Social anxiety disorder in review: two decades of progress

Rosario B. Hidalgo, Stewart D. Barnett and Jonathan R. T. Davidson
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Abstract
Social anxiety disorder (SAD) is among the most common of all psychiatric disorders. It presents with a lifetime prevalence rate of up to 16% in the general population and, like other anxiety disorders, is more frequent in women. Patients with SAD suffer from considerable psychiatric comorbidity that is often preceded by social anxiety. Social anxiety affects people early in life and provokes a great deal of impairment and cost, much being related to the under-recognition and/or under-treatment of this disorder, which occurs frequently with GPs and others specialists. There is a clear need among GPs for training and awareness about the existence of this disorder, its assessment, differential diagnosis and available treatments. In this paper we review the development of the concept of SAD and its epidemiology, and discuss the available information regarding cost and how SAD presents in primary-care settings. Potential aetiologies and studies concerning possible neurobiological mechanisms are also reviewed. Pharmacological and psychosocial treatments for SAD are examined and effect sizes calculated for placebo-controlled pharmacological studies of five medication categories.

Received 20 September 2000; Reviewed 4 February 2001; Revised 17 March 2001; Accepted 20 March 2001

Key words: Anxiety, anxiety treatment, diagnosis of anxiety, neurobiology of anxiety, social phobia.

Introduction
Social anxiety disorder (SAD) is characterized by persistent anxiety when exposed to observation or scrutiny by others and fear of acting in a way that will be embarrassing or humiliating. Even though this disorder is highly prevalent, it has been neglected and trivialized for decades by society and science. Nevertheless, throughout the 1990s it gained increasing interest and recognition that promises to continue further in the new millennium. Recent reviews have drawn attention to different aspects of social anxiety disorder (e.g. Ballenger et al., 1998; Brunello et al., 2000).

Definition and development of the concept
In this article we will review the impact of SAD, its prevalence and epidemiology in the community and other specific populations. Findings regarding impairment and comorbidity of SAD will be also addressed. We will also present available data on the cost of SAD and its presentation in primary care. Because SAD can at times be confused with other superficially similar conditions, the important issue of differential diagnosis will be addressed below. Different aetiological mechanisms will also be discussed. Lastly, we will describe the neurobiology and treatment for SAD. Unless otherwise specified, most studies reviewed in this paper did not distinguish between the different subtypes of SAD.

SAD, or social phobia (SP) in older literature, often appears early in life, most frequently during adolescence, and usually follows a chronic course characterized by increasing impairment if left untreated. In DSM-IV, the term social anxiety disorder (SAD) appeared, and now seems to be used to an increasing extent. As a result we will be using this term throughout, except in referring to data from studies which specifically looked at SP.

SAD had emerged as an independent diagnosis in 1980 with the Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (DSM-III) (APA, 1980). Previously, it was grouped along with all other phobias (DSM-I and DSM-II) (APA, 1952, 1968). In DSM-III, excessive fear of scrutiny in specific performance situations (i.e. speaking, using a public restroom, etc. in front of other people) was the core of the diagnosis. Patients with more generalized social avoidance could not be diagnosed as having SP. Instead the diagnosis of avoidant personality disorder (APD) was given. Nevertheless, since many patients with SAD feared a wide range of social situations, DSM-III-R (APA, 1987) incorporated the description of the generalized subtype. Hence, the presence of APD was no
longer considered an exclusionary criterion, but an additional diagnosis for some subjects with the generalized subtype of SAD.

The definition was further modified in DSM-IV (APA, 1994). In adolescents and adults, social anxiety is now characterized as being excessive and unrealistic; in children, however, this is not always the case. There is impairment in functioning and/or marked distress caused by the disorder. In subjects under 18 yr of age the duration of symptoms must be of at least 6 months. Neither a medical illness nor the direct effects of a substance (i.e. medications, drugs) can be the cause of the social fear. The diagnosis of SAD is not better explained by another psychiatric disorder [e.g. panic disorder (PD) with or without agoraphobia, separation anxiety disorder, etc.].

SAD is divided into generalized and non-generalized subtypes. In the former, most social situations are feared. In the latter, either a single or several social or performance situations are feared. The relationship between these types is not yet fully understood.

Different studies had been done to address this issue. Heimberg et al. (1990) compared the characteristics of patients with generalized SAD and public-speaking phobia. They found that patients with the generalized subtype were younger, less educated and less likely to be employed than patients suffering from public-speaking phobia. The authors found that even though subtypes appeared to be distinct, they both showed a higher fear of negative evaluation than did normal controls or patients with generalized anxiety disorder. They concluded that, since this fear of scrutiny and criticism is the main characteristic of SAD, it is valid to classify public-speaking phobia as a subtype of SAD.

Mannuzza et al. (1995) compared the demographic and clinical characteristics of patients with SAD to investigate if the generalized and non-generalized subtypes of the disorder could be reliably distinguished. Patients with the generalized subtype were more frequently single, had an earlier onset of the disorder, they presented more fears of interpersonal interactions, and had higher rates of comorbid disorders (i.e. alcoholism and atypical depression). The authors concluded that both subtypes may represent distinct clinical syndromes.

Impact of SAD

Prevalence and epidemiology

Two major population-based surveys have been conducted in the USA after SP was described as an independent diagnosis in DSM-III. These studies are the Epidemiologic Catchment Area (ECA) and the National Comorbidity Survey (NCS), which respectively used DSM-III and DSM-III-R criteria.

The ECA survey was a multi-site study of the prevalence and incidence of adult psychiatric disorders and the associated use of health services. DSM-III criteria were used. Results showed a lifetime prevalence of the disorder of 2.4%, with a higher prevalence in females than males (3.1 vs. 2.0%), as were those who were younger, less well educated, single and of lower socioeconomic status (Schneier et al., 1992).

Davidson et al. (1993c), from the Duke University site of the ECA, reported a lifetime prevalence of 3.8% and 6-month prevalence of 2.7%. They also found that subjects were more likely to be younger, less educated, of lower income, unmarried, female and to have an unstable employment record compared with controls. These investigators pointed out that many of these characteristics were due to the presence of other comorbid disorders. Nevertheless, urban residence, younger age and education continued to differentiate between SP and controls after controlling for comorbidity.

Similar results were reported by Degond and Angst (1992) from the Zurich study, in which they found a lifetime prevalence rate of 3.8% using the DSM-III. However, an equal sex ratio was observed for SP. Lower lifetime prevalence rates (1%) were reported by Faravelli et al. (1989) in another European study conducted in Florence using the DSM-III criteria.

Kessler et al. (1998) conducted the NCS, a nationally representative face-to-face survey carried out in 48 coterminous states using a revised version of the Composite International Diagnostic Interview. They surveyed 8098 non-institutionalized civilian persons aged 15–54 yr, along with a representative supplemental sample of students living in campus housing. This was the first survey to administer a structured psychiatric interview to a representative sample of the USA population.

Data from the National Comorbidity Survey showed a lifetime prevalence of 33.3%, also with higher rates in women than men (15.5 vs. 11.1%). The 12-month prevalence rate was 7.9% overall (female, 9.1%; male, 6.6%) (Kessler et al., 1998). Previous epidemiologically based estimates may have been unrealistically low and the striking difference in prevalence rates between studies is most likely related to the diagnostic criteria and different interview assessments used; DSM-III assessments covered fewer social and performance situations.

The NCS almost certainly gave a more accurate picture of this disorder’s epidemiology, finding it to be the most common of all anxiety disorders and the third most common psychiatric disorder after major depression and alcohol dependence (lifetime prevalence of 17.1 and 14.1%, respectively).
Stein et al. (1994) looked at how different diagnostic thresholds impact on the prevalence of SAD. They studied a community sample in Canada surveying a wider range of social situations, finding that 61% of the respondents reported being much or somewhat more anxious than other people in at least 1 of the 7 social situations surveyed. Public-speaking fear was endorsed by 55% of the respondents. However, when the threshold was raised taking into account impairment and distress, the prevalence rates varied dramatically (see below). The authors raised the issue about the public-speaking subtype of SAD, and showed that even though public-speaking phobia appeared to be very common in the community, only 1% of the people in that group will meet the DSM-III-R criteria for SP solely on the basis of public-speaking fears. They concluded that public-speaking phobia may not always be entirely benign.

Among 2000 consecutive primary-care patients in Paris, France, Weiller et al. (1996) observed a 4.9% 1-month prevalence of SAD, diagnosed according to DSM-III-R. Wacker et al. (1992) found a lifetime prevalence of 16% in a Swiss community study using the DSM-III-R, and one of 9.6% when using ICD-10.

The first community study using the DSM-IV criteria was the Early Developmental Stages of Psychopathology (EDSP) study, conducted in Munich, Germany by Wittchen et al. (1998). They surveyed 3021 individuals aged 14–24 yr and reported a lifetime rate of SAD of 3.5% (females, 4.8%; males, 2.2%). However, when ‘subthreshold’ SAD was included the lifetime prevalence increased to 7.3% (females, 9.5%; males, 4.9%). They also evaluated 1-yr prevalence rates. The past year prevalence rates for subjects who met full diagnostic criteria for social anxiety was 2.6% (females, 3.6%; males, 1.5%). For subjects with subthreshold SAD, prevalence was 5.2% (females, 7.2%; males, 3.2%). These values are much lower than the ones found when using DSM-III-R criteria (Kessler et al., 1998; Wacker et al., 1992). The authors claimed that it may be related to the stricter questions for the DSM-IV severity and impairment criterion for phobias.

Some differences also exist, when comparing prevalence rates using ICD or DSM criteria. Some surveys provide prevalence rates based on DSM and others on ICD-10. There are a number of differences between these criteria, as outlined succinctly by Westenberg (1998). ICD-10 prevalence rates appear to be lower than DSM-III-R but higher than DSM-IV (Andrews et al., 2001; Wacker et al., 1992).

Threshold of caseness
The concept of ‘subthreshold’ social phobia (SSP) was originally studied by Davidson et al. (1994) in the Duke University Epidemiological Catchment Area Study. They investigated whether patients with SSP were more similar to social phobics or to normal controls (C) regarding (i) demographic characteristics, (ii) familial characteristics, (iii) impaired school performance, (iv) conduct disturbance in adolescence, (v) social support, (vi) confidence, (vii) stressful life events, (viii) health status, (ix) health-seeking behaviours and (x) psychiatric comorbidities. These investigators found many statistically significant overall differences, and almost all of them were accounted for by SSP vs. C and SP vs. C comparisons. Few differences were found between SSP and SP respondents after adjustments for the smaller size of these groups were made. They concluded that in many ways SSP closely resembles SP diagnosed according to DIS/DSM-III criteria.

Stein et al. (1994) had also investigated the issue of thresholds for diagnosis and how this may prevent recognition and thus prevalence in epidemiological samples. They conducted a telephone survey to study the prevalence of social anxiety in a community sample from Winnipeg, Canada. First, they set a diagnostic threshold to include respondents with at least moderate interference or distress in any social situation and they found a prevalence of 18.7%. When the threshold was raised to include only those who reported marked interference or distress (as is required by DSM-III-R) the rate dropped to 7.1%. When the threshold was further raised to include only those who reported marked interference (i.e. distress alone was considered insufficient) the rate found was 1.9%. This latest value resembles the prevalence found in the ECA study, where similar criteria were used.

In summary, SAD is among the most common of all psychiatric disorders. Like other anxiety disorders it is more frequent in women and it presents with a lifetime prevalence rate of up to 16% in the general population. The restrictive influence of criterion (v) needs further exploration, as many individuals with social anxiety may not meet this criterion, yet still could benefit from treatment. Studies concur in suggesting that social anxiety may usefully be seen as existing along a continuum, and it is not only those who meet full diagnostic criteria who are unimpaired, or who could benefit from intervention.

Morbidity and comorbidity
Schneier et al. (1992), using data from the ECA study, looked at several aspects of SP in the general population. They studied distress and morbidity (suicidal ideation, suicide attempt and financial dependence), treatment utilization; and comorbidity with other DSM-III/DIS psychiatric disorders during lifetime. They defined
‘financial dependence’ as subjects currently under disability or welfare.

Rates of suicidal ideation were significantly higher in patients with SP overall, after controlling for sociodemographics and comorbidity (ORs = 1.71 vs. 1.92). Patients with uncomplicated SP had significantly elevated rates of suicidal ideation when compared with subjects with no disorder. History of attempted suicide was not significantly different in patients with uncomplicated SP compared with normal controls (0.9 vs. 1.1%, respectively). Among patients with SP and comorbid disorder the rate of having a lifetime history of attempted suicide was significantly elevated (15.7%; OR = 5.73; p < 0.001). The rates of suicide attempts remained higher in patients with SP after controlling for comorbidity when compared to subjects without SP (OR = 1.88; p < 0.01).

There were higher rates of financial dependence in uncomplicated SP compared to no disorder (22.3 vs. 10%; OR = 1.89; p < 0.01). In comorbid SP, financial dependency was not increased after controlling for comorbidity.

Regarding the presence of comorbidity, these investigators found that 69% of patients with SP had comorbidity with other lifetime psychiatric disorders. There was elevated risk for each disorder examined, the highest co-occurrence being with agoraphobia (OR = 11.81), simple phobia (OR = 9.44), somatization disorder (OR = 8.02), major depression (OR = 4.41), obsessive–compulsive disorder (OCD) (OR = 4.36), dysthymia (OR = 4.30), and bipolar disorder (OR = 4.09). For subjects with comorbid disorders (other than agoraphobia, simple phobia and schizophrenia), SP preceded the comorbid disorder in 76.8%. Most subjects with comorbid alcohol abuse, major depression, drug abuse, and OCD reported SP symptoms as chronologically primary (85, 71, 77 and 61%, respectively).

Davidson et al. (1993c) showed that SP was associated with greater impairment during the developmental years. Non-comorbid SP was associated with increased rates of playing truant, runaway behaviour, fighting, telling lies and stealing.

Kessler et al. (1998), also found similar trends regarding impairment and comorbidity. These investigators distinguished between SP with public-speaking fears and SP with non-speaking fears. They found that of the respondents with lifetime SP, 39.1% endorsed at least one grade of impairment/interference. This percentage was approximately twice as high for respondents with non-speaking fears as for those with pure speaking phobia. Within the sub-sample of respondents with SP having at least one non-speaking fear, moreover, the endorsement rate was consistently related with the number of fears. Comorbidity with mood disorder, anxiety disorder, and antisocial personality disorder were all significantly more common among respondents who had SP with at least one non-speaking fear than among those with SP having pure speaking fears.

In a French study conducted in Paris in the general health care sector, Weiller et al. (1996) showed that patients with SP present with significant rates of comorbidity, especially major depression. Among patients with current SP they found a 33% rate of current major depressive episode, compared with only 10% in non-SP (p < 0.01; OR = 4.44); 26% had generalized anxiety disorder (12% in non-SP; ns); and 18.5% met criteria for agoraphobia (3.2% in non-SP; p < 0.001). With lifetime SP they found similar values: SP was often comorbid with agoraphobia and major depression (19.2 and 44.2%, respectively; both statistically significant when compared with non-SP). In this study, SP was also found to develop more than 1 yr prior to the first depressive disorder in 75.9% of cases.

In another primary-care sample, patients with pure SAD showed greater disability than age and sex-matched controls with a chronic physical illness, especially in respect of partner and family relationships, education and career development, and household or work management (Wittchen and Beloch, 1996).

Stein et al. (1999b), in a primary-care clinic in San Diego, found that comorbidity with major depression was extensive (58.3%); important rates were also shown for generalized anxiety disorder (30.6%) and PD (27.8%). SAD presented more impairment in all functional domains than patients without mental disorders; and this was more important in patients with the generalized subtype of SAD.

In other words, patients with SAD suffer from considerable comorbidity (i.e. depression, agoraphobia, substance abuse, etc.) that usually is preceded in time by social anxiety. This comorbidity has been demonstrated to increase the grade of impairment for these subjects and also the risk of suicidal ideation and suicide attempts (the latter, mainly in patients with comorbid major depression). It is important to assess whether SAD predisposes patients for the development of other psychiatric disorders; or if these affictions share a common physiopathology with SAD.

Costs

Social anxiety commonly starts in childhood/adolescence and impedes social, familial and professional development. Even though social anxiety affects people early in life and provokes a great deal of impairment, it has been shown that patients with uncomplicated SP rarely seek help in the health-care system.
Schneier et al. (1992), analysing data from the ECA study, measured treatment utilization based on lifetime use of treatment for problems with emotions, nerves, alcohol, other drugs, or mental health. Different kinds of treatments were grouped in: psychiatric outpatient, psychiatric in-patient, emergency department, and general medical (help from a medical physician in private practice for emotional problems). Overall, SP showed elevated rates of any outpatient treatment for emotional problems (OR = 1.49; p < 0.01) and of psychiatric outpatient treatment (OR = 1.43; p < 0.05). However, non-comorbid SP presented with significantly elevated rates of outpatient medical treatment (OR = 1.85; p < 0.05) but not overall outpatient treatment, psychiatric hospitalization, or emergency department utilization. Interestingly, only 5.4% of patients with non-comorbid SP had sought help in outpatient psychiatric facilities for emotional problems, compared with 8.0% of normal controls. On the other hand, over 50% of respondents with comorbid social anxiety sought outpatient treatment, and 38% used psychiatric outpatient help. Thus, it was clear that comorbidity increased the cost of this disorder by increasing treatment utilization and that primary-care physicians are visited more frequently than mental health professionals by patients with SP.

This issue was also assessed by Kessler et al. (1999), who evaluated the relationship between DSM-III-R disorders and service use. They found that 5.9% of patients with SP had used general medical services and 11.3% had sought help in psychiatric services during the past 12 months. These investigators also reported that patients with SP made an average of 6 visits in the general medical sector (the highest among anxiety disorders) and 14.7 visits in mental health services. Unfortunately they did not distinguish between pure and comorbid SP.

Greenberg et al. (1999), also using data from the NCS, looked at direct and indirect costs of anxiety disorder in general. Direct cost was defined by (i) psychiatric service costs (e.g. counselling, hospitalization, etc.), (ii) non-psychiatric medical costs (e.g. primary-care visits, emergency room, etc.), and (iii) prescription drug costs. Indirect cost included excess absenteeism as well as anxiety-related reductions in at-work productivity. They estimated the economic burden of anxiety disorders at $42.3 billion in 1990 dollar terms, or $63.1 billion in 1998 dollars. The 1990 results imply an average annual cost per sufferer of $1542, and an average annual cost in the workplace of $256 per suffering worker, of which 88% is attributable to lost productivity while at work as opposed to absenteeism. The largest component of the societal cost of anxiety disorder derived from direct non-psychiatric treatment costs, which accounted for 54% of the total, while direct psychiatric treatment cost accounted for an additional 31%. This particular cost distribution suggests that inappropriate treatment of undiagnosed and misdiagnosed sufferers appears to contribute meaningfully to the overall economic burden.

Kessler and Frank (1997) reported that SP showed greater work cutback than absenteeism (1.11 vs. 0.44 d, respectively). They also reported that comorbid anxiety—depression was associated with the largest average number of work days lost and comorbidity between anxiety and depression, substance abuse and depression/substance abuse was associated with the largest average numbers of work cutback days. The average number of work cutback days associated with comorbid disorders were significantly higher than those of pure disorders (Z = 3.8; p < 0.001).

Katzelnick et al. (1998) also looked at the cost of generalized SP in a managed care population. They calculated direct costs (i.e. health-care utilization) and indirect costs (i.e. lost wages, reduced productivity, disability, and decreased quality of life). The investigators reported that patients with generalized SP had higher medical utilization ($2.466 vs. $1959 in controls; p = 0.04), significantly lower quality of life, and substantially reduced occupational functioning.

In summary, SAD is costly and, much of the cost is related with the under-recognition and/or under-treatment of this disorder.

**Recognition of SAD in primary care**

As many other psychiatric disorders, social anxiety is frequently under-recognized in the primary-care sector. It may also happen that if diagnosed, the primary-care provider may underdiagnose its impact on the patient’s life and, thus, leave it untreated with the consequent burden on the individual’s health and the health-care system and society as a whole.

Different studies in the primary-care population have evaluated SAD. Weiller et al. (1996) explored the recognition of this disorder by general practitioners (GPs) in a general health facility in Paris, France. They found that the main reason for social phobics without depression to seek help from GPs was rarely psychological problems. They pointed out that the level of GP recognition of SP was very low. There was no difference in recognition of ‘psychological cases’ between controls (32.6%) and non-depressed SAD patients (46.7%). The ability of GPs to diagnose a psychological problem increased when there was social anxiety with comorbid depression. However, this did not mean the recognition of SAD itself but rather the existence of a psychological problem. Diagnosis of SAD was made in only 24.2% of cases. The investigators interpreted that this may be due to the fact that patients...
with SAD did not report their phobic symptomatology; in fact, they rarely sought help from their GPs for psychological distress, unless comorbid depression was present. Nevertheless, although depressive symptoms helped GPs to recognize the presence of a psychological disorder, their presence impeded the diagnosis of SAD, which was particularly under-diagnosed in the presence of depression.

In another study done in a primary-care setting, Stein et al. (1999b) noted that few patients with SAD were prescribed psychotropic agents. Only 16% (50% of whom had the generalized subtype) were taking a psychotropic agent of any kind. All of them had concurrent major depression, suggesting that this was probably the focus of treatment.

In summary, SAD is frequently under-recognized by GPs and others; this lack of diagnosis is in part related to the fact that patients with uncomplicated SAD usually do not complain about psychological symptoms. When comorbid major depression is present, there is a better recognition of a psychological problem, but this does not necessary mean that SAD is identified. This has the logical consequence of leaving this disorder untreated or partially treated, with the possibility of further complications. Evaluation of patients in primary-care settings should include the assessment of both depression and anxiety. There is a clear need among GPs for training and awareness in the existence of social anxiety, its assessment and available treatments. Early recognition and treatment might have an impact on the individual’s quality of life and especially in prevention of development of comorbidity.

We have developed a brief, and highly accurate, 3-item self-rating scale for detection of SAD, the Mini-SPIN, which has excellent sensitivity in distinguishing between presence or absence of SAD (Connor et al., 2000). This can potentially help at low cost and for a minimal investment of physician time, in enhancing the recognition of SAD.

**Differential diagnosis**

Firstly it is worth mentioning again that SAD often does not present alone: comorbidity is common and it is possible that two or more disorders may also coexist. The core of SAD is a primary and exaggerated fear of scrutiny or embarrassment. In addition, an often very distinguishing feature of SAD is blushing, which appears less frequently in other disorders.

**Shyness**

Based on existing data, there is no clear way to distinguish between shyness and SAD, as there are both cognitive, behavioural and physical similarities between the two. Shyness is much more prevalent, at 20–50% according study. Shyness is a larger and more heterogeneous condition and does not require impairment or distress, yet is not simply the less severe form of the SAD spectrum (Schneier et al., 1996).

**Major depression**

Depressive patients usually present with social withdrawal, loss of confidence, and some feeling of awkwardness while with other people. It is crucial to ask about psychiatric history to distinguish if this social withdrawal or other social anxiety symptoms preceded the onset of depression. If they were absent, they are most likely part of the depressive syndrome. In many cases major depression appears over a year after SP had been present. In these cases with comorbid social anxiety and depression it is very important to evaluate suicidal risk, as this combination increases the possibility of suicidal attempts.

**Agoraphobia**

Agoraphobia may resemble SAD in that sufferers usually avoid social situations in which they may be afraid of not being able to find escape in case of having a panic attack. But in patients with SAD avoidance is related to fear of humiliation or embarrassment. Moreover, while many patients with agoraphobia may need 1 or 2 support people, social phobics rarely will show such need.

**Avoidant personality disorder (APD)**

In this case, a symptomatic continuum is present between SAD and APD and both diagnoses can be made, especially in the context of generalized SAD. Patients with comorbid APD and SAD present with more severe anxiety, increased functional impairment, and a higher incidence of comorbidity compared with patients with social anxiety alone (Herbert et al., 1992; Holt et al., 1992). This combination represents a group of more severely affected patients, which may present a challenge regarding treatment.

We agree with Fahlen (1995), who found that patients with SAD generally have characteristic abnormal personality traits, and that there was no support for dividing symptoms and traits in two separate diagnoses.

**Body dysmorphic disorder**

Patients with this disorder worry about an imagined defect in their appearance or, if some physical anomaly is
present, they exhibit excessive concern about it. This concern leads to social avoidance and withdrawal and functional impairment. A key for differential diagnosis will be addressing the cause of avoidance and anxiety.

Aetiology and mechanisms

Today, as with most psychiatric disorders, no single mechanism can account for the development of SAD. Different theories have been presented to date to explain the development of SAD. Some of them will be described below.

Ethology

Marks (1987) described social phobics’ fear of being watched as an exaggeration of the normal sensitivity to eyes, which is present since early childhood. Marks compares the effects of staring throughout different animals, finding consistency regarding the inhibitory effect that staring has on the animals’ conduct. The author describes the cuttlefish Sepia officinalis and its threat display. This fish, when attacked, displays two black ‘eye’ spots on the back which has a deterrent effect on the would-be predator.

Among human beings, the eyes are one of the first figures that an infant perceives. Staring is not always frightening for humans. Being looked at in a non-threatening situation may be a sign of empathy or affection. Nevertheless, direct gaze may provoke a very uncomfortable feeling and is one of the most upsetting stimuli for persons with SAD. The issue of culture must be also considered, since while for some cultures direct gaze is a correct form of social contact, for other cultures gaze avoidance is a sign of respect.

Mineka and Zinbarg (1996) address the development of different anxiety disorders in the context of the ‘Stress-in-dynamic-context anxiety models’ (SIDCA), and they compare this model with previous models that they describe as ‘Stress-in-total isolation anxiety models’ (SITIA). The authors present the SIDCA as a learning model of SP, based on the conditioning theory. Moreover, this model takes into account the important role of experiential variables that occur before, during and after both direct and vicarious learning experiences. This model also includes the preparedness of certain signs for social anxiety and gives a role for temperament variables as well, which will put certain subjects under higher risk than others. Another aspect that is included by the SIDCA model is the role of perceptions of uncontrollability over important life events in influencing the presence of SP.

Trauma

Stein et al. (1996b) looked at the effect of childhood physical and sexual abuse in developing anxiety disorders. They compared a clinical sample of patients with anxiety disorders with a matched community sample. They found that patients with DSM-IV anxiety disorders (PD, SP and OCD) had higher rates of childhood physical and sexual abuse than community subjects (23 vs. 8%). All forms of sexual abuse before the age of 18 yr were very rare in men in both samples; therefore they limited these comparisons to the group of women. Anxious women were more than twice as likely to have experienced genital touching or fondling than non-anxious women (39.6 vs. 15.1%; OR = 3.69). More serious forms of sexual abuse (oral sex or any form of penetration) were reported in 13.5% of women with anxiety disorders compared to 1.9% of women from the community sample (OR = 7.91). Unfortunately the authors did not specify which percentages were found for SP alone.

Magee (1999) has studied the impact of traumatic experiences in the onset of phobias as defined by DSM-III-R. This author found that having experienced sexual assault by a family member and verbal aggression between parents have significant effects on the development of SP. The effect on SP of sexual assault perpetrated by a relative was confined to women, and to phobics starting before the age of 12 yr. Verbal aggression by an adult had a borderline effect. Magee suggests that the effect of sexual assault is consistent with conditioning theory, in which the victims of incest are usually blamed for their victimization. Blame may be the mediator for the development of conditioned fears of being criticized by others. If these fears became generalized, hypersensitivity to criticism may occur in a wide range of social situations.

Parenting/genetics

Parker (1979) compared characteristics of a group of social phobic patients, a group of agoraphobics and a matched control group. Participants were asked to complete a Parental Bonding Instrument (PBI) for each parent. The PBI is a self-administered scale (measuring care and overprotection). He found that social phobics recalled their parents (i.e. mother and/or fathers) as less caring and more overprotective than controls. However, and perhaps somewhat surprisingly, he also found that higher SP scores were associated specifically with greater maternal care and overprotection.

Similar findings were reported by Arrindell et al. (1983) in a study of the perceived parental attitudes and their association with different phobias (i.e. agoraphobia, SP and simple phobia). To assess this they used ‘Egna Minnen Betriffande Uppfostran’ (EMBU) scale, which measures
the respondents’ own memories of their upbringing. They compared the results of each phobia group with normal controls. Social phobics differed significantly from normal controls on fathers’ emotional warmth (Z = -3.958; p < 0.0001) and overprotection (Z = 2.560, p < 0.01). The mothers were rated as being less emotionally supportive (Z = -2.981; p < 0.01) and as more overprotective (Z = 2.343; p < 0.01) than mothers in the normal control group.

Regarding the issue of parenting, there are at least two factors that are not easily distinguished: one is the way parents interact with their children and how this interaction will influence the child development; and the other possible factor is the existence of a genetic reason for a parent to interact in a certain way. In other words what is the reason parents do not expose their children to social environments or overprotect them? Is it possible that they do it because they consider their children incapable for dealing with such situation, or may it be just because of their own avoidance and or social fears? Moreover, does the child develop SAD because of the way it interacts with its parents, because of genetic predisposition, or both?

There are four major studies that have investigated the genetics of SAD: Kendler et al. (1992) studied 2000 female twins from the population-based Virginia State Twin Registry. Three family risk studies have looked at the differences between social anxiety patients and healthy volunteers, and their first-degree relatives (Fyer et al., 1993; Mannuzza et al., 1995; Stein et al., 1998a). Kendler et al. (1992) found that the concordance of SAD was approx. 10% greater in identical (monozygotic) than non-identical (dizygotic) twins.

All three family studies found a significantly elevated risk for SAD in relatives of participants with SAD. Fyer et al. (1993) reported a 16% rate of SAD in relatives of social phobics compared with only 5% in controls. Another study, looking only at generalized SAD, found a similar increased risk to the disorder in relatives of probands with this subtype. Relatives with the non-generalized subtype of SAD did not show greater likelihood of having the disorder than relatives of normal controls (Mannuzza et al., 1995). Similar findings were reported by Stein et al. (1998a), who found that first-degree relatives of respondents with generalized SAD had an approx. 10-fold higher risk of developing SAD than relatives of comparison probands. However, the differences were not significant when both groups were compared regarding non-generalized SAD.

Probably, like other psychiatric disorders, SAD may have a multi-factorial aetiology; thus these two factors (i.e. genetics and parenting) among others may interact in the development of the disorder.

Neurobiology

Chemical challenge studies

A number of chemical challenge studies have been conducted in an effort to reproduce anxiety symptoms using exogenous compounds in patients with anxiety disorders. While most chemical challenge studies have been conducted in PD, some have examined effects in SAD. Reviewed below are findings from chemical challenge studies with SAD patients that have employed compounds including lactate, CO₂, caffeine, pentagastrin, clonidine and epinephrine.

Chemical challenges with lactate and CO₂ are well known to stimulate anxiety and panic symptoms in PD patients (Coward and Arana, 1990; Gorman et al., 1988; Perna et al., 1994); in SP, these same agents appear to stimulate anxiety and/or panic more frequently than in healthy controls, but less frequently than in PD (Caldirola et al., 1997; Gorman et al., 1988, 1990; Holt and Andrews, 1989; Liebowitz et al., 1985). Such results suggest chemoreceptors associated with the ‘suffocation alarm system’ may be somewhat hypersensitive in SAD, though to a lesser degree than in PD (Bell et al., 1999).

Challenge with caffeine produced panic in equal numbers of SP and PD patients but in none of the control subjects in one study (Tancer et al., 1994–95a), but anxiety produced by caffeine appears to be of a generalized nature and not diagnosis-specific. Challenge studies with cholecystokinin and its subunit pentagastrin have been shown to produce panic attacks more frequently in PD patients than in controls and the symptoms produced appear similar to those occurring in SAD (e.g. sweating and flushing). Studies with pentagastrin in SP suggest that, as compared to controls, there is a slightly increased sensitivity to this compound in SP that is less pronounced than the sensitivity found in PD (McCann et al., 1997; van Vliet et al., 1997). Interestingly, the anxiety symptoms induced by challenges with the above agents have most often been described as similar to naturally occurring panic attacks, but dissimilar to symptoms experienced in SAD.

In one challenge study growth hormone response was measured following oral administration with the α-2 adrenergic agonist clonidine, and there were no significant observed differences between SP patients and controls; however, an intravenous challenge study with clonidine in SP patients resulted in a blunted growth hormone response (Tancer and Golden, 1992; Tancer et al., 1993). The observed blunted response could be due to reduced post-synaptic α-2 function secondary to norepinephrine hyperactivity in SAD. In another study, increased heart rate was observed when SP patients were infused with epinephrine (Papp et al., 1988), yet there was no significant
exacerbation of anxiety; however, poor penetration of exogenous epinephrine through the blood–brain barrier could have been a mitigating factor.

Neurotransmitter function

Adrenergic function

Involvement of endogenous adrenergic catecholamines in SAD is suggested by the physiological symptoms often experienced in this condition (trembling, elevated heart rate, diaphoresis, flushing), and the role of the autonomic nervous system has been examined in a limited number of studies (in addition to pharmacological challenges). One study incorporated an orthostatic challenge as a measure of autonomic activity and found that patients with SP had higher plasma norepinephrine levels both before and after the orthostatic challenge, as compared to PD and healthy control groups (Stein et al., 1992). In that study, SP patients also had greater mean diastolic blood pressure changes upon standing as compared to controls, while PD patients experienced a change of intermediate magnitude (Stein et al., 1992). However, these findings were not replicated in a subsequent study (Stein et al., 1994a) in which indications of parasympathetic, not sympathetic, dysfunction in generalized SP were reported. Other studies have shown that when confronted with a public-speaking behavioural challenge, patients with a discrete (non-generalized) performance phobia had a greater increase in heart rate than patients with generalized SP, whose response was not significantly different from controls (Heimberg et al., 1990). This may imply different pathophysiological mechanisms for discrete and generalized forms of SAD.

Serotonin (5-HT)

Potential involvement of serotonergic mechanisms in SAD is suggested by the observed ability of certain pharmacological agents to alleviate the symptoms of SAD, namely the selective 5-HT reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs); however, results from studies directly examining the role of 5-HT in SAD have collectively yielded a less than complete understanding of the role of this neurotransmitter. For instance, in a study of peripheral 5-HT function, platelet $[^{3}H]$paroxetine binding was not significantly different in SP patients as compared to PD patients and healthy controls (Stein et al., 1995). On the other hand, challenge studies with the partial 5-HT agonist m-chlorophenylpiperazine (m-CPP) (Hollander et al., 1998) and the 5-HT-releasing agent fenfluramine (Tancer et al., 1994–95b) resulted in increased anxiety and increased cortisol responses, but no prolactin response abnormality in SP patients as compared to control subjects. These limited data are similar to findings in PD and possibly point to hypersensitivity of some, but not all, 5-HT receptors (Bell et al., 1999). Though speculative, 5-HT-1 receptors, responsible for prolactin response, may be normal while 5-HT-2 receptors, associated with the anxiety response, may be hypersensitive in SAD (Nutt et al., 1998).

Dopamine

Low dopaminergic functioning in SAD has also been hypothesized, in part because of the efficacy of the MAOIs observed in this disorder (Liebowitz et al., 1987). Indirect evidence suggesting a role for dopamine also includes: (i) reports of social anxiety induced by dopamine-blocking drugs (Mikkelsen et al., 1981); (ii) high rates of SP in Parkinson’s disorder patients (Berrios et al., 1995); and (iii) low cerebrospinal fluid (CSF) levels of the dopamine metabolite homovanillic acid (HVA) in patients with comorbid panic and SP (Johnson et al., 1994). Furthermore, low CSF dopamine levels in depressed patients have been correlated with measures of introversion (King et al., 1986), a feature possibly related to social anxiety. Dopamine involvement in SAD has also been suggested by certain neuroimaging studies, discussed below. On the other hand, in a neuroendocrine study measuring prolactin and the eye-blink response, indicators of dopamine activity, there were significant differences between normal controls and SP patients in response to l-dopa administration, indicating no abnormality of dopamine function (Tancer and Golden, 1992).

Gamma amino butyric acid (GABA) and benzodiazepines

Involvement of GABA in social anxiety (Kaleneff and Nutt, 1996–97) has been suggested by the symptom relief many SAD patients experience with certain benzodiazepines. In a study of peripheral benzodiazepine receptors, generalized SP patients were found to have a significantly lower receptor density than normal controls (Johnson et al., 1998), an abnormality shared with a number of other anxiety disorders but not with OCD or major depressive disorder. Flumazenil, a benzodiazepine antagonist, has been shown to precipitate panic attacks in patients with PD (Nutt et al., 1990), but produced rates of panic in SP patients not significantly different from normal controls, which does not seem to support a GABA–benzodiazepine abnormality in SAD (Coupland et al., 2000). However, the induction of panic may be a poor model of the disorder.
Other mechanisms

The alleviation of SP symptoms observed in response to treatment with the novel anticonvulsant compounds gabapentin (Pande et al., 1999) and pregabalin (Feltner et al., unpublished observations) leads to inquiry about their mechanisms of action. Gabapentin acts at neither benzodiazepine nor GABA receptor sites, yet it appears to modulate GABA and glutamate synthesis. It is not known to directly affect 5-HT, but some decrease in release of monoamine oxidase has been noted (Schlicker et al., 1985); however, this is not likely to fully explain its effects in SAD. The anxiolytic effects of both gabapentin and pregabalin may be related to their identified action at a presynaptic auxiliary subunit of voltage-sensitive calcium channels, theoretically leading to modulation of multiple neurotransmitters (Dooley et al., 2000; Taylor, 1997; Taylor et al., 1998); other possible mechanisms may involve inhibition of voltage-activated sodium channels, inhibition of glutamate synthesis, and/or competition for the amino-acid transporter system (Taylor et al., 1998).

Neuroendocrine abnormalities

Only a limited amount of information is available concerning neuroendocrine functioning in SAD. No abnormalities have been identified in SP patients in the functioning of the thyroid or the hypothalamic–pituitary–adrenal (HPA) axis (Potts et al., 1991; Tancer et al., 1990a; Uhde et al., 1994), though thyroid-releasing hormone (TRH) in SP patients has been noted to evoke an exaggerated pressor effect, as compared to PD patients and normal controls (Tancer et al., 1990b). An association has been suggested between anxiety and growth hormone in patients with SP and PD (Uhde, 1994), and the blunted growth hormone response observed following clonidine challenge (Tancer et al., 1993; Tancer and Golden, 1992) could indicate a global decrease in that hormone. While height differences between SAD patients and normal controls have not been documented (Nicholas et al., 1997), individuals with short stature who received growth hormone treatment as children have a high frequency of SP (Stabler et al., 1996).

Neuroimaging studies

Several neuroimaging studies in SAD have been conducted, but results should be considered preliminary until replicated. One magnetic resonance imaging (MRI) study (Potts et al., 1994) showed that volumes of the caudate, putamen, thalamus, and overall cerebral volume did not differ significantly between patients with SP and healthy controls, but revealed an age-related decline in putamen volume in SP. In addition to these structural imaging results, functional imaging studies have revealed interesting results. For instance, in a study in which subjects were exposed to slides of neutral faces and to aversive odour stimuli, functional MRI showed selective activation of the amygdala in SP patients (Birbaumer et al., 1998) indicating different subcortical processing (Schneider et al., 1999). In another study, magnetic resonance spectroscopy revealed a decrease in choline and creatine signal-to-noise ratios in subcortical, thalamic and caudate brain areas in SP patients (as compared to controls), perhaps indicating a state-dependent neurobiological disturbance of brain function or neuronal loss (Davidson et al., 1993a). A follow-up study (Tupler et al., 1997) found evidence of higher ratios of choline: N-acetyl aspartate (NAA) and myo-inositol (MI):NAA in SP, most prominently in the cortical grey matter region. Abnormal choline levels in SP may represent cellular membrane or second-messenger function abnormalities; furthermore, these MI:NAA ratio patterns also could reflect abnormalities of neurotransmitters involved in MI and choline regulation, namely 5-HT and/or dopamine.

Dopamine involvement in SAD has been implicated by single photon emission computerized tomography (SPECT) findings, with results of one study indicating an association between generalized SP and low binding of a D2 receptor radiotracer to D2 receptors in the striatum (Schneider et al., 2000). Another SPECT study likewise found markedly lower dopamine reuptake site densities in SP patients than in controls when a cocaine analogue was utilized, indicating striatal dopaminergic dysfunction (Tuohonen et al., 1997).

SPECT has been also employed to examine regional cerebral blood flow, with no significant basal differences between SP patients and healthy controls identified in one study (Stein and Leslie, 1996). In a cerebral blood flow study using positron emission tomography (PET), SP patients engaging in an anxiety-provoking task exhibited blood flow patterns resembling those associated with conditioned anticipatory anxiety in healthy volunteers (Malizia et al., 1997). Brain areas determined to be uniquely activated in SP, but not in conditioned anxiety, included the dorso-lateral prefrontal cortex and the left parietal cortex (Bell et al., 1999; Nutt et al., 1998). These brain areas are thought to be involved in planning of affective responses and in awareness of body position (Bell et al., 1999), functions presumably disrupted in SAD.

Treatments for SAD

Reports of both open and controlled studies, reviewed in the following sections, have shown SAD to be responsive to both pharmacological and psychosocial interventions.
Pharmacological treatments

Several medications have shown the ability to beneficially impact patients with SAD. Goals for pharmacotherapy include relief of fearful affect and associated cognitions, lessening anticipatory anxiety, attenuation of avoidance behaviour, reduction of autonomic and physiological symptoms of anxiety, and improvement in function and quality of life (Ballenger et al., 1998; Davidson, 1998). In this review, emphasis has been placed on examination of response rates based on intent-to-treat data from controlled studies in adult populations. Unless otherwise stated, response rate values listed were obtained from placebo-controlled study reports and represent the percent of subjects classified as ‘responders’ based on Clinician Global Impression – Improvement Scale (CGI–I) evaluations (rated as ‘much improved’ or ‘very much improved’) by the end of the study period.

Monoamine oxidase inhibitors (MAOIs)

Gelernter et al. (1991) conducted the first placebo-controlled pharmacological study of SP in which 65 patients were randomized to receive 12 wk of treatment with either phenelzine (mean dose = 55 mg/d), alprazolam, group cognitive–behavioural therapy (CBT), or pill placebo. While all active treatment groups were associated with substantial improvements in severe and chronic SP, phenelzine was superior to the other treatments on several measures. Of the 13 phenelzine-treated patients, 69% were responders, as based on the Social Phobia Subscale of the Fear Questionnaire (Marks and Mathews, 1979), compared to 20% of the 15 placebo patients. In a study conducted by Liebowitz et al. (1992) phenelzine, atenolol and placebo were compared, with results indicating that phenelzine was significantly more efficacious than either placebo or atenolol for generalized SP after 8 wk of treatment in 74 patients. In that study, the 64% (CGI) response rate for the 25 patients treated with phenelzine (mean dose = 75.7 mg/d) was statistically significantly higher than the 23% response rate for the 26 placebo patients, and phenelzine remained superior to placebo after 16 wk. Similar effects were also reported in a Versiani et al. (1992) study comparing phenelzine (n = 26), moclobemide (n = 26) and placebo (n = 26) in 78 SP patients. By week 8, phenelzine (mean dose = 67.5 mg/d) and moclobemide were significantly more effective than placebo, with CGI response rates of 85, 65 and 15%, respectively. The phenelzine patients experienced a particularly rapid and robust response, with a 79% decrease in the mean Liebowitz Social Anxiety Scale (LSAS) score at the end of week 8, and further improvement was noted after a further 8 wk of treatment.

A more recent controlled study involving 133 SP patients (Heimberg et al., 1998) found that after 12 wk, both phenelzine and group CBT were associated with marked positive responses. Although phenelzine was superior to group CBT on some measures, both treatments were significantly better than the two control conditions (pill placebo and an educational-supportive group therapy used as the psychotherapy control). Of the 31 patients receiving phenelzine, 65% were responders, compared to 33% for the 33 patients who received pill placebo. Although efficacy of the MAOI phenelzine for SP has been clearly documented, drawbacks of MAOIs that limit their usefulness in routine clinical practice include the risk of hypertensive crisis, dietary restrictions, as well as other less serious but frequently occurring undesirable side-effects.

Reversible inhibitors of monoamine oxidase A (RIMA)

The results of Verisiani et al.’s (1992) aforementioned study indicated that the RIMA moclobemide (mean dose = 581 mg/d) was statistically and clinically significantly more effective than placebo in treating SP, though not as effective as phenelzine. Moclobemide was much better tolerated than phenelzine in that study, and further improvements observed between weeks 8 and 16 were especially notable in the moclobemide group. In contrast to that Versiani et al. (1992) study, other controlled studies have shown less obvious differences between the effects of moclobemide and placebo. Noyes et al. (1997) found no significant differences between placebo (n = 85) and moclobemide (n = 421) in five fixed doses (75, 150, 300, 600 and 900 mg/d) in a SP study conducted at 13 USA sites. At week 12, approx. 38% (highest response rate) of subjects on the 150 mg/d dose (n = 86), 35% on the maximum 900 mg/d dose (n = 83) and 33% on placebo were responders. Schneier et al. (1998) similarly found no significant differences between moclobemide (n = 40) and placebo (n = 37) groups after 8 wk of treatment for SP, observed response rates were 17.5% for moclobemide (mean dose 728 mg/d) and 13.5% for placebo. A fourth controlled study of moclobemide in SP (IMCTG, 1997), conducted in 35 centres around the world, included 384 patients treated with moclobemide (fixed doses of 300 or 600 mg/d) and 194 with placebo. Though the (maximal) 47% response rate for the 193 patients taking moclobemide at a daily dose of 600 mg was statistically superior to the 34% placebo response rate, the magnitude of the response was modest.

Three controlled studies of another RIMA, brofaromine, in SP (Fahlen et al., 1995; Lott et al., 1997; van Vliet et al., 1992) resulted in response rates (78, 50 and 73%) for brofaromine-treated patients (n = 101 com-
bined) that were significantly better than response rates (23, 19 and 0%, respectively) for those taking placebo (n = 106 combined). The overall treatment effect was considered only moderate in one of these studies (Lott et al., 1997), possibly because of the lower brofaromine dose utilized (mean dose = 107 mg/d). In the other two studies (Fahlen et al., 1995; van Vliet et al., 1992), a 150 mg/d dose was associated with more robust effects. Unfortunately, brofaromine is not presently available for clinical use.

The RIMAs have clear safety advantages over the irreversible MAOIs in that they do not show clinically relevant potentiation of the tyramine pressor effect and may therefore be taken without burdensome dietary restrictions; however, the equivocal efficacy of currently available RIMAs does not encourage their use as first-line treatments for SAD.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs represent the class of medication most studied for SAD, with the most extensive database existing for paroxetine. Three large multi-centre placebo-controlled trials (Allugander, 1999; Baldwin et al., 1999; Stein et al., 1998b) including a combined total of 565 patients (nparoxetine = 274; nplacebo = 291) have been reported for paroxetine in SAD, all of which incorporated a 12-wk treatment period and doses of between 20 and 50 mg/d. In all 3 studies, CGI–I response rates for paroxetine (55, 70 and 66%) were significantly greater than placebo response rates (24, 8 and 32), respectively. Furthermore, pronounced LSAS score reductions occurred in paroxetine-treated groups in all 3 studies.

Sertraline and fluvoxamine have been examined in SP in two controlled studies each. In a small cross-over study with sertraline involving 12 SP patients (Katzelnick et al., 1995), the 50% response rate (based on the Liebowitz Social Phobic Disorders Rating scale) for sertraline (mean dose = 133 mg/d) was significantly better than the 9% rate for placebo after 10 wk, and statistically significant improvements on LSAS scores were found for sertraline but not placebo. Preliminary results from a larger (n = 203) controlled study (Van Ameringen et al., 1999b) also support sertraline’s efficacy in treating SP, with a 53% CGI–I response rate for sertraline-treated patients (n = 134) that was significantly higher than the 29% rate for placebo patients (n = 69). Trials with fluvoxamine have suggested similar efficacy. In a small (n = 28) study (van Vliet et al., 1994), 15 patients taking fluvoxamine (150 mg/d) experienced a mean (LSAS) response rate of 46% compared to 7% for 13 placebo patients. Another, larger (n = 86) study (Stein et al., 1999a) revealed a CGI response rate of 43% for 42 patients treated with fluvoxamine (mean dose 202 mg/d) vs. 23% for those treated with placebo (n = 44). The fluvoxamine/placebo differences were statistically significant in both studies.

In conjunction with well-established overall very good safety and side-effect profiles, the efficacy data reviewed above have led to the current position of SSRIs, most notably paroxetine, as first-line agents for the treatment of SAD.

Benzodiazepines

The benzodiazepines alprazolam, bromazepam and clonazepam have been evaluated for SP in three controlled trials. In the Gelernter et al. (1991) study comparing alprazolam, phenelzine, group CBT, and pill placebo, 38% of the 12 alprazolam-treated (mean dose = 4.2 mg/d) patients were responders, which was significantly better than the 20% response rate for the 15 placebo patients, though not nearly as robust as the 69% response rate for phenelzine. In a 10-wk study of involving 37 clonazepam-treated (mean maximum dose = 2.4 mg/d) and 35 placebo-treated SP patients, Davidson et al. (1993b) demonstrated that clonazepam was superior to placebo on most measures, with respective response rates of 78 and 20%. When Versiani et al. (1997) studied bromazepam in 60 SP patients, 30 on active medication (mean dose = 21 mg/d) and 30 on placebo, significantly different response rates of 82 and 20%, respectively, were reported. Bromazepam was superior to placebo on all outcome measures at weeks 8 and 12, and LSAS scores decreased markedly by 70% for bromazepam-treated patients by endpoint. Collectively, these three studies suggest that certain benzodiazepines can have significant beneficial effects in SP, though the alprazolam results are not as compelling as those for clonazepam and bromazepam. Then again, the benzodiazepines are less than ideal as a first choice for treatment of SAD in most instances because of their potential for abuse and/or dependence, particularly in a population with known predisposition towards alcohol abuse.

Anticonvulsants

Two of the newer anticonvulsant medications, gabapentin and pregabalin, have been investigated in controlled studies of SAD. Pande et al. (1999) reported results of their study with 69 SP patients, 24 treated with gabapentin (mean dose = 2100 mg/d) and 35 with placebo for 14 wk. Gabapentin-treated patients had statistically significant reductions in SP symptoms as compared to placebo patients, with CGI response rates of 38% for gabapentin vs. 17% for placebo. LSAS response rates were similar at 32 vs. 14%, respectively. Gabapentin was
associated with mild to moderate dizziness, dry mouth, somnolence, and nausea, but no serious adverse events were reported and the overall risk–benefit ratio was considered favourable. Pregabalin was studied in an 11-wk controlled trial in 135 patients with generalized SP, with 42 patients randomized to low-dose pregabalin (150 mg/d), 47 to high dose pregabalin (600 mg/d), and 46 to placebo (Feltner et al., unpublished observations). Forty-three percent of the high-dose pregabalin patients were considered responders, which was significantly better than the 22% response rate for placebo-treated patients. The high-dose pregabalin was also associated with statistically significant superiority over placebo on a number of other measures, while low-dose pregabalin effects were less pronounced and did not separate statistically from placebo. Somnolence was the most frequent adverse event in the high-dose pregabalin group. Studies now underway are looking at mid-range doses of pregabalin.

Other drugs

Early studies with β-adrenergic receptor blocking agents found them to be effective for performance anxiety (Gorman et al., 1985; James and Savage, 1984; Neftel et al., 1982) and prompted speculation about potential to benefit SP patients; however, these studies were unclear as to the precise diagnoses of the study subjects involved, who may or may not have had generalized SP. Later, two controlled trials in SP with the cardioselective β-blocker atenolol failed to show efficacy. Also, in the previously described Leibowitz et al. (1992) study, phenelzine's clear efficacy after 8 wk was sharply contrasted by the relatively low 30% response rate for the 23 patients taking atenolol (mean dose = 98 mg/d), which was not significantly different than placebo. In another placebo-controlled study with 72 SP patients (Turner et al., 1994), atenolol was compared with behaviour therapy (flooding). Results revealed that atenolol was not statistically superior to placebo, with response rates of 38 and 30%, respectively, but that flooding (response rate = 62%) was superior to both.

The clinical effects of buspirone, a 5-HT-1A receptor agonist, in SP have been examined in open pilot studies (Schneier et al., 1993; Van Ameringen et al., 1996) and one controlled study (van Vliet et al., 1997). The 12-wk controlled study involved 30 SP patients treated with either buspirone 30 mg/d (n = 15) or placebo (n = 15), with only a single patient (7%) from each group classified as a responder (defined as ≥50% reduction on the anxiety subscale of the Social Phobia Scale). Though buspirone was well tolerated, these results do not support findings of open studies suggesting efficacy.

Unpublished results of a controlled study (Bell and DeVeaugh-Geiss, 1994) with the 5-HT receptor (5-HT-3) antagonist ondansetron have indicated positive effects in SP, though the effect size was reportedly small (Bell and DeVeaugh-Geiss, 1994). In an open trial (Simpson et al., 1998) and an unpublished controlled study (Emmanuel et al., 1998), imipramine has shown no significant benefit in SP. Response rate data from these unpublished studies were not available for review. Uncontrolled studies and reports of other drugs including venlafaxine (Altamura et al., 1999; Kelsey, 1995), nefazodone (Van Ameringen et al., 1999a; Worthington et al., 1998), bupropion (Emmanuel et al., 1991), selegeline (Simpson et al., 1998b) and others have suggested beneficial effects in SAD, but controlled investigation is required before definitive conclusions can be drawn.

Drug class effects

In order to compare the overall effectiveness in SAD of each major medication class discussed above, effect sizes were calculated using response rate and sample size data derived from placebo-controlled studies appearing in the text (Figure 1). The effect sizes (non-weighted and weighted) were calculated using arcsin transformation of the sample size of each study, and reflect differences between proportions responding to drug vs. placebo. For studies with multiple fixed dose groups, only data from the dose group associated with the highest end point response rate were used for effect size calculations.

Figure 1 illustrates that the MAOI, benzodiazepine and SSRI treatments yielded the highest effect sizes, with more modest effect size values for the RIMA and anticonvulsant treatments. The low-effect size value presented for the ‘other’ treatment category reflects the documented lack of significant effectiveness of atenolol and buspirone. When the liabilities associated with the clinical use of MAOIs and benzodiazepines are taken into account, as compared to the relative safety and tolerability of the SSRLs, these effect size data support the use of an SSRI as a first-line treatment for SAD.

Non-pharmacologic interventions

A number of types of cognitive–behavioural interventions have been shown to provide benefit in SAD including exposure therapy, cognitive therapy, combined cognitive and exposure therapy, and social skills training. Taylor (1996) performed a meta-analysis of studies of cognitive–behavioural treatments for SP and determined effect sizes for these four types of therapy and compared them to pill placebo and waiting list control conditions.
Figure 1. Drug class effect sizes for placebo-controlled pharmacotherapy studies of SAD. Effect sizes (non-weighted and weighted) were calculated using arcsin-transformation tables of Cohen (1988) and response rate and sample size data appearing in the text on a per-study basis, adjusted for the sample size of each study, and reflect differences between proportions responding to drug vs. placebo. For studies with multiple fixed dose groups, only data from the dose group associated with the highest end-point response rate were used for effect-size calculations. MAOI, monoamine oxidase inhibitors; RIMA, reversible inhibitors of monoamine oxidase A; SSRI, selective serotonin reuptake inhibitors; BZ, benzodiazepines; AC, anticonvulsants.

Effect sizes at post-treatment (mean duration of trials = 9.3 wk) for cognitive therapy and social skills training were nearly identical at 0.63 and 0.65, respectively, and the effect size for exposure therapy was 0.82. All treatments were significantly better than the waiting list control condition, which yielded an effect size of −0.13 indicating slight worsening of SP symptoms. While effect sizes for the three active treatments were numerically higher than the pill placebo effect size of 0.48, differences were not statistically significant. There appeared to be an increased benefit from the combined cognitive and exposure therapy, which was associated with a 1.06 effect size that was significantly larger than pill placebo. To retain proper perspective, smaller effect sizes may be expected when the control is a pill placebo, as compared to a control such as a waiting list condition as is often the case in studies of psychosocial treatments.

A limited amount of information directly comparing cognitive–behavioral and pharmacological therapies in SAD is available. Heimberg et al. (1998) found that the effects of group CBT (response rate = 58%) were similar to phenelzine after 12 wk of treatment, though phenelzine appeared to produce a more rapid and possibly more robust response. In contrast, Gelernter et al. (1991) reported a 24% response rate for group CBT-treated patients (n = 17) that was inferior to the effects of phenelzine and alprazolam. Nevertheless, overall data suggests that CBT and pharmacological treatments can potentially provide similar acute (2–4 months) benefits. Whether combination treatment, including both pharmacological and psychosocial modalities, has advantages over either one has not been fully explored, but at least one placebo-controlled study to address this issue is currently in progress (Davidson and Foa, unpublished observations).

Relapse prevention/maintenance treatment
Few studies have addressed the issue of preventing relapse by employing maintenance pharmacotherapy and at present there is no clear consensual definition of relapse for SAD. Nevertheless, some studies do exist which shed light on the issue of maintenance therapy and relapse prevention. When Fahlen et al. (1995) compared brofaromine to placebo, responders were continued on their treatments for 9 months: while the relapsed rate for the 10 patients continued on placebo was 60%, none of the 22 patients continued on brofaromine relapsed. In a study with 16 SP patients (Stein et al., 1996), those who responded to paroxetine during an 11-wk open phase were randomized to receive an additional 12 wk of treatment with either paroxetine or placebo: 62% of patients changed to placebo vs. 12% of those continued on paroxetine subsequently relapsed. In the Versiani et al.
(1992) study with phenelzine and moclobemide, patients withdrawn from 16 wk of active treatment relapsed by week 24. In another report, Versiani et al. (1996) described a high 88% relapse rate after moclobemide was abruptly discontinued after 2 yr of treatment. However, when Connor et al. (1998) utilized a very gradual withdrawal of clonazepam after treatment of SP with this medication openly for 6 months, only 21% of those patients relapsed, and none of the patients who continued active clonazepam relapsed. These results suggest that clinicians should consider continuing drug therapy for SP patients for 12 months or more; furthermore, when a decision is made to discontinue medication, abrupt cessation should be avoided in favour of a gradual tapering of the dose.

CBT may produce beneficial effects that continue for months or years after the completion of active treatment. In Taylor’s meta-analysis (1996), effect sizes for the CBTs tended to improve after post-treatment at 3-month follow up, ranging from 0.92 for exposure therapy to 1.08 for combined cognitive and exposure therapy. Others have reported maintenance of psychotherapeutic treatment gains after 2–5 yr (Heimberg, 1993; Turner et al., 1995), though confounding effects of additional post follow-up treatments may not have been completely accounted for. Similar findings could possibly occur with long-term medication, but no data yet exist to confirm this.

Predictors of response

It is currently unclear if certain features are associated with preferential response to medication, CBT, or both. It has been suggested that the generalized and non-generalized forms of SAD may respond to treatment differently. Liebowitz et al. (1992) concluded that patients with generalized SP (76% of the study sample) were preferentially responsive to treatment as compared to patients with discrete SP. On the other hand, it has been suggested that generalized SP represents a more severe form of the disorder that may be less responsive to CBT than specific SP (Masia and Schneier, 1999; Turner et al., 1994). Along the same line of thought, Sutherland et al. (1996) identified a negative association between the baseline severity of illness, including SP symptoms and/or coexisting depression, and outcome after 2 yr. There has been some indication that alcohol abuse (Versiani et al., 1998), the presence of a personality disorder (Slaap et al., 1996) and a family history of SP (Davidson, 1998) may be negative predictors of treatment response, but supporting data is limited. Furthermore, observations (Slaap et al., 1996) that non-responders in two pharmacology trials had higher heart rates and systolic blood pressures than responders may suggest that high baseline sympathetic arousal is negatively associated with treatment outcome (Davidson, 1998), but more study is needed to clarify this.

Conclusion

SAD is one of the most common of all psychiatric disorders. It usually presents during childhood or adolescence, is more frequent in women and has a lifetime prevalence of up to 16% in the general population. Recognition and differential diagnosis of SAD is important for both mental health professionals and primary-care physicians, since left untreated it predisposes to the development of comorbid conditions and further impairment. Moreover, it has been shown that under-recognition and/or under-treatment of SAD is responsible for a substantial portion of this disorder’s high cost. Different theories have been postulated to explain the origin of SAD (i.e. ethological, traumatic, parental, genetic, neurobiological, etc.); however, to date there is no definitive data to confirm one hypothesis as the sole cause for the disorder. Thus, SAD may be the result of different and complex mechanisms interacting together. Moreover, the three subtypes of SAD, generalized, non-generalized and discrete (public-speaking phobia) may differ in many important ways.

While the precise neurobiological underpinnings of SAD remain elusive, several lines of evidence suggest the condition may be associated with abnormalities of neurotransmitters including 5-HT, dopamine, norepinephrine, and/or GABA. Preliminary neuroimaging findings have identified possible alterations in function of the amygdala and other subcortical (e.g. caudate) and cortical (grey matter) brain regions; however, more precise functional or structural correlates to SAD remain unclear. Limited evidence points to an association with low growth hormone, but no other significant endocrine abnormalities have been identified. Chemical challenges with lactate, CO₂ and other compounds have revealed differential responses between SAD, normal controls, and other anxiety disorders (PD in particular) in some cases. Overall, the emerging findings suggest SAD is neurobiologically separate from other anxiety disorders; however, this supposition awaits confirmation and many studies have shown no difference relative to other anxiety disorders or controls.

SAD is responsive to both cognitive–behavioural and pharmacological treatments with strong effect sizes found for both, and comparisons of these two modalities suggest they are of comparable efficacy. Though CBT is a valid treatment option for SAD, pharmacotherapy will often represent the most pragmatic initial intervention and available evidence supports consideration of an SSRI as first line treatment. The anticonvulsants gabapentin and
Pregabalin may offer some advantages relative to SSRIs (e.g. side-effects, metabolic pathways, drug–drug interactions), but their efficacy in SAD has not been as well established. Phenelzine is clearly effective in SAD and certain benzodiazepines can offer significant relief of symptoms; however, because use of each entails inherent risks, these medications should be used with caution, especially phenelzine. The RIMA moclobemide appears safe and well tolerated but has limited effectiveness in SAD; the RIMA brofaromine appears more effective, but is not currently available for clinical use. Because early discontinuation will likely trigger relapse, an effective medication should be continued for at least a year in most cases.

Acknowledgements

Thanks are due to Dr Larry A. Tupler for assistance with statistical analysis. The authors acknowledge grant support from NIMH R10-MH49339-05A to Dr Davidson and unrestricted educational support from Pfizer/Parke–Davis.

References


Davidson JR, Potts N, Richichi E, Krishnan R, Ford SM, Smith...


Kessler RC, Frank RG (1997). The impact of psychiatric disorders on work loss days. Psychological Medicine 27, 861–873.


Schneider F, Weiss U, Kessler C, Muller-Gartner HW, Posse S,


Staber B, Tancer ME, Ranc J, Underwood LE (1996). Evidence for social phobia and other psychiatric disorders in adults who were growth hormone deficient during childhood. *Anxiety 2*, 86–89.


