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Comorbidity and social phobia: evidence from clinical, epidemiologic, and genetic studies

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Abstract This paper reviews evidence from clinical, epidemiologic, and family studies regarding the association between social phobia and other syndromes. Social phobia is strongly associated with other anxiety disorders, substance abuse, and affective disorders in both clinical and community samples. An average of 80% of social phobics identified in community samples meet diagnostic criteria for another lifetime condition. Social phobia is most strongly associated with other subtypes of anxiety disorders, with an average of 50% of social phobics in the community reporting a concomitant anxiety disorder including another phobic disorder, generalized anxiety, or panic disorder. Approximately 20% of subjects in the community meet lifetime criteria for a major depressive disorder. The onset of social phobia generally precedes that of all other disorders, with the exception of simple phobia. Both clinical severity and treated prevalence are consistently greater among social phobics with comorbid disorders. The results of family and twin studies reveal that shared etiologic factors explain a substantial proportion of the comorbidity between social phobia and depression, whereas the association between social phobia and alcoholism derives from a nonfamilial causal relationship between the two conditions. Clinical and phenomenologic implications of these findings are discussed.

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Introduction

The classification of anxiety disorders has generated a considerable degree of controversy, particularly since the introduction of pharmacologic agents with differential efficacy among the different subtypes of anxious states. Much of the uncertainty regarding the distinctions between the categories of anxiety disorders in general, and phobic states in particular, arises from a lack of empirical evidence regarding their validity as discrete entities. Indeed, both clinical and epidemiologic studies have revealed that the overlap within the specific subtypes of anxiety and between anxiety disorders and depression is far more common than the pure expression of these conditions.

The term comorbidity, introduced by Feinstein, refers to the presence of any additional coexisting ailment in a patient with a particular index disease (Feinstein 1970). Failure to classify and analyze comorbid diseases can create misleading medical statistics and may cause spurious comparisons during the planning and evaluation of treatment for patients. Comorbidity can alter the clinical course of patients with the same diagnosis by affecting the time of detection, prognostic anticipations, therapeutic selection, and post-therapeutic outcome of an index diagnosis (Kaplan and Feinstein 1974).

Nonrandom concurrence of two conditions may be attributable to several methodologic artifacts including: (a) samples selected from clinical settings that are non-representative of persons with the index disease in the general population (i.e., "Berkson's Bias"; Berkson 1946), (b) assessment bias, in which the concurrence of two conditions is an artifact of overlap in the diagnostic criteria or in the assessments employed to ascertain the criteria, and (c) the lack of an appropriate comparison or control group with which to account for factors that confound the association between the two conditions.

Aside from identification of bias, investigation of patterns of comorbidity is important for several reasons. Firstly, identification of differential patterns of comorbidity may lead to the identification of subtypes of a particular index disorder for which the comorbid condition may indicate a different form or subtype, thereby enhancing the validity of their distinction in the classification system. Secondly, differential associations between particular pairs of diseases may yield clues regarding the pathogenesis of the index disease. If two conditions emanate from the same underlying etiologic factors, investigations of their etiology focus on risk factors that are common to both conditions. Finally, if the comorbid disorder is a consequence of the index disease, interventions can be developed to prevent the development of the secondary condition.

This paper reviews multiple sources of evidence regarding the association between social phobia and other syndromes. Specifically, we review evidence from clinical and epidemiologic studies to estimate the magnitude of comorbidity, and evidence from family/genetic studies to identify the specific mechanisms for comorbid associations.

Review of studies

Clinical studies

Social phobia and other anxiety disorders

The association between social phobia and other major psychiatric disorders has been investigated in numerous clinical studies, as presented in Tables 1–3. These studies are divided according to the disorder of the index case. The wide range in proportions of comorbid disorders may be attributed to methodologic variations across studies. Table 1a shows the proportion of social phobics with an

Table 2a, b Association between social phobia and affective disorders: clinical studies

a Index case: social phobia	No. of patients	Major depression (%)	Dysthymia (%)
Argyle and Roth (1989)	37	37	–
Stein and Gelernter (1990)	16	94	–
Perugi and Savino (1990)	25	36	–
Turner et al. (1991)	71	3	6
Van Ameringen et al. (1991)	57	70	32
Lépine et al. (1993)	58	56	19
b Index case: affective	No. of patients	Social phobia (%)	
Schapira and Roth (1970)	45	33	
Lépine et al. (1993)	116 (major depression)	28	
	64 (dysthymia)	9	

additional anxiety disorder. The results suggest that approximately one-third of the persons in treatment for social phobia report a concomitant anxiety disorder including generalized anxiety disorder, panic disorder, or agoraphobia. A similar proportion of index patients with the latter types of anxiety disorders report a lifetime history of social phobia as well. The symmetry in these findings suggests that approximately one-third of patients with an anxiety disorder manifest at least one of the other major subtypes at some time during their lifetime.

Social phobia and affective disorders

The association between social phobia and affective disorders in clinical studies is presented in Table 2. The results reveal that on the average, 60% of persons in treat-

Table 1a, b Association between other subtypes of anxiety, social phobia, and anxiety: clinical studies

a Index case: social phobia	Percent with other anxiety				
	No. of patients	Generalized anxiety disorder	Panic	Agoraphobia	All
Barlow and Vermilyea (1986)	19	21	32	37	48
Perugi and Savino (1990)	25	36	–	–	–
Turner et al. (1991)	71	33	3	–	–
Van Ameringen et al. (1991)	57	49	19	7	93
b Index case: panic ± agoraphobia	Percent with other anxiety				
	No. of patients	Generalized anxiety disorder	Agoraphobia	Social phobia	
Argyle and Roth (1989)	90	96	62	41	
Stein and Gelernter (1990)	35	–	66	46	
Perugi and Savino (1990)	25	36	–	–	
Andersch and Hanson (1993)	123	–	–	26	

Table 3a, b Association between substance abuse and social phobia: clinical studies

a Index case: Alcoholism	No. of patients	Social phobia (%)	
Mullaney and Trippett (1979)	102	32	
Stockwell et al. (1984)	42	57	
Bowen et al. (1984)	48	8	
Smail et al. (1984)	60	18	
Weiss and Rosenberg (1985)	84	2	
Stravynski et al. (1986)	96	8	
Chambless and Caputo (1987)	75	19	
Thevos and Latham (1991)	33	15	
b Index case: social phobia	No. of patients	Alcoholism (%)	Drugs (%)
Amies and Shaw (1983)	87	20	–
Thyer and Curtis (1986)	42	36	–
Perugi and Savino (1990)	25	20	4
Van Amerigen et al. (1991)	57	28	16

ment for social phobia report a history of either major depression or dysthymia. In contrast, only approximately 30% of those persons receiving treatment for an affective disorder report concomitant social phobia. However, when considered in terms of the population base rates of these conditions, there is a strong degree of concurrence between affective disorders and social phobia.

Social phobia and substance abuse

Table 3 presents the association between social phobia and substance abuse in clinical settings. The findings regarding the association between alcoholism and social phobia are very consistent and symmetric: The association between these disorders is very strong, irrespective of the target disorder for treatment. An average of 15% of treated alcoholics meet criteria for social phobia, and 25% of social phobics in treatment settings report a history of alcoholism.

Epidemiologic studies

The associations presented in the previous tables derive from clinical samples, which may be biased with regard to comorbidity, severity, and other sociodemographic or clinical factors that may facilitate treatment. Therefore, it is critical to confirm the associations identified from clinical settings in samples that are not biased with regard to factors that may increase the likelihood of comorbidity. The magnitude of comorbidity of social phobia and other anxiety disorders, affective disorders, and substance abuse in community samples is shown in Table 4. A brief description of the designs of each of the epidemiologic studies in which comorbidity of social phobia and other conditions was assessed is presented in the following section.

Patients and methods

Basel epidemiologic study

The Basel Epidemiologic Study is a community study of 470 randomly selected community residents of Basel, Switzerland, between the ages of 18 and 65 years (Wacker et al. 1992). The Composite International Diagnostic Interview (CIDI; Robins et al. 1988; Wittchen et al. 1991), a standardized diagnostic instrument, was administered by trained professionals to obtain psychiatric diagnoses by DSM-III-R and ICD-10 criteria to obtain lifetime and 1-year prevalence rates.

Epidemiologic catchment area study (ECA)

The ECA is a large-scale epidemiologic study of a probability sample of adults in five locations in the United States. Diagnostic information necessary for ascertaining the DSM-III criteria for the major psychiatric disorders was collected via a structured diagnostic instrument, the Diagnostic Interview Survey (DIS; Robins et al. 1981), administered by lay interviewers.

Zurich cohort study of young adults

The subjects in the Zurich Cohort Study were selected in 1978 from symptom screen of a general population sample of young adults ages 18–19 years in the canton of Zurich, Switzerland (Angst 1993). The cohort has been followed for 11 years with a total of four interviews across the total observation period. Diagnostic criteria from multiple classification systems including the RDC, DSM-III, and DSM-III-R were elicited from a semi-structured diagnostic interview administered by clinically experienced interviewers. The results on comorbidity in this study are based on longitudinal diagnoses of a total of 591 subjects who completed at least one interview during the course of the study. A fifth wave of interviews of the cohort at the age of 35 years has recently been completed.

Epidemiologic study of Puerto Rico

Canino et al. (1987) conducted an epidemiologic study of the major psychiatric disorders among 1551 island Puerto Ricans (age 17–64 years) in 1984. The methods employed were identical to those of the ECA, using a Spanish version of the DIS to obtain DSM-III criteria for lifetime and 6-month prevalence rates (Canino et al. 1987).

Munich follow-up study

The epidemiologic sample of the Munich follow-up study includes 483 people (age 25–65 years) from the general population. The DIS interview was conducted by clinicians to obtain DSM-III criteria for the major psychiatric disorders (Wittchen et al. 1991).

Summary of findings

The concurrence of social phobia with other anxiety disorders, affective disorders, and alcoholism in epidemiologic studies is shown in Table 4. As described below, the results of the community studies confirm all of the associations described in the clinical samples.

Table 4a shows the association between social phobia and other anxiety disorders in epidemiologic studies in the United States and Switzerland. Social phobia is most strongly associated with other phobic states, with odds ratios ranging between 12 and 17. A significant association also emerged between social phobia

Table 4a-c Association between social phobia and
a other anxiety disorders

Sites	Author	No. of subjects	Odds ratio				
			Phobias		Panic	GAD ^a	OCD ^b
			Agoraphobia	Simple			
Switzerland	Angst (1993)	591	16.7	5.8	3.1	5.8	3.0
USA (ECA ^c)	Schneier and Hornig (1992)	10,314	11.8	9.2	3.2	—	4.4
USA (North Carolina)	Davidson and George (1993)	1936	12.1	8.3	10.6	4.2	8.3

b affective disorders

Sites		Author	No. of subjects	Odds ratio	
				Major depression	Dysthymia
Germany	Munich	Wittchen and Essau (1989)	483	6.9	4.9
Puerto Rico		Canino (1987)	1551	18.1	4.9
Switzerland	Basel	Wacker and Klein (1992)	470	2.2	1.1
	Zurich	Angst (1993)	591	2.8	3.4
USA	ECA ^c	Schneier and Hornig (1992)	10,314	4.4	4.3
	North Carolina	Davidson and George (1993)	1936	6.8	—

c substance abuse

Study			No. of subjects	Odds ratio	
Site		Author		Alcoholism	Drug abuse
Switzerland	Zurich	Angst (1993)	591	3.5	2.1
USA	ECA ^c	Schneier and Hornig (1993)	10,314	2.2	2.9

^a Generalized anxiety disorder; ^b obsessive compulsive disorder; ^c epidemiologic catchment area

and panic disorder, and with generalized anxiety disorder, with average odds ratios of 4 and 5, respectively. There was also an association between obsessive – compulsive disorder and generalized anxiety disorder, with average odds ratios of 3 and 8 respectively.

Evidence for the association between social phobia and affective disorders was available from several epidemiologic studies in the United States and Europe. Although the magnitude of the association is variable across the studies, there is still a consistent association between major depression and social phobia, with an average odds ratio of approximately 3. Dysthymia also exhibits a strong degree of concurrence with social phobia, but to a somewhat lower magnitude.

Finally, a significant association also emerged between substance abuse and social phobia. The magnitude of the association was fairly consistent across studies with average odds ratios of 3.0 for alcoholism and 2.5 for drug abuse.

Order of onset

The results of both the clinical and epidemiologic studies that provided information regarding the order of onset of social phobia with regard to that of the other disorders were also reviewed. The onset of social phobia generally tended to precede that of the comorbid disorder for affective disorders (95%), generalized anxiety disorder (90%), agoraphobia (80%), panic (80%), and alcoholism (65%) (Wittchen et al. 1989; Angst 1993). Simple phobia was the only disorder that tended to begin prior to social phobia; more than half of the comorbid cases reported that the simple phobia had occurred prior to the onset of the social fears.

Treatment patterns

Treatment patterns as a function of comorbidity with social phobia were also investigated in the epidemiologic studies described previously. It was consistently found that treatment was facilitated by the presence of a comorbid disorder, with a seven fold increase in a history of treatment among social phobics with at least one comorbid lifetime condition as compared with those with social phobia alone. This confirms the bias that characterizes clinical samples and further underscores the importance of consideration of community samples in gaining understanding of the nature of the relationship between social phobia and other psychiatric conditions.

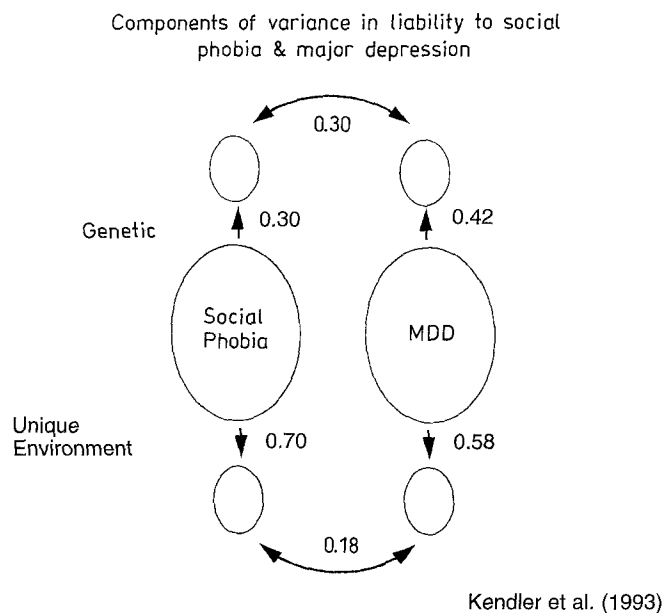
Family studies

There have been two published family studies of social phobia; one that was conducted using the family-history method (Reich and Yates 1988), and one that incorporated direct interviews of the relatives (Fyer et al. 1983). Both revealed a three fold increase in the rates of social phobia among relatives of social phobics as compared with controls. These findings were confirmed in the results of our family study of alcoholism and anxiety disorders (Merikangas et al. 1994), which also yielded a relative risk of 3.0 for social phobia among the relatives of social phobic probands (Table 5).

Family study may also yield information on possible mechanisms for comorbidity through investigation of patterns of the co-aggregation of social phobia and other disorders in families (Merikangas et al. 1994). If there is an elevation in the rates of a comorbid disorder among the relatives of probands with a particu-

Table 5 Familial transmission of social phobias

Study	Probands	No. of patients	Social phobia in relatives (%)	Relative risk
Reich and Yates (1988)	Social phobia	76	6.6	3.0
	Controls	46	2.2	
Fyer and Chapman (1993)	Social phobia	30	16.0	3.1
	Controls	77	5.2	
Merikangas et al. (1994)	Social phobia	72	15.0	2.0
	Controls	61	8.2	

**Fig. 1** Components of variance in liability to social phobia & major depression

lar index condition without comorbidity, then the two disorders may derive from shared underlying etiologic factors. In contrast, specificity of transmission in families provides evidence for distinct etiologic pathways of the respective disorders. Investigation of coaggregation of social phobia with other subtypes of anxiety disorders in the previously mentioned family study of Fyer et al. (1993) revealed that although the aggregate rates of anxiety disorders were elevated among the relatives of social phobics when compared with those of controls, there was no increase in the risk of other subtypes of anxiety disorders among the relatives of social phobics. In contrast, the rates of major depression were elevated among the relatives of social phobics irrespective of the presence or absence of comorbid depression. These findings suggest that there is a certain degree of specificity of the subtypes of anxiety, and that comorbidity of social phobia and major depression results to some extent from shared underlying etiologic factors, rather than representing truly distinct disorders (Merikangas 1990; Merikangas et al. 1994). These findings are inconclusive, because they are based on secondary analyses of the published data, and the analyses were not stratified according to comorbidity of depression and social phobia in the relatives.

Twin studies

The results of a recent twin study of women also suggest that genetic factors are involved in the etiology of social phobia (Kendler and Kessler 1992), and that common genetic factors contribute to the comorbidity of social phobia and depression (Kendler et al. 1993). Figure 1 depicts this relationship schematically. The straight arrows in the upper part of the figure indicate that both

social phobia and major depression are heritable, with genetic factors explaining 30% of the variance in social phobia and 42% of the variance in major depression. The curved arrow above each disorder indicates the correlations in the genetic liability between the two conditions, whereas the curved arrow below the figure depicts the correlations attributable to nongenetic factors. The results suggest that there is a significant degree of shared genetic variation between social phobia and depression ($r = 0.30$), and that to a lesser extent, nongenetic factors, such as environmental influences unique to each twin or depression arising as a consequence of social phobia, underlie the comorbid association between social phobia and depression (Kendler et al. 1993).

Discussion

This review has demonstrated that social phobia is strongly associated with other subtypes of anxiety disorders, affective disorders, and substance abuse in both clinical and community samples. An average of 80% of social phobics identified in community samples meet diagnostic criteria for another lifetime condition. Social phobia is most strongly associated with other subtypes of anxiety disorders. An average of 50% of social phobics in the community report a concomitant anxiety disorder, including another phobic disorder, generalized anxiety; or panic disorder; a history of substance abuse is found in approximately 15% of social phobics; and approximately 20% of subjects in the community meet lifetime criteria for a major depressive disorder. The onset of social phobia generally precedes that of all other disorders, except simple phobia. Both clinical severity and treated prevalence are consistently greater among social phobics with comorbid disorders.

When taken together the results of the family and twin studies of social phobia revealed that shared etiologic factors explain a substantial proportion of the comorbidity between social phobia and depression. In contrast, the association between social phobia and alcoholism appeared to derive from a nonfamilial causal relationship between the two conditions.

These findings have important clinical and phenomenologic implications. The concurrence of social phobia with other disorders is so frequent that individuals with social phobia alone constitute a small minority of the general population. The magnitude of both the cross-sectional and longitudinal comorbidity between social phobia and other anxiety disorders further suggests that classification of social phobia as a distinct disorder be reconsidered. Additional evidence from longitudinal and family genetic studies as well as treatment-outcome studies will be re-

quired to determine whether social phobia should continue to be considered as a unique category or as a subtype of an anxiety or affective disorder.

The strength of the association between social phobia and other conditions in epidemiologic studies excludes biased samples in treatment settings as an artifactual source of comorbidity. Additionally, although the absolute rates of nearly all of the disorders considered herein differ by gender, the magnitude of the associations between social phobia and most of the other disorders did not differ substantially between males and females.

Summaries of the clinical and epidemiologic data revealed that the onset of social phobia preceded that of affective disorders in the vast majority of persons with both conditions. Similarly, the onset of nearly all of the other subtypes of anxiety, except simple phobia, predated that of social phobia across studies. The consistency of this pattern suggests that social phobia may represent the expression of an underlying trait with diverse pathways and consequences. Longitudinal studies with prospective designs are necessary to investigate the order of onset and course of comorbid conditions with regard to social phobia.

The familial relationship between social phobia and other anxiety disorders, depression, and/or substance abuse also requires further investigation. However, the limited number of family and twin studies that specifically examine the transmission of social phobia precludes application of these data to elucidate underlying mechanisms for the concurrence of social phobia and other disorders.

These findings have major significance for treatment of socially phobic persons. Recognition of a lifetime history of affective disorders in persons seeking treatment for social phobia is critical to treatment and intervention in the course of this condition. Even if prominent depressive symptoms are not apparent, a history of depression is likely to be present in a majority of persons undergoing evaluation of social phobic symptoms. Moreover, because comorbidity among socially phobic patients may not be limited to a single disorder, the entire spectrum of anxiety, affective, and substance abuse disorders must be evaluated in developing treatment plans for these individuals. Pharmacologic agents that have demonstrated efficacy for both conditions, such as the monoamine oxidase inhibitors, would be the most economical treatments of choice for persons with prominent symptoms of both disorders (Liebowitz et al. 1985). Conversely, drugs that have side effects of depression or its correlates should be discouraged or monitored carefully in persons with social phobia.

The results of this review also suggest that a history of social phobia should be investigated among individuals in treatment for substance abuse. The use of alcohol to assuage symptoms of anxiety has been described throughout medical history. Hippocrates prescribed a walking stick, a trusted companion, and wine for his patients with agoraphobia (Wood 1886). The use of alcohol to minimize the fear response to public speaking was described among

persons with public-speaking phobia over a century ago (Westphal 1871). Such attempts to self-medicate may ultimately lead to the development of alcoholism among persons who possess the necessary background vulnerability factors for alcoholism.

Finally, awareness of the strong degree of comorbidity between substance abuse and alcoholism could ultimately lead to the prevention of substance abuse. Early recognition of social phobia and enhancement of treatment entry to minimize its consequences could eliminate the degree to which individuals with distressing social phobia attempt to alleviate these symptoms themselves. Moreover, clinicians should be aware of the degree to which such individuals may use alcohol or misuse prescribed drugs in selection of appropriate agents to treat symptoms of social phobia.

If additional evidence confirms that shared underlying etiologic factors may contribute to both social phobia and affective disorder, future studies should be designed to investigate the source of these shared risk factors including temperament, neurochemical factors such as dysregulation of the autonomic nervous system, or shared familial environmental factors, such as learned patterns of stress response.

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