Social anxiety disorder

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Our understanding of social anxiety disorder (also known as social phobia) has moved from rudimentary awareness that it is not merely shyness to a much more sophisticated appreciation of its prevalence, its chronic and pernicious nature, and its neurobiological underpinnings. Social anxiety disorder is the most common anxiety disorder; it has an early age of onset—by age 11 years in about 50% and by age 20 years in about 80% of individuals—and it is a risk factor for subsequent depressive illness and substance abuse. Functional neuroimaging studies point to increased activity in amygdala and insula in patients with social anxiety disorder, and genetic studies are increasingly focusing on this and other (eg, personality trait neuroticism) core phenotypes to identify risk loci. A range of effective cognitive behavioural and pharmacological treatments for children and adults now exists; the challenges lie in optimum integration and dissemination of these treatments, and learning how to help the 30–40% of patients for whom treatment does not work.

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Introduction

Anxiety disorders are the most pervasive class of mental disorders, with a 12-month prevalence in the community of about 18%.[1] Social anxiety disorder (also known as social phobia) is classified in the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV; panel 1)[2] and in the *International Classification of Diseases 10* (ICD-10; panel 2)[3] as a phobic (anxiety) disorder, alongside agoraphobia and specific phobias (from which it was first distinguished only 40 years ago[4]). People with social anxiety disorder fear and avoid the scrutiny of others. The concern in such situations is that the individual will say or do something that will result in embarrassment or humiliation. These concerns can be so pronounced that the individual shuns most interpersonal encounters, or endures such situations only with intense discomfort. Once largely neglected by the medical community, social anxiety disorder came to the attention of the general medical community a decade ago,[5] and is now garnering increased attention and recognition as a widespread, impairing, but treatable condition.[6]

Individuals with social anxiety disorder are typically shy when meeting new people, quiet in groups, and withdrawn in unfamiliar social settings. When they interact with others, they might or might not show overt evidence of discomfort (eg, blushing, not making eye contact), but invariably experience intense emotional or physical symptoms, or both (eg, fear, heart racing, sweating, trembling, trouble concentrating). They crave the company of others, but shun social situations for fear of being found out as unlikable, stupid, or boring. Accordingly, they avoid speaking in public, expressing opinions, or even fraternising with peers; in some situations, this can lead to such individuals being mistakenly labelled as snobs. People with social anxiety disorder are typified by low self-esteem and high self-criticism,[7] and as detailed below, often have depressive symptoms. The specific fear of urinating in public restrooms (paruresis, or so-called shy bladder syndrome) can be regarded as a discrete, relatively rare subtype of social anxiety disorder.[8]

DSM-IV recognises a common subtype of social anxiety disorder that it refers to as generalied. Recent studies find little evidence for distinct subtypes based on the content or number of fears.[9] But retention of the term generalised in the diagnostic nomenclature might be useful for denoting a pervasive form of the illness characterised by fear and avoidance of a wide range of situations (eg, speaking to others in small groups; socialising at parties; speaking to authority figures).[10] Believed to account for about half of cases in the community, and most individuals seeking treatment for social anxiety disorder,[11] generalised social anxiety disorder is also the most disabling form of the disorder.[10,11] Although people with generalised social anxiety disorder can fear and avoid specific performance situations such as public speaking,[12] their social fears and avoidance extend far beyond that relatively common sphere of concern.

Epidemiology

The National Comorbidity Survey-Replication provides prevalence estimates of 12-month and lifetime DSM-IV social anxiety disorder as 7·1% (SE 0·3%) and 12·1%, respectively, with higher prevalence in females.[1,9] The contemporaneous National Epidemiologic Survey on Alcohol and Related Conditions prevalence estimates of 12-month and lifetime DSM-IV social anxiety disorder were 2·8% (95% CI 2·5–3·1) and 5·0% (95% CI 4·6–5·4), respectively.[13] The lower rates in this study are

Search strategy and selection criteria

We searched Medline, PsychInfo, and the Cochrane Library from 1980, to April, 2007 for the terms "social anxiety disorder" and "social phobia" in combination with "behaviour therapy", "childhood", "cognitive therapy", "developmental", "diagnosis", "epidemiology", "genetics", "neuroimaging", "personality", "pharmacotherapy", "psychotherapy", and "treatment". We focused on studies reported in the past 10 years but also included commonly referenced and highly regarded older publications. Review articles and book chapters are cited to provide readers with more details and additional references than can be accommodated within this Seminar.

Panel 1: DSM-IV diagnostic criteria for social anxiety disorder (social phobia)[2]

- A notable and persistent fear of one or more social or performance situations with exposure to unfamiliar people or possible scrutiny by others
- The person fears that he or she will act in a way (or show symptoms of anxiety) that will be humiliating or embarrassing
- Exposure to the feared social situation almost invariably provokes anxiety, which can take the form of a panic attack
- The person recognises that the fear is excessive or unreasonable
- The feared social or performance situations are avoided or endured with intense anxiety or distress
- The condition interferes substantially with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or they have notable distress about having the phobia
- The fear or avoidance is not due to the direct physiological effects of a substance or a general medical condition and is not better accounted for by another mental disorder
- If a general medical condition or another mental disorder is present, the social or performance fear is unrelated to it (eg, the fear is not of trembling in Parkinson's disease)
- Specify the disorder as generalised if fears include most social situations

Panel 2: ICD-10 diagnostic criteria for social anxiety disorder[3]

F40 phobic anxiety disorders

A group of disorders in which anxiety is evoked only, or predominantly, in certain well-defined situations that are not dangerous. As a result these situations are characteristically avoided or endured with dread. The patient's concern can be focused on individual symptoms such as palpitations or feeling faint, and is often associated with secondary fears of dying, losing control, or going mad. Contemplation of entering the phobic situation usually generates anticipatory anxiety. Phobic anxiety and depression often coexist. Whether two diagnoses (phobic anxiety and depressive episode) are needed, or only one, is determined by the duration of the two conditions and by therapeutic considerations at time of consultation.

F40.1 social phobias

Fear of scrutiny by other people leading to avoidance of social situations. More pervasive social phobias are usually associated with low self-esteem and fear of criticism. Patients might present with a complaint of blushing, hand tremor, nausea, or urgency of micturition, sometimes being convinced that one of these secondary manifestations of their anxiety is the primary problem. Symptoms can progress to panic attacks.

probably attributable to methodological differences, including having used a threshold for disability that exceeds that needed by DSM-IV when assigning the diagnosis.

Studies in other western nations (eg, Australia, Canada, Sweden) note similar prevalence rates as in the USA, as do those in culturally westernised nations such as Israel.[14] Even countries with strikingly different cultures (eg, Iran[15]) note evidence of social anxiety disorder (albeit at lower rates) among their populace. The syndrome of *taijin kyofusho*, in which social–evaluative concerns involve the belief (sometimes of near-delusional intensity) that the individual makes other people uncomfortable (eg, "my gaze frightens people so they look away and avoid me"), is a form of social anxiety disorder more commonly seen in some Eastern cultures.[16]

Social anxiety disorder has a very early onset, with many cases—especially those of the generalised type—beginning in childhood or early adolescence.[17] The prevalence of social anxiety disorder in youth (6·8 % [SE 1·8%] in one study)[18] is similar to that reported in adults. Social anxiety disorder is a common reason for school refusal in young children, and it is the only mood or anxiety disorder that has consistently been shown to be associated with dropping out of school early.[19] Although it typically begins in early life, this disorder not infrequently persists into adulthood and even old age.[20]

Social anxiety disorder is frequently seen in primary care patients (3–7%).[21] Even in people with chronic physical conditions, social anxiety disorder (like many of the other anxiety and depressive disorders)[22] has its own independent burden of functional disability (including reduced workplace productivity), increased financial costs, and reduced health-related quality of life.[23] Despite the extent of suffering and impairment associated with social phobia, only about half of individuals with the disorder ever seek treatment, and they do so after 15–20 years of symptoms.[24]

Children with social anxiety disorder do not show evidence of high rates of childhood maltreatment or other specific forms of early-onset psychosocial adversity.[17] However, research consistently shows that a heritable temperamental trait known as behavioural inhibition is commonly an antecedent to the development of social anxiety disorder.[25] Social anxiety disorder, notably the generalised type, is familial.[26] Family studies reveal a recurrence risk ratio for first-degree relatives in the range of 2–6, suggesting moderate heritability.[27] Studies in twins confirm that social anxiety traits are heritable[28] and that susceptibility to social anxiety disorder involves the interplay of disorder-specific and non-specific (eg, shared with neuroticism) genetic factors.[29]

Diagnosis and evaluation

In medical settings, people with social anxiety disorder might speak quietly or offer only cursory answers to questions. Eye contact is often kept to a minimum. But,

more often, they will reveal their problems with social anxiety only upon direct questioning, rarely offering their symptoms up to their caregiver without solicitation. This reticence might be due to embarrassment about their symptoms, their belief that the practitioner would not take their problem seriously, or it could simply reflect their discomfort with authority figures.[30] These aspects of the patient–practitioner transaction, and insufficient knowledge (on the part of patients and practitioners) about the diagnosis, present substantial barriers to care for patients with social anxiety disorder. Asking of suspected sufferers, "Do you think that you might have problems with excessive shyness or social anxiety?" can open a productive dialogue that can rapidly lead to diagnosis. Self-administered screening questionnaires can help with this process (table 1).[31–35] Similar approaches to screening in children have been proposed.[36]

Critics of psychiatric nosology have been quick to suggest that the codification of social anxiety disorder is a prime example of mental health experts ascribing pathology to normal variation in human personality and behaviour.[37] The criticisms seem to centre around the arguments that social anxiety disorder is merely a pathological label for shyness. Only a few shy children—some of whom have additional risk factors such as a family history of liability to social phobia[38]—have their extreme shyness persist into adolescence and adulthood and manifest as social anxiety disorder; additionally, about 50% of adults with social anxiety disorder do not report excessive shyness in childhood.[39] Clearly, then, shyness is neither a requisite precursor for, nor can it be considered as synonymous with, the disorder.

A somewhat overlapping, though usually less well-reasoned, set of criticisms has at times arisen from the popular press, which has accused the pharmaceutical industry of creating social anxiety disorder in order to sell treatments. This argument is not accepted by any national drug licensing agency that has granted approvals for the treatment of social anxiety disorder. Social anxiety disorder has been ranked as among the top ten chronic disorders—mental or physical—in terms of its effects on objective outcomes such as days of work lost;[40] the effects of this disorder are therefore not merely on subjective distress, but also on measurable outcomes—such as health-related quality of life[41]—relevant to society and to public health. Although decisions to label particular entities as pathological clearly entail a sociopolitical process, this process can be rational.[42]

Differential diagnosis

Social anxiety disorder is not especially difficult to diagnose in a clinical context—once an index of suspicion is high enough and appropriate queries are made. However, the differential diagnosis can be somewhat more challenging (figure 1) for several other disorders.

Normal shyness: as discussed earlier, shyness (ie, social reticence) is a common personality trait, and is not by itself regarded as pathological. But when combined with concern on the part of the individual about their shyness and evidence that it has a detrimental effect on functioning, it can no longer be regarded as normal and a diagnosis of social anxiety disorder is probable.

	Format	Comments
Anxiety and Depression Detector (ADD)[31]	5-item self-report	Sensitive to anxiety disorders and major depression; not specific for social anxiety disorder
Generalized Anxiety Disorder-7 (GAD-7)[22]	7-item self-report	Sensitive to anxiety disorders but not intended to be specific for social anxiety disorder
Liebowitz Social Anxiety Scale (LSAS)[32]	24-item self-report	Sensitive and specific for social anxiety disorder (including generalised subtype)
Social Interaction Anxiety Scale (SIAS)[33]	20-item self-report	Preliminary evidence of usefulness for screening
Social Phobia Inventory (SPIN)[34]	17-item self-report	Sensitive and specific for social anxiety disorder
Mini-Social Phobia Inventory (Mini-SPIN)[35]	3-item self-report	Very brief yet sensitive and specific for generalised social anxiety disorder

Table 1: **Screening instruments for social anxiety disorder in adults**

Panic disorder and agoraphobia: panic attacks are sudden, unexpected paroxysms of severe anxiety, often characterised by intense physical symptoms such as tachycardia and breathlessness. Agoraphobia is the avoidance of situations where the individual fears a panic attack might occur and from which escape would be difficult. Not all panic attacks are caused by panic disorder and not all phobic avoidance is due to agoraphobia.[43] Inquiring about the cognitions the individual experiences during or in anticipation of their anxiety symptoms, ("What were you thinking about when you felt anxious and uncomfortable?") almost invariably resolves this diagnostic dilemma. The individual with social anxiety disorder is keenly aware of the source of anxiety (ie, scrutiny by others), whereas the individual with panic disorder or agoraphobia, or both experiences physically frightening symptoms for which they have no good explanation (ie, symptoms are unexpected).

Major depression: social anxiety disorder can, and frequently does, co-occur with major depression.[44] Social anxiety disorder should not be diagnosed if social avoidance is confined to periods of depression. Social anxiety disorder—like other anxiety disorders—is a powerful risk factor for the subsequent onset of major depression.[45]

Other psychiatric disorders: social fears and discomfort can occur as part of schizophrenia,[46] but other evidence of psychotic symptoms will be present in the latter. Social anxiety disorder is frequently comorbid with bipolar disorder;[47] in such instances, differential diagnosis is not the issue as both disorders may be present. Social anxiety may co-occur with eating disorders,[48] but in such instances it is important to determine that embarrassment about eating disorder symptoms or behaviours (eg, purging and vomiting) is not the sole source of social anxiety before a diagnosis of social phobia is made.

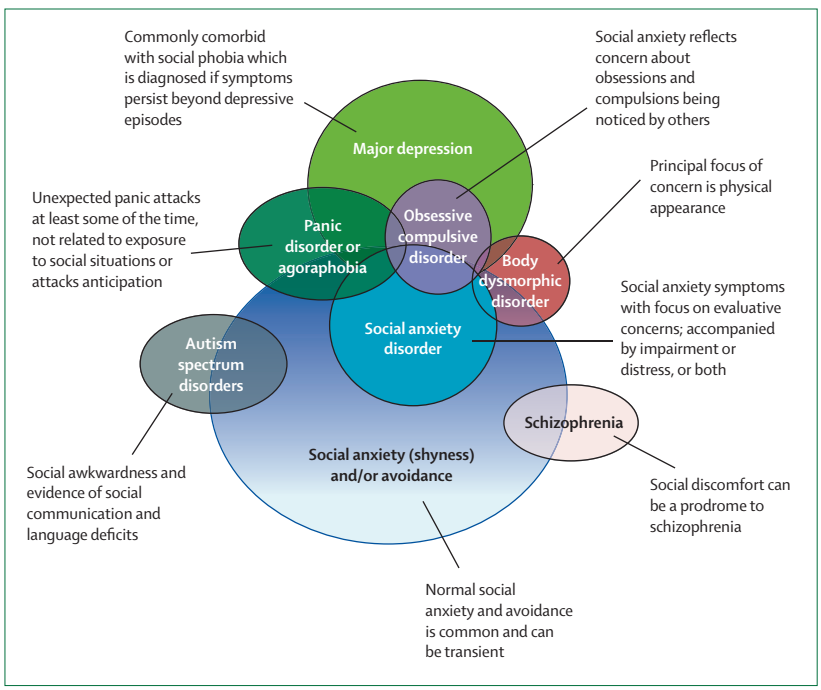

Figure 1: **Conditions that commonly overlap with social anxiety disorder (social phobia) and might be considered in the differential diagnosis of an individual with social anxiety symptoms**

Similarly, obsessive compulsive disorder might be associated with social anxiety, but the additional diagnosis of social phobia is only given if social fears and avoidance are independent of the focus of the obsessions and compulsions. In the case of body dysmorphic disorder, wherein the patient has a fixed belief that particular features render them misshapen or ugly, social fears and avoidance can be merely a product of their opinion of their appearance; but evidence also suggests genuine comorbidity for the two disorders that could sometimes be more difficult to treat.[49] Individuals with social anxiety disorder are prone to substance misuse,[50] which in some cases is an attempt to self-medicate, and so this diagnosis should be considered in people who present with alcohol or other substance use problems.

Personality disorders: in view of the usual onset of social anxiety disorder in childhood and its persistence into and through adulthood,[17] social anxiety disorder can resemble a personality disorder. Schizoid personality disorder is readily discernible because such individuals do not desire social contact; they are the loners who prefer living that way, by contrast with people with social phobia who intensely desire to be more comfortable around others. However, one particular DSM-IV personality disorder, avoidant personality disorder, is diagnosed in 50–90% of people with social anxiety disorder.[51,52] The criteria for diagnosis of generalised social anxiety disorder and avoidant personality disorder overlap such that discussions are underway to possibly delete avoidant personality disorder from DSM-V. For the time being, the presence of avoidant personality disorder in someone with social anxiety disorder can be considered as a way of denoting an especially severe, persistent (41% lower likelihood of remission over 5 years)[53] form of social anxiety disorder.

Childhood developmental disorders: social anxiety and social communication deficits are hallmarks of autistic spectrum disorders such as Asperger's syndrome,[54] and can sometimes present a challenge in terms of differential diagnosis. Children with social anxiety disorder typically have adequate capacity to communicate socially, though they can seem impaired when first interacting with unfamiliar peers or adults. Selective mutism, a syndrome wherein children have normal language skills in the presence of parents and other familiar individuals at home, but fail to speak to unfamiliar peers, is almost invariably associated with a diagnosis of social anxiety disorder.[55,56] In such instances, selective mutism may be regarded as a severe variant of social anxiety disorder.[17]

Physical disorders: any disorder that raises concerns about being the source of negative attention by others can be associated with social anxiety. Examples are Parkinson's disease or essential tremor,[57] stuttering,[58] severe obesity, severe burns, acne, or other disfiguring conditions. Although DSM-IV strangely precludes the diagnosis of social anxiety disorder in the context of such physical conditions, data suggest that when social anxiety symptoms are especially prominent, approaching the problem as if it is diagnosable social anxiety disorder (ie, validating the patient's concerns and offering appropriate treatment) makes good clinical sense.[6]

Causes and pathogenesis

The causes and pathogenesis of social anxiety disorder are not well elucidated, but progress is being made. In the only reported genome-wide linkage analysis for social phobia, chromosome 16 seemed to be implicated, in a region proximate to a candidate gene, the norepinephrine transporter.[59] Nature is not compelled to adhere to our psychiatric diagnostic nomenclature (ie, DSM or ICD). In this regard, some underlying behavioural trait (eg, behavioural inhibition or neuroticism)[25,29] is thought to be genetically transmitted, contributing to spectrums of psychopathology, rather than to any individual disorder. Several plausible candidate genes have been associated with traits related to social anxiety, though none consistently so thus far. Findings have included association of low extraversion (ie, introversion, a trait characteristic of individuals with social anxiety disorder and their family members[60]) with a functional variant at the β_1-adrenergic receptor (*ADRB1*) gene,[61] and in women with two single nucleotide polymorphisms (SNPs) and a three SNP haplotype within the catechol-*O*-methyltransferase (*COMT*) gene.[62]

Smoller and colleagues[63] have detected a strong association between the corticotropin releasing hormone gene, *CRH*, and behaviourally inhibited temperament. A widely-studied polymorphism (5HTTLPR) in the

promoter region of the serotonin transporter gene has been related to shyness in two separate studies of children (though the risk allele differed across studies).[64,65] Smoller and colleagues[66] found an association between the human orthologue of a gene influencing mouse anxiety behaviour, *RGS2*, and several anxiety-related traits including introversion and increased insula and amygdala activation to emotional faces. In a population-based study, investigators recorded that variation in the glutamic acid decarboxylase 1 (*GAD1*) gene (involved in synthesis of γ-aminobutyric acid from glutamate) was significantly associated with an internalising-neuroticism factor[67] that might be especially relevant to social anxiety disorder.

These studies strengthen the premise that detection of susceptibility genes for social anxiety-related traits and other intermediate phenotypes will be possible, but that their identification will need larger samples and more powerful designs than previous trials. Consideration should also be given to exploring the familial aggregation of social anxiety disorder and related traits in families with autistic spectrum disorder;[27] specifically, interrogation of recently-discovered susceptibility genes for autism might help with identification of effects that are specific to the processing of socially relevant information. Genome-wide association approaches to studying social anxiety and genetically related phenotypes, such as neuroticism,[29] beginning with inexpensive pooling studies[68] offer the opportunity to move beyond candidate genes to an unbiased survey of the entire genome.

Patients with Parkinson's disease, an illness characterised by deficits in striatal dopamine function, have raised rates of social anxiety disorder.[69] Dopamine receptor PET studies have shown changes in striatal dopaminergic function in patients with generalised social anxiety disorder.[70,71] And, in a recent study, patients with generalised social anxiety disorder were shown to have significantly reduced activation in the left caudate head during an implicit learning task, thereby further implicating the striatum in this disorder.[72]

The amygdala is thought to play an important role in the response to fear, as evidenced by amygdala activation to emotional human faces in many functional imaging studies.[73] Amygdala activation to emotional human faces has been shown to correlate with the severity of social anxiety symptoms,[74] as does the extent of activation in bilateral insular cortex (a region of the brain also thought to play an important part in anxiety disorders through its mediation of interoceptive processing)[75] in anxious non-patients (figure 2).[76] Adults susceptible to anxiety defined on the basis of behavioural inhibition in childhood also show increased amygdala activation to new emotional faces.[77] Conversely, amygdala activation to threatening emotional faces is reduced in individuals with Williams syndrome, a rare disorder characterised by social fearlessness.[78] Findings from recent neuroimaging studies in social anxiety disorder are summarised in table 2.[79–83]

Studies on the neural underpinnings of social anxiety disorder implicate abnormalities of corticolimbic and, possibly, corticostriatal circuitry in the cause or maintenance, or both of social anxiety disorder. These circuits mediate a range of cognitive and affective processes, allowing integration of studies of brain imaging with cognitive theories focusing on distorted assumptions about the self and the social world[84] and with empirical data for information-processing biases in attention, memory, judgment, and interpretation. Findings that brain imaging abnormalities, such as those in the amygdala and

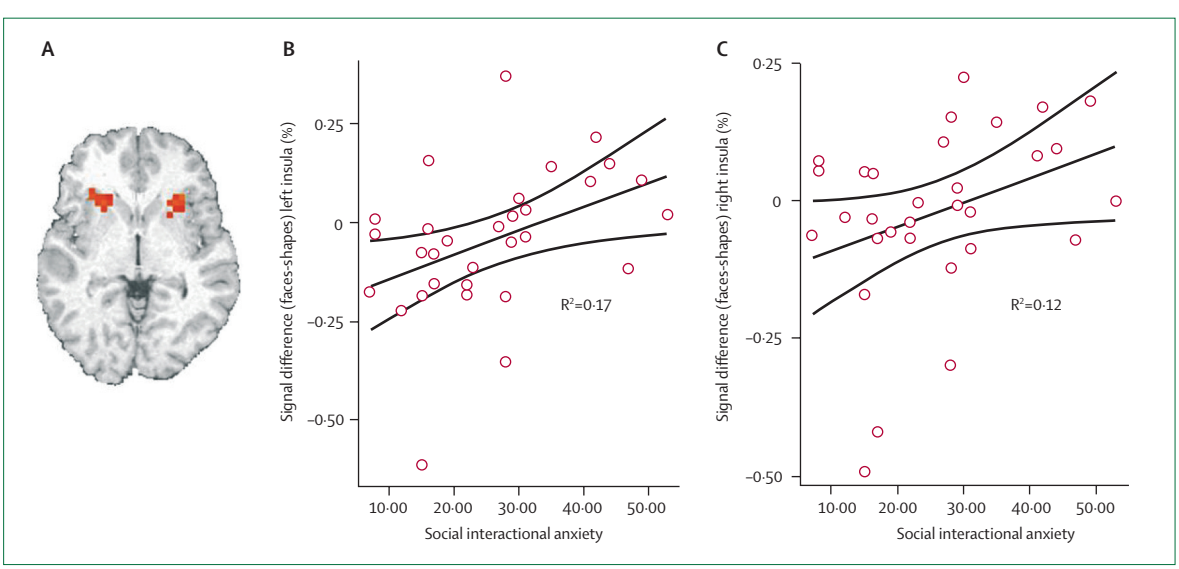

Figure 2: **(A) functional MRI BOLD activation in bilateral insular cortex during faces-shapes contrast during emotional face processing task in healthy students aged 18–21 years. (B) linear regression of activation in left insula in relation to social anxiety scores. (C) Linear regression of activation in right insula in relation to social anxiety scores**

Data are from, Stein MB et al, unpublished. Functional neuroimaging methods and task details are described elsewhere.[76]

	Findings
Proton (^{1}H) magnetic resonance spectroscopy	Increased glutamate in anterior cingulate cortex versus healthy controls[79]
PET regional cerebral blood flow	Increased amygdala blood flow during public speaking in patients versus healthy controls. Reduction in amygdala blood flow with cognitive behavioural therapy or pharmacological treatment[80]
PET receptor density with specific ligands	Reduced striatal dopamine reuptake site density in patients.[71] Low striatal dopamine D2 receptor binding potential in patients.[70] Reduced serotonin-1A (5-HT1A) binding potential in amygdala, anterior cingulate, and insula in patients[81]
Functional MRI BOLD response	Increased amygdala activation in patients during emotional face processing.[74,82] Increased anterior cingulate activation in patients during disgust face processing[83] Reduced striatal (left caudate activation) activation in patients during implicit sequence learning[72]

Table 2: **Summary of neuroimaging studies in social anxiety disorder**

insula, might normalise with successful drug treatment or psychotherapy,[80,85] variation in the serotonin transporter gene promoter region affects the extent of activation in these regions,[86] and serotonin depletion reverses the benefits of antidepressant treatment,[87] all point to a role for serotoninergic dysfunction. Investigation of neuroendocrine substrates involved in social affiliation (eg, oxytocin and vasopression)[88] and neural systems mediating such socially relevant emotions as trust and rejection might also be useful.[89] Preliminary evidence that neuropeptides such as oxytocin can affect the neural circuitry of social fear[90] might lead to development of new drug treatments.

Treatment

A large database of randomised controlled trials shows efficacy of medications and cognitive behavioural therapy in social anxiety disorder,[91,92] with relatively high effect sizes. In a meta-analysis, selective serotonin reuptake inhibitors had an effect size of 1·5, and exposure therapy and cognitive restructuring had an effect size of 1·8 on clinician-rated scales.[91] Comparison of effect sizes in pharmacotherapy and psychotherapy trials is difficult, because of differences in the design of the relevant trials (eg, psychotherapy trials often use a wait-list comparison). Nevertheless, seminal trials comparing drug treatment versus cognitive behavioural therapy in social anxiety disorder suggested that drugs can have faster effects, but the effects of cognitive behavioural therapy might last longer.[93,94] Treatment guidelines often suggest that either pharmacotherapy or cognitive behavioural therapy are acceptable first-line interventions for social anxiety disorder.[95] At present, no clear evidence shows that combined pharmacological and cognitive behavioural treatment is more effective than single modality treatment.[96,97] The choice to begin one modality rather than another, or to use combined treatment, therefore often relies on clinical judgment about individual patients (eg, drug treatment might be advisable in a patient who was too anxious or depressed to begin psychotherapy, or did not complete psychotherapy homework). A proof-of-principle study showing that the glutamatergic agent, D-cycloserine, which has been shown to enhance extinction of conditioned fear in animal models, was also useful for augmenting the psychotherapy of social phobia,[98] suggests that in the future more mechanistically informed combination treatments could become standard.

Early work showing that generalised social anxiety disorder responded to monoamine oxidase inhibitors, but not to β blockers,[99] had a substantial effect on the understanding and management of the disorder. Nevertheless, the monoamine oxidase inhibitors were (and continue to be) of limited usefulness because they need strict and inconvenient dietary restrictions, and can be associated with substantial adverse events. Similarly, although high-potency benzodiazepines, such as alprazolam or clonazepam, can be useful for social anxiety disorder,[93,100] and are understudied, concerns remain about their safety, which has restricted their use. The introduction of reversible inhibitors of monoamine oxidase A, such as moclobemide, that did not need dietary restriction and that had fewer side-effects than traditional monoamine oxidase inhibitors, promised to be an important step forward in the management of social anxiety disorder. However, short-term clinical trials of moclobemide were not consistently positive,[92] and the medication was not approved in the USA. Nevertheless, this drug is an option in some countries where it is available.

The efficacy of a selective serotonin inhibitor in the treatment of social anxiety disorder was first shown a decade ago. Since then, randomised trials with many of the selective serotonin reuptake inhibitors and the dual serotonin–noradrenaline reuptake inhibitors have shown efficacy in social anxiety disorder (table 3),[101–116] and treatment guidelines have increasingly suggested that these classes of drugs are the pharmacotherapy intervention of choice in social anxiety disorder.[95] Summary statistics calculated for clinical response (on the Clinical Global Impressions scale improvement item or equivalent) from comparisons of antidepressants and other agents, showed that patients who received medication were significantly less likely to be non-responders than those who received placebo (n=26; relative risk [RR] of non-response 0·64, 95% CI 0·57 to 0·73; random effects model). This result was seen for selective serotonin reuptake inhibitors (n=11, RR 0·67, 95% CI 0·59 to 0·76), the monoamone oxidase inhibitors (n=3, RR 0·43; 95% CI 0·24 to 0·76), and for moclobemide (n=5, RR 0·89, 95% CI 0·8 to 0·98).[92] On the most commonly used outcome measure, the Liebowitz Social Anxiety Scale,[117] the weighted mean difference for the selective serotonin reuptake inhibitors was –13·67 (95% CI –19·97 to –7·37) and for moclobemide was –7·24 (95% CI = –12·14 to –2·35).

Several general points can be made about trials of selective serotonin or serotonin–noradrenaline reuptake inhibitors. First, large trials of escitalopram, fluvoxamine (immediate and controlled release), paroxetine, sertraline,

and venlafaxine extended release in social anxiety disorder have shown both efficacy and tolerability. However, results of studies of fluoxetine have been inconsistent.[106] Number needed to treat in pharmacotherapy trials was calculated at 3·7 in a meta-analysis,[118] which compares very favourably with that of antidepressants for depression and with medications used widely in many areas of general medicine.

Second, some of the studies have used a fixed-dose design, suggesting that the dose–response curve for these agents in social anxiety disorder is somewhat flat.[107,114] Although some patients probably respond only to higher doses, more than 25% of patients who do not respond at 8 weeks of treatment will respond by week 12.[110] Such information could be useful for bolstering the patience of both clinicians and patients.

Third, most trials of selective serotonin or serotonin–noradrenaline reuptake inhibitors have been short (ie, 12 weeks or less). Nevertheless, large relapse prevention trials with escitalopram, paroxetine, and sertraline recorded relapse rates of 4–14% with continued drug treatment, versus 36–39% with placebo.[119–121] Thus, after an acute response is achieved, treatment for 12 months or longer seems reasonable to prevent the return of symptoms after medication is stopped. A reasonable hypothesis is that the addition of cognitive behavioural therapy during long-term treatment of social anxiety disorder would enable the maintenance of response after stopping drug treatment, but systematic data for these issues have not been reported.

Fourth, almost all large multicentre trials of selective serotonin reuptake inhibitors have been done in tertiary medical centres, aiming to gain registration for drugs for generalised social anxiety disorder. An exception is a large study of sertraline in primary care; which noted that both sertraline and exposure therapy were useful in the treatment of social anxiety disorder.[96] However, few data document the extent to which treatment in real world contexts is effective. Such data would be useful for establishment of precise economic benefits of social anxiety disorder treatment, although modelling approaches suggest that present treatments are very cost-effective.[122]

Fifth, a few studies only have compared different selective serotonin or serotonin–noradrenaline reuptake inhibitors directly. A randomised comparison suggested some advantages for escitalopram 20 mg a day versus paroxetine 20 mg a day.[101] However, in a comparison study of venlafaxine versus paroxetine, few clinically significant differences were seen.[108] Caution is needed before extending findings from trials comparing different doses and different medications, but noradrenergic reuptake blockade is possibly not requisite to response to drugs in social anxiety disorder,[114] whereas serotoninergic reuptake blockade almost certainly is needed.[128]

Sixth, studies of predictors of response to medication suggest that clinicians have little ability to predict outcome accurately. Only the length of treatment predicted response to paroxetine.[110] S/S variants of the SLC6A4 promoter polymorphism 5HTTLPR might predict a worse response to treatment with selective serotonin reuptake inhibitors.[123]

	Dose (mg per day)	Number of patients	Response rate for drug	Response rate for placebo
Citalopram[85]	40	36	50%	8%
Escitalopram[101,102]	5–20	1028	54–71%	39–50%
Fluvoxamine[103–105]	50–300	422	43–48%	7–44%
Fluoxetine[97,106]	20–60	108	40–51%	30–32%
Paroxetine[101,107–110]	20–50	2188	55–72%	8–50%
Sertraline[96,111–113]	50–200	616	40–53%	9–29%
Venlafaxine[108,114–116]	75–225	1547	44–69%	30–36%

*Patients undergoing concomitant cognitive behavioural psychotherapy were excluded.

Table 3: **Usefulness of selective serotonin and serotonin–noradrenaline reuptake inhibitors for social anxiety disorder**

Seventh, most studies have been done in adults. A study of fluvoxamine for several anxiety disorders in children and adolescents, including social anxiety disorder, noted that this agent was more effective than placebo.[124] Paroxetine has also shown substantial efficacy in child and adolescent social anxiety disorder.[125] Although selective serotonin reuptake inhibitors were safe and effective in trials in children and adolescents with social anxiety disorder,[126] careful monitoring of such patients for adverse events (including suicidal ideation) is warranted.[127]

Cognitive behavioural therapy was effective for the treatment of social anxiety disorder in many studies.[91] Components of this treatment can include psychoeducation, progressive muscle relaxation, social skills training, imaginal and in-vivo exposure, video feedback, and cognitive restructuring.[128] Generally, cognitive behavioural therapy entails a time-limited collaboration between clinician and patient, is focused on the present rather than the past, and aims to teach patients the behavioural and cognitive skills that will allow them to function efficiently. In social anxiety disorder, such therapy has been adapted on the basis of cognitive models that emphasise the relationship between dysfunctional belief systems and behavioural avoidance.[83]

The question of which component of cognitive behavioural therapy is the most effective remains controversial, though recent evidence suggests that including a cognitive component is crucial.[129] Recent research suggests that individual therapy is more effective than group therapy.[130] As in the case of drug treatment, additional work is needed to establish the efficacy of cognitive behavioural therapy in real-world contexts.[131]

Reports indicate the value of cognitive behavioural therapy in children and adolescents with social anxiety

disorder,[17] and the potential of these techniques for prevention.[132] In view of the early age of onset of social anxiety disorder, and the potentially modifiable underlying risk factors such as behavioural inhibition, the effect of early cognitive behavioural intervention to treat social anxiety disorder and prevent its consequences is an important area for future research and practice.

Not all patients respond to the first treatment, whether drug therapy or psychotherapy. Few controlled studies of augmentation have been done in patients with social anxiety disorder. Published studies offer some preliminary support for the combination of a selective serotonin reuptake inhibitor with a benzodiazepine,[133] but not with pindolol.[134] Several new drugs have been studied but their place in treatment is, as yet, unclear. The antidepressant mirtazapine was effective in a small (n=66) controlled trial.[135] The anticonvulsants gabapentin and pregabalin were effective in controlled trials,[136,137] whereas the anticonvulsant levetiracetam was ineffective (Stein MB et al, unpublished). Second generation (atypical) antipsychotic drugs could have a role in the treatment of refractory anxiety disorders[138] but they have yet to be studied in randomised trials in social anxiety disorder, and the adverse event profile of these agents (including weight gain and adverse effects on lipids and glycaemic control) needs careful consideration. Psychotherapy augmentation in drug-refractory patients seems reasonable, but systematic data on this issue are absent.

Conclusion

In the past two decades, significant advances have been made in the nosology, epidemiology, psychobiology, pharmacotherapy, and psychotherapy of social anxiety disorder. At the same time, many challenges remain. Despite validation of the diagnostic construct, the opinion that social anxiety disorder is merely shyness or an entity designed by the pharmaceutical industry to expand the market is still common. We argue that a view that accepts the validity of expanding markets for general medical disorders (eg, hypertension, hyperlipidaemia), but that is automatically critical of psychiatric diagnosis and treatment, is questionable and reinforces stigmatisation of mental disorders.

As psychiatry increasingly becomes a clinical neuroscience, delineation of the underlying endophenotypes associated with social anxiety disorder should be a key focus of research. Secondary prevention with the aim of reduction of long-term adverse consequences is a viable goal but will need much more research. Additionally, too many patients remain undiagnosed and untreated, and too many do not respond to first-line therapies. Additional research is needed at all levels, from basic science through to health services research, to improve and appropriately implement the management of social anxiety disorder.

Conflict of interest statement

MBS has, in the past 3 years, received consultant honoraria or research grants from AstraZeneca, Avera Pharmaceuticals, BrainCells Inc, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Hoffmann-La Roche, Jazz Pharmaceuticals, Johnson & Johnson, and Sanofi-Aventis. DJS has received consultant honoraria or research grants from AstraZeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, and Wyeth.

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