found 26% of 187 generalized anxiety disorder subjects free of other lifetime diagnoses. Different definitions and instruments will yield different numbers, but seem unlikely to alter the general impression that diagnostic purity is atypical of these patients. This suggests that "pure culture" subjects, even when they can realistically be found, may not adequately represent the usual situation in clinical practice.

In this report, we have highlighted the rarity of patients who present for treatment with only one disorder. We have attempted to illustrate the consequential disservice we do ourselves as clinicians by focusing on only a small segment of the treatment-seeking population in studies of treatment, course, and predictors of these disorders. Most critically, we hope to have heightened awareness of the constraints that this selection practice imposes on generalizability to the patients we treat.

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Appendix 1. Comorbid Diagnoses Obtained From Diagnostic Interview

Diagnosis	% Affected: In Episode at Intake	% Affected: By History Only
Anxiety disorder diagnoses		
Panic disorder	11.4	6.6
Panic disorder with agoraphobia	50.2	8.4
Agoraphobia without panic	4.2	2.0
Social phobia	24.8	3.2
Generalized anxiety disorder	25.3	4.4
Obsessive-compulsive disorder	15.9	2.1
Posttraumatic stress disorder	7.6	2.1
Simple phobia	16.2	0.7
Anxiety disorder NOS	8.3	4.4
Affective disorder diagnoses		
Major depressive disorder	27.0	30.4
Bipolar disorder Type I	1.4	0.6
Bipolar disorder Type II	1.1	0.7
Hypomania	0.1	1.3
Cyclothymic disorder	0.3	0.0
Intermittent depressive disorder	15.3	0.1
Minor depression	5.8	8.6
Depressive disorder NOS	1.1	3.8
Substance abuse/dependence diagnoses		
Alcohol	4.8	23.2
Opioid	0.1	3.0
Sedative	0.6	5.9
Cocaine	0.0	4.8
Cannabis	0.8	7.3
Amphetamine/stimulant	0.0	3.9
Hallucinogen	0.0	1.5
Not otherwise specified	0.1	1.7
"Other" diagnoses		
Psychotic disorder NOS	0.0	0.3
Somatoform disorder	5.8	0.8
Somatization disorder	0.1	0.0
Somatoform plain disorder	0.4	0.1
Anorexia nervosa	1.1	1.5
Bulimia	1.4	2.4
Eating disorder NOS	0.4	1.0
Conduct disorder	0.0	3.8
Antisocial personality disorder	0.8	0.3
Schizotypal personality disorder	0.1	0.0
Schizotypal personality features	0.6	0.1
Unspecified mental disorder	0.4	0.1