Seroxat/Paxil fact file

Section 2

New indications

Chapter 1: Social anxiety disorder / social phobia

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Introduction

What is social anxiety disorder / social phobia?

Social anxiety disorder (also known as social phobia) is the least well known of the anxiety disorders and it is also the least well understood. Social anxiety disorder is the marked and persistent fear of social or performance situations, where the sufferer is concerned that they will be humiliated or suffer intense embarrassment. This leads to anxiety and distress and avoidance behaviour.

Most people have experienced feelings of nervousness at a social event, but it is important to distinguish normal social discomfort or shyness from the exceptional anxiety felt by sufferers with social anxiety disorder. These patients fear situations where they may be exposed to the scrutiny / negative evaluation of others, for example performance situations (eg public speaking). Sufferers fear any form of social interaction, including speaking to a teacher or employer, writing a cheque whilst being observed, or eating in a public place. Sufferers believe that they will say something embarrassing or humiliating, or that others will notice their anxiety. Although they are aware that their fears are excessive or unreasonable, the intensity of their distress will often lead to avoidance of these situations.

Symptoms

When patients with social anxiety disorder are exposed to a feared situation, they experience physical symptoms appropriate to a fear response or a panic attack.[1,2] Blushing is one of the main physical symptoms that distinguishes social anxiety disorder from the symptoms of other anxiety disorders. Trembling, sweating, and speech block are other notable symptoms. Some patients do not complain of physical symptoms, but experience great self-consciousness, fear, and apprehension. The apprehension and worrying, 'anticipatory anxiety', can occur minutes, days or even months before a difficult social or performance situation. The greatest source of impairment is the 'phobic avoidance', which may range from avoiding eye contact to avoiding all interpersonal contacts outside the immediate family. To make matters worse, patients are often extremely self-critical.[3]

Aetiology

The exact cause of social anxiety disorder is unknown. No specific biological abnormality has been identified, although there is evidence for the involvement of the neurotransmitters, serotonin and dopamine. However, only serotonergic agents (eg the selective serotonin reuptake inhibitor [SSRI], paroxetine) have shown clear efficacy in social anxiety disorder. Thus, whilst the precise mechanism underlying social anxiety disorder is unknown, there is clear evidence for a definite role for serotonin in the development of the disorder, similar to the mechanisms which underlie depression and other anxiety disorders. Parental behaviour is an important factor in maintaining and, perhaps, contributing to social anxiety disorder.[4] Family and genetic studies have also suggested a genetic component.[5]

Precipitating situations

Patients with social anxiety disorder experience excessive fear of being humiliated or judged negatively in social or performance situations, and there is a strong tendency for sufferers to avoid the feared social interaction or social situation. The most common precipitating situations are speaking or eating in public, writing (or using a keyboard) in front of others, and meeting new people, members of the opposite sex, or people in authority.

Epidemiology of social anxiety disorder / social phobia

Prevalence

The term 'social phobia' was coined in 1903, but the disorder did not become an official part of the diagnostic nomenclature until the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980. As a result, research on social anxiety disorder lagged behind other anxiety disorders and the condition, referred to as 'the neglected anxiety disorder',[6] was initially considered to be rare. However, as new diagnostic criteria and rating scales have become available, it has emerged that social anxiety disorder is more common than it was originally thought. Epidemiological studies have determined that 2-5% of the general population will be affected by social anxiety disorder at some point in their lives.[7] However, estimates of the lifetime prevalence rates have varied widely (0.6-16%).[8-13] The variation in these reports may be partly explained by methodological and cultural differences.

Age of onset

The onset of social anxiety disorder occurs before the age of 20 in 95% of sufferers.[14] Most commonly, the disorder develops between the ages of 14 and 16 years.[4,15,16] This is a critical time when social and personal relationships are being formed, and the onset of the disorder can interfere with normal development and may lead to harmful coping mechanisms. The earlier the onset, the more severe and disabling the impairment to personal development, educational attainment, and career progression. Despite the early onset, the majority of sufferers will not present to their physician for treatment until later in life, often only for treatment of comorbid disorders that develop if the social anxiety disorder is left untreated. The disorder is chronic and, unless treated, unremitting.[2]

The burden of social anxiety disorder / social phobia

Characteristics of social anxiety disorder / social phobia sufferers

Social anxiety disorder is an illness which develops in adolescence, but has lifetime consequences. By interfering with the normal development of social and personal relationships, the disorder has a long-term effect on the social, familial, and working lives of sufferers. Patients with social anxiety disorder are likely to have less than 11 years of education, earn a low income, be single and have no occupation.[20] As a consequence, patients are likely to remain in the parental home and are often financially dependent on their families.[9,20] If the disorder is left untreated, patients are likely to develop additional psychiatric disorders and may turn to alcohol or drugs in an attempt to self-medicate. Compared with patients with panic disorder, social anxiety disorder sufferers report greater levels of distress, fear of negative evaluation by others, and avoidance of social situations.[21]

Common comorbidities

As many as 80% of patients with social anxiety disorder report at least one other psychiatric disorder during their lifetime (affective disorders, other anxiety disorders, and / or substance abuse).[19] Over one-third of patients will become depressed during their life and around about one-fifth of patients will develop dependency on alcohol and / or experience panic attacks. The co-existence of other psychiatric disorders typically makes the treatment of social anxiety disorder more difficult and the outcome less favourable than it is for the single, uncomplicated disorder. Other psychiatric illnesses are also seen more often in these patients than in those with panic disorder.[21] Patients often present to their physician because of the symptoms of the comorbid disorder, rather than to the symptoms of social anxiety disorder itself.

Development of depression

Social anxiety disorder usually precedes the development of comorbid psychiatric disorders and would appear to predispose individuals to the development of other conditions.[9] It is important, therefore, for physicians to recognise social anxiety disorder when it first arises, before other conditions develop. Most commonly, patients become depressed about the extent of their symptoms and disability; social anxiety disorder has been shown to precede depression by at least 1 year in three-quarters of patients in whom both conditions are present.[9] This differs from panic disorder where the development of major depression and panic disorder is concurrent in approximately one-third of comorbid cases.

Comorbid alcoholism

Due to the nature of social anxiety disorder, patients are reluctant to seek professional help, and some turn to alcohol in an attempt to self-medicate.[9,20] Social anxiety disorder patients are more than twice as likely as the general population to have problems with alcohol.[22] The incidence of alcoholism in these patients has been reported to be around 15% to 40%.[13,23-28] Similar to the situation with depression, problems with alcohol usually start after the onset of social anxiety disorder.[28] The co-existence of the disorders has direct implications for the treatment of both alcoholism and social anxiety disorder. For example, some medications (eg benzodiazepines) may be incompatible with alcohol, or even dangerous for patients with alcohol problems.

Why is comorbidity important?

Simple, uncomplicated social anxiety disorder is a distressing and disabling condition. The comorbid condition is undoubtedly worse. When social anxiety disorder is comorbid with other psychiatric symptoms, (eg panic attacks) the patient is more likely to seek medical help, is more likely to be receiving medication, and experiences more impairment in role functioning, than when social anxiety disorder occurs on its own.[12] Thus, it is particularly important to recognise and treat social anxiety disorder when it is comorbid with other conditions.

Use of medical services

Patients with social anxiety disorder tend to make more use of medical outpatient services than those patients without a psychiatric disorder, though this is seldom for treatment of social anxiety disorder itself. One reason for this may be because patients are not aware that the disorder is treatable: patients with social anxiety disorder often share the common public misconception that what they experience is severe shyness. Furthermore, the very

nature of their condition means they are reticent about social contact, including medical consultation, and it is often the presence of a comorbid condition, such as depression, that eventually makes them visit their physician.

Work productivity

Throughout the working lives of patients with social anxiety disorder, continuing functional impairment has an economic impact, reflected in the loss of working days to illness and reduced work performance. Patients are more likely than the general population to have an unstable employment record, to perform badly when in work, and to be dismissed repeatedly.[20] Productivity is significantly reduced in at least one-third of patients compared with patients who have a recurring physical illness. Therefore, not only is social anxiety disorder negating patients' contributions to the economy, it is also increasing the likelihood that they will require financial assistance from the state; over 20% of patients with social anxiety disorder are dependent on disability or welfare payments compared with 10% in the general population.[9] The co-existence of other psychiatric disorders in these patients makes matters worse.

Risk of suicidality

Patients with social anxiety disorder think about death more often than the general population.[20] When these patients suffer from other psychiatric disorders in addition to social anxiety disorder, the amount of time that they spend pre-occupied with committing suicide rises; the increase is directly related to the number of comorbid disorders present.[20] However, patients with 'pure' social anxiety disorder rarely try to take their own life. The incidence of actual suicide attempts is only increased in the presence of other psychiatric disorders; patients with social anxiety disorder and other comorbid psychiatric disorders are nearly six times more likely than the general population to try to kill themselves.[9]

Recognition / diagnosis of social anxiety disorder / social phobia

A difficult diagnosis

Social anxiety disorder is undertreated. One reason for this is that patients just do not present for treatment. They fear scrutiny and will avoid situations which involve social interaction, such as visits to their physician. The diagnosis itself can be complicated by the presence of other psychiatric disorders, and although patients are presenting for treatment, social anxiety disorder can go unrecognised. Furthermore, the presentation of social anxiety disorder can resemble agoraphobia or panic disorder. It is the reasons which underlie patients' fears that enable the conditions to be distinguished. For example, a patient with social anxiety disorder fears buying goods in a small shop, where they will have to ask for what they want, whereas a patient with agoraphobia fears supermarkets or shopping malls, where the crowded nature of the setting drives the fear.

Diagnostic tools

The main diagnostic criteria for social anxiety disorder (social phobia) are the Tenth International Classification of Diseases (ICD-10)[30] and the Fourth Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[1] Patients are assessed according to these criteria during psychiatric interviews with their clinician. The Mini International Neuropsychiatric Interview (MINI) and the Structured Clinical Interview for DSM (SCID) are useful screening tools. The MINI is used predominantly in Europe, whereas the SCID

is used more frequently in the USA. The Social Phobia Inventory (SPIN) is a relatively new patient-rated screening tool.

ICD-10 criteria for social phobia

The ICD-10 uses the term 'social phobia' rather than 'social anxiety disorder'. ICD-10 criteria describe social phobia as centred around a fear of scrutiny by other people in comparatively small groups (as opposed to crowds), usually leading to avoidance of social situations. The fear may be discrete (ie restricted to particular situations such as eating or speaking in public and encounters with the opposite sex), or diffuse (ie involving almost all social situations outside the family circle). If the distinction between social phobia and agoraphobia is difficult, ICD-10 states that precedence should be given to agoraphobia.

DSM-IV criteria

DSM-IV criteria recognises the term 'social phobia (social anxiety disorder)'. The condition is described as a marked and persistent fear of one or more social or performance situations in which the individual is exposed to unfamiliar people or to possible scrutiny by others. The individual fears acting in a way (or showing anxiety symptoms) that will be humiliating or embarrassing. For a diagnosis of social anxiety disorder, the fear or avoidance should not be related to any co-existing psychiatric or general medical conditions (eg fear of trembling in Parkinson's disease, or fear of exhibiting abnormal eating behaviour in anorexia nervosa or bulimia nervosa).

Differences between ICD-10 and DSM-IV criteria

There are essential differences between ICD-10 and DSM-IV which account for some of the reported variation in the prevalence rates of social anxiety disorder. In ICD-10, fear of being scrutinised in small groups but not in crowds is recognised as social phobia, whereas the DSM-IV criteria for social anxiety disorder do not make the distinction. ICD-10 specifies that the patient may experience blushing, shaking, fear of vomiting, or fear of urinary incontinence in a social situation and that these symptoms may progress to a panic attack. DSM-IV merely states that anxiety may take the form of a panic attack. ICD-10 suggests that if the distinction between social phobia and agoraphobia is difficult, precedence should be given to agoraphobia, whereas DSM-IV differentiates between the two conditions on the basis of fear of social situations.

Mini International Neuropsychiatric Interview (MINI)

The MINI is a fast and accurate screening tool which assesses individuals for the presence of psychiatric disorders (DSM criteria).[31] The MINI poses four initial screening questions for social anxiety disorder; a diagnosis is rejected when one or more of these are answered negatively. If the diagnosis is accepted, then the patient is questioned further about specific symptoms of the disorder. The MINI does not explore severity, disability, or physically explained problems symptom by symptom. Also, it gives priority to the identification of current, rather than lifetime disorders. As a result, the time taken to train interviewers and to administer the interview is shorter than with the SCID (approximately 20 min for the full MINI versus 80 min for the SCID).

Social Phobia Inventory (SPIN)

The Social Phobia Inventory (SPIN) is a relatively new scale which specifically assesses the spectrum of fear, avoidance, and physiological symptoms of social anxiety.[32] It is a useful

screening tool for social anxiety disorder which also allows a measurement of the severity of the disorder. Patients complete a questionnaire with 17 items, rating on a five-point scale (0=not at all, 4=extremely) how much their symptoms have bothered them during the past week. Preliminary research with this instrument indicates that a cut-off total score of 19 distinguishes between subjects with and without social anxiety disorder.

Rating scales

There are three principal domains in which improvement in social anxiety disorder should be assessed during treatment studies: overall improvement and severity of illness, symptoms, and disability. A combination of rating scales is required because no single instrument can measure improvement across the three domains. The most widely applied rating scales for assessing social anxiety disorder are the Clinical Global Impression (CGI) Scale Global Improvement and Severity of Illness items,[33] for rating overall improvement and severity of the disease; the Liebowitz Social Anxiety Scale (LSAS),[34] for measurement of symptoms; and the Sheehan Disability Scale (SDS),[35] for assessment of associated functional disability.

Clinical Global Impression (CGI) Scale

Two components of the Clinical Global Impression (CGI) scale,[33] the Global Improvement and Severity of Illness items, have been extensively used to measure overall improvements with treatment and severity of illness in psychopharmacological trials since their introduction in 1976. Clinicians use the CGI Global Improvement item to indicate total improvement or worsening following treatment on a 7-point scale. Patients are generally considered to have responded to treatment when a score of 1 (very much improved) or 2 (much improved) is achieved. The CGI Severity of Illness item is also assessed on a 7-point scale and the change from baseline in CGI Severity of Illness score is recorded as a measure of improvement.

Liebowitz Social Anxiety Scale (LSAS)

The Liebowitz Social Anxiety Scale (LSAS)[34] can be completed by the clinician or self-rated by the patient. It was designed specifically for the assessment of the clinical severity of social anxiety symptoms and is the most widely applied rating scale for the disorder. The LSAS comprises 24 items and rates 13 performance and 11 social interaction situations separately on subscales for fear / anxiety (0-3; none, mild, moderate, and severe) and avoidance (0-3; never, occasionally, often, and usually). Changes in the overall total score (range 0-144) and individual subscale scores for fear / anxiety and avoidance (each range 0-72) are common outcome measures in pharmacotherapy efficacy studies.

Social Avoidance and Distress Scale (SADS)

The Social Avoidance and Distress Scale (SADS) is a 28-item true-or-false scale which is rated by the patient.[36] It was originally developed to assess the levels of anxiety and avoidance in a college student population. While it was not specifically designed for social anxiety disorder and cannot differentiate this condition from other anxiety disorders, the SADS has since become one of the more widely used rating scales, both in clinics and during treatment studies, for assessing improvements in symptoms in patients with social anxiety disorder.

Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS) measures disability and has been used extensively in trials across a range of psychiatric indications. It is reliable and useful tool in these patients.[35] It comprises three items: work, social life, and family life. Patients are asked to indicate how much aspects of their life are impaired by their social anxiety disorder on a scale of 0-10 (0=not at all, 10=very severely); common analyses are changes in score overall and for each subscale.

Social anxiety disorder / social phobia: treatment options

Treatment goals

The significant burden of social anxiety disorder on sufferers and the tendency for patients to become depressed or dependent on alcohol as a means of coping with their symptoms are pressing reasons for early and effective treatment. Social anxiety disorder is currently under-treated, with only one-quarter of patients receiving therapy.[37] Also, it has been suggested that when treatment is offered to these patients, it is often inappropriate.[38] An effective treatment for the condition needs to control both anxiety and avoidance symptoms while also reducing associated disability. Ideally, the treatment should also treat the most common comorbid disorders which occur in these patients (eg depression). Because social anxiety disorder is a chronic disorder, the treatment should be effective in the long term.

Ineffective treatments

Beta-blockers are often used by musicians and other professional performers to help with normal performance anxiety,[39] but a small number of controlled trials have shown that they are not helpful for the pathological anxiety of social anxiety disorder.[40-42] Similarly, there is no evidence that the azaspirone anxiolytic, buspirone, has a beneficial effect in patients with social anxiety disorder.[43] Also, in contrast to the efficacy of some tricyclic antidepressants (TCAs) in panic disorder, there are no controlled data for the efficacy of TCAs in social anxiety disorder. A recent open study in 15 patients with social anxiety disorder showed imipramine to be ineffective in the treatment of this condition.[44]

Treatment options

A number of treatment approaches have been shown to benefit patients with social anxiety disorder. Although both the irreversible and reversible monoamine oxidase inhibitors (MAOIs) and high potency benzodiazepines have shown promise, SSRIs appear to be the best first-line option for the treatment of social anxiety disorder. Cognitive behavioural therapy (CBT) can also be an effective part of management in these patients.

Monoamine oxidase inhibitors (MAOIs)

The earliest placebo-controlled evidence for the efficacy of MAOIs was obtained with the irreversible inhibitor, phenelzine,[40,45,46] but concerns about its tolerability and safety make it an inappropriate choice of first-line therapy for social anxiety disorder. Promising results were obtained in clinical trials of brofaromine, a reversible MAOI,[47-49] but this agent is no longer marketed. Placebo-controlled studies with another reversible inhibitor, moclobemide, have proved disappointing overall, with a much smaller treatment effect than that observed in Seroxat/Paxil studies.[50-52]

Benzodiazepines

There are limited, but well-controlled data for the efficacy of clonazepam in social anxiety disorder,[53,54] but the only controlled trial of alprazolam suggests that it is significantly less effective in this condition than clonazepam.[45] There is no evidence that benzodiazepines, as a class, are effective in social anxiety disorder. Furthermore, there is concern about using a class of compounds which are associated with dependency in the long term, in a group of patients who are already at an increased risk of substance and alcohol abuse.[55]

Selective serotonin reuptake inhibitors (SSRIs)

Most of the data which support the efficacy of the SSRIs in social anxiety disorder come from large placebo-controlled studies with Seroxat/Paxil.[56] Smaller studies with other SSRIs[57-59] have also reported positive results. The consistent positive outcome with SSRIs in social anxiety disorder provides support for the use of these agents for first-line therapy in patients with social anxiety disorder. To date, however, Seroxat/Paxil is the only SSRI to have demonstrated efficacy in social anxiety disorder in large, placebo-controlled studies.

Cognitive behavioural therapy (CBT)

One of the goals of cognitive behavioural therapy (CBT) is to encourage patients to confront their anxiety. Group therapy sessions are particularly appropriate to the treatment of social anxiety disorder, and Cognitive Behavioural Group Therapy has been the most studied approach in patients with this disorder, although much of the evidence for its efficacy, so far, has been gained in small trials.[60,61] The benefits of CBT are clear - efficacy in the long term and few side effects - but the approach does not work for all patients. Furthermore, CBT can be hard to perform, time-consuming, and costly. At present the availability of sophisticated psychological therapies such as CBT and Cognitive Behavioural Group Therapy varies greatly between one country and another. While in some countries CBT is easily accessible and sometimes free of charge, in others access to this type of therapy is very restricted and / or very expensive. However, it appears that sometimes pharmacotherapy may be needed to facilitate effective CBT. As for pharmacotherapy, CBT is not effective for every patient, but sometimes the two combine well to provide effective treatment for the patient.

Clinical efficacy studies with Seroxat/Paxil

Seroxat/Paxil clinical study overview

The clinical programme to register Seroxat/Paxil for social anxiety disorder consisted of three short-term studies and one long-term extension study. Study 454 was a 12-week, dose-range finding investigation; two flexible-dose studies with the same design (studies 502 and 382) assessed the efficacy of treatment over 12 weeks; and study 470 was a 40-week, long-term extension of study 382. In all, 861 patients (aged 18 years or older) with a primary diagnosis of social anxiety disorder (DSM-IV) were recruited at centres in North America, Europe, and South Africa. Patients were excluded from the studies if they had a primary diagnosis of an Axis I disorder, including major depression, dysthymia, simple phobia, obsessive compulsive disorder (OCD) and panic disorder, within the past 6 months. In addition, studies 454 and 502 excluded patients with a baseline score of 15 or more on the 17-item Hamilton Depression Rating Scale to ensure that the effect of Seroxat/Paxil on social anxiety disorder was not attributable to its antidepressant activity.

Patient demographics

Across the studies, the patients in the Seroxat/Paxil and placebo groups were well balanced in terms of age, gender and race. The same pattern was seen in the individual studies (not shown). The mean age of patients across the studies was 36.5 years (range 18-85 years). The wide age range of patients underlines the chronic, unremitting, lifelong course of social anxiety disorder. The mean age of the population in these studies underlines that patients take a long time to present to their doctors and is consistent with data from other studies.

Efficacy measures

The rating scales used during these studies were all well established and accepted. The primary efficacy variables were the percentage of responders based on a CGI Global Improvement score of 1 or 2 ('very much improved' or 'much improved'), and the mean change from baseline in LSAS total score. The secondary efficacy variables for these studies were the mean change from baseline in the SADS total score, the LSAS fear/anxiety and avoidance subscales, and the SDS work, social life, and family life subscales. In addition, studies 454 and 502 used the mean change from baseline in the CGI Severity-of-Illness score as a secondary efficacy variable.

Dose-ranging study 454

Dose-ranging study 454: study design

The appropriate dosage for Seroxat/Paxil in social anxiety disorder was assessed in a 12-week, double-blind study conducted at centres in Canada and the USA. A total of 384 patients were randomised to receive either fixed doses of Seroxat/Paxil (20, 40 or 60 mg/day) or placebo. All patients on Seroxat/Paxil received 20 mg/day for the first week. For patients in the higher dose groups, the dose was increased in 20-mg/day increments in the second and third week to 40 and 60 mg/day.

Dose-ranging study 454: LSAS total score

In all three groups treated with Seroxat/Paxil there was a continuous improvement in symptoms of social anxiety disorder, as shown by decreasing LSAS total symptom scores. Seroxat/Paxil at each dosage level produced significant ($p<0.05$) reductions in LSAS symptom scores compared with placebo at weeks 8 and 12. The results presented here use unadjusted pairwise comparisons between each dosage group and placebo. The results were similar when Dunnett's correction for multiple comparisons was applied (the adjusted level of significance was $p<0.019$). When the paroxetine dosage groups were combined in a post-hoc analysis, the reduction in LSAS total score at endpoint was significantly improved compared to the placebo group ($p=0.001$), providing further evidence of paroxetine's efficacy.

Dose-ranging study 454: LSAS subscale scores (week 12)

Seroxat/Paxil improved both the avoidance and anticipatory anxiety symptoms of social anxiety disorder, as demonstrated by the results of the LSAS fear / anxiety and avoidance subscales. All three dosage groups had a greater positive effect on each symptom type than placebo. By the end of the study, Seroxat/Paxil at all three dosage levels reduced social avoidance and anxiety symptoms significantly more than placebo on the LSAS fear / anxiety and avoidance subscales ($p<0.05$, unadjusted pairwise comparisons), in addition to

the overall LSAS total score. Patients treated with Seroxat/Paxil 40 or 60 mg/day experienced no more treatment benefits than those receiving 20 mg/day.

Dose-ranging study 454: CGI Global Improvement (% responders)

The CGI Global Improvement scale is a measure of the clinician's global impression of the overall improvement in the patient's condition. At the end of the study, the response rate to Seroxat/Paxil 20, 40, and 60 mg/day was almost twice that of placebo (45%, 47% and 43% versus 28%, respectively); the difference from placebo was statistically significant for all three dosage groups ($p<0.05$, unadjusted pairwise comparisons). There was no advantage, in terms of benefits of treatment with Seroxat/Paxil, in increasing the dose from 20 to 40 or 60 mg/day.

Dose-ranging study 454: CGI Global Improvement (week 12)

By the end of the study, almost three times as many patients treated with Seroxat/Paxil (20, 40 and 60 mg/day) than placebo were 'very much improved' on the CGI Global Improvement scale (19%, 21%, 22% versus 8%, respectively). When the paroxetine dosage groups were combined, a post-hoc analysis showed that the proportion of responders to treatment was significantly greater than that in the placebo group ($p=0.006$), providing further evidence of paroxetine's efficacy.

Dose-ranging study 454: SADS score

The positive effect of Seroxat/Paxil on the symptoms of social anxiety disorder was also shown using the SADS. By week 4, the reduction in SADS score was numerically greater in all groups treated with Seroxat/Paxil than with placebo. The advantage was maintained throughout the study and at week 8 and week 12, the difference from placebo was statistically significant for each dosage group ($p<0.05$, unadjusted pairwise comparisons).

Dose-ranging study 454: CGI Severity of Illness

At the start of the study, all patients were moderately to markedly ill, according to the CGI Severity-of-Illness item. After 12 weeks' treatment with Seroxat/Paxil, the Severity of Illness scores had decreased in all active treatment groups and more Seroxat/Paxil than placebo patients were assessed as normal, borderline mentally ill, or mildly ill. Overall, the CGI Severity of Illness scores improved for patients treated with Seroxat/Paxil, but were either unchanged or deteriorated for patients on placebo (not shown on slide).

Dose-ranging study 454: SDS scores (baseline and week 12)

As the symptoms of social anxiety disorder improved during treatment with Seroxat/Paxil, there was a corresponding improvement in disability. At all three doses, treatment with Seroxat/Paxil produced greater improvements than placebo in the disability experienced by sufferers in their work, social and family lives, as shown by changes on the SDS subscales.

Dose-ranging study 454: conclusions

Seroxat/Paxil is effective in the treatment of social anxiety disorder producing clinical improvements in symptoms and disability. Seroxat/Paxil 20 mg/day was statistically significantly superior to placebo as measured by both primary outcome measures (LSAS and CGI Global Improvement) in addition to a number of secondary outcome measures (CGI Severity of Illness, SADS, and SDS social life item). These data support

Seroxat/Paxil 20 mg/day as an effective dose for the treatment of patients with social anxiety disorder.

Short-term efficacy studies 502 and 382: study design

Studies 502 and 382 were 12-week, flexible-dose studies comparing Seroxat/Paxil (20-50 mg/day) and placebo. Study 502 was conducted at centres in Europe and South Africa, while study 382 was conducted in the USA and Canada. The diagnosis of social anxiety disorder (DSM-IV) was made following a full psychiatric interview. This was confirmed using either the MINI (study 502) or a modified version of the SCID (study 382), depending on clinical practice in the region where the study was performed. Patients on Seroxat/Paxil were initially treated with 20 mg/day for 2 weeks. The dose could then be increased, as necessary, by 10 mg/day each week to a maximum of 50 mg/day.

Short-term efficacy study 502

Short-term efficacy study 502: LSAS total score

Seroxat/Paxil produced a marked improvement in the symptoms of social anxiety compared with placebo, as shown by the progressive decrease in LSAS total score. The difference was significant from week 4 onwards. Seroxat/Paxil was similarly effective in improving fear / anxiety and avoidance behaviour, as assessed by the decrease in LSAS scores on both LSAS subscales (fear / anxiety and avoidance) [see **Short-term efficacy study 502: LSAS scores (week 12)**].

Short-term efficacy study 502: LSAS scores (week 12)

The symptoms of both fear / anxiety and avoidance were improved in sufferers with social anxiety disorder after 12 weeks' treatment with Seroxat/Paxil, as assessed by the fear / anxiety and avoidance subscales of the LSAS. The improvement observed on both subscales in patients on Seroxat/Paxil was significantly greater than that seen in patients receiving placebo.

Short-term efficacy study 502: CGI Global Improvement (% responders)

As the symptoms of social anxiety improved during the study, there was a corresponding improvement in the percentage of responders on the CGI Global Improvement scale. Patients improved more rapidly and to a greater extent with Seroxat/Paxil than with placebo; the difference was significant from week 4 onwards.

Short-term efficacy study 502: CGI Global Improvement (week 12)

At the end of the study, three times as many patients receiving Seroxat/Paxil as placebo (26% versus 9%), were reported to be 'very much improved' on the CGI Global Improvement scale. Almost twice as many patients treated with Seroxat/Paxil than placebo had a response of 'much improved' (39% versus 23%, respectively).

Short-term efficacy study 502: SADS score

In line with the improvements in symptoms observed using the LSAS, Seroxat/Paxil produced a more rapid and greater improvement in SADS symptom score than placebo. The difference in SADS score between the two groups was significant from week 4

onwards demonstrating the beneficial effect of Seroxat/Paxil on social anxiety symptoms in these patients.

Short-term efficacy study 502: CGI Severity of Illness

During the course of the study, the severity of social anxiety disorder (classified using the CGI Severity of Illness item) decreased more rapidly and to a greater extent in patients receiving Seroxat/Paxil than patients receiving placebo. The difference between the two treatment groups was significant from week 4 onwards. Analysis of individual patient scores (not shown on slide) showed that, while the severity of illness in patients taking Seroxat/Paxil tended to improve, the severity of social anxiety disorder in patients on placebo tended to remain unchanged or deteriorate.

Short-term efficacy study 502: SDS scores (baseline and week 12)

The effect of Seroxat/Paxil on social anxiety-related disability was demonstrated using the SDS work, social life, and family life items. At the end of the study, Seroxat/Paxil had produced significantly greater improvements than placebo on all three items indicating its efficacy in improving the disability to the work, social and family lives of these patients.

Short-term efficacy study 382

Short-term efficacy study 382: LSAS total score

Seroxat/Paxil produced significant improvements in symptoms in patients with social anxiety disorder compared with placebo from week 2 onwards, as measured by the decrease in LSAS total score.

Short-term efficacy study 382: LSAS scores (week 12)

The results of the fear / anxiety and avoidance subscales of the LSAS were in line with the pattern observed for the LSAS total score. By the end of the study, the results from the LSAS subscales demonstrated that the fear / anxiety and avoidance experienced by sufferers with social anxiety disorder had been significantly reduced in patients receiving Seroxat/Paxil compared with those taking placebo.

Short-term efficacy study 382: CGI Global Improvement (% responders)

The proportion of patients responding to treatment on the CGI Global Improvement item throughout the 12-week study showed that Seroxat/Paxil was superior to placebo from week 2 onwards. The difference between Seroxat/Paxil and placebo reached statistical significance by week 4 and this was maintained during the rest of the study. At the end of the study, more than twice as many patients had responded to treatment with Seroxat/Paxil than to placebo (55% versus 24%, respectively).

Short-term efficacy study 382: CGI Global Improvement (week 12)

At the end of the study, approximately three times as many patients on Seroxat/Paxil as placebo were classed as 'very much improved' on the CGI Global Improvement item (26% versus 9%, respectively). Twice as many patients in the Seroxat/Paxil group had a response of 'much improved' (29% versus 15%). In contrast, more patients on placebo were only 'minimally improved', or their well-being was unchanged.

Short-term efficacy study 382: CGI Global Improvement (% responders at endpoint by LSAS total score at baseline)

In addition to the efficacy results in the overall study population, the proportion of patients with moderate or severe social anxiety disorder who responded to treatment on the CGI Global Improvement item was evaluated. These results showed that Seroxat/Paxil is equally effective in the treatment of those patients with both moderate and severe levels of social anxiety disorder (classified according to LSAS total score at baseline).

Short-term efficacy study 382: SADS score

The improvement in social anxiety symptoms during treatment with Seroxat/Paxil was confirmed by a concurrent reduction in SADS score over 12 weeks. The improvement in symptoms was greater in the Seroxat/Paxil group than in the placebo group, and from the second week of the study onwards, this difference was statistically significant.

Short-term efficacy study 382: SDS scores (week 12)

As the symptoms of patients with social anxiety disorder improved during the course of the study, the disability experienced by these patients also decreased. At the end of the study, patients taking Seroxat/Paxil reported a lower level of disability to their work, social, and family lives on the SDS, compared with patients on placebo. For the work and social life items, the difference between Seroxat/Paxil and placebo was statistically significant.

Short-term efficacy: summary of studies 454, 502, and 382

Short-term studies: response rates with Seroxat/Paxil (week 12)

There was a higher response rate to Seroxat/Paxil than to placebo in all three short-term studies, as shown by the proportion of patients who were 'very much improved' or 'much improved' on the CGI Global Improvement item. In all instances, the difference between the two groups was significant.

Short-term studies: improvements in disability (week 12)

Seroxat/Paxil improved the level of disability in the work, social, and family lives of sufferers, as indicated by the results of the SDS. It is well documented that the symptoms of social anxiety disorder cause considerable problems in functionality for patients; the effect of Seroxat/Paxil on the burden of disability should lead to an improved quality of life for these patients.

Short-term flexible-dose efficacy studies 502 and 382: maximum total daily dose of Seroxat/Paxil

In both of the short-term flexible dose studies, a higher proportion of patients receiving Seroxat/Paxil remained on the lowest dose level (20 mg/day) while a higher proportion of patients receiving placebo were titrated to higher dose levels.

Recommended dose of Seroxat/Paxil in social anxiety disorder / social phobia

The recommended dose and effective dose range for Seroxat/Paxil in social anxiety disorder were determined from the results of the dose-finding study (study 454) and the two short-term, flexible-dose efficacy studies (studies 502 and 382). The recommended

starting dose for the treatment of patients with social anxiety disorder is 20 mg/day. Some patients who do not respond to this dose may benefit from having the dose increased in 10-mg/day increments, up to a maximum of 50 mg/day. Data from the dose-finding study did not suggest an advantage in increasing the dose to 60 mg/day.

Short-term efficacy studies: conclusions

Seroxat/Paxil (20-50 mg/day) is an effective, well-tolerated treatment for social anxiety disorder. Not only does Seroxat/Paxil improve the disabling symptoms of the disorder, but it also leads to concomitant improvements in work, social, and family life activities.

Long-term efficacy study (study 470)

Long-term efficacy study: study design

The long-term study (study 470) was designed to assess whether the benefit of treatment with Seroxat/Paxil seen in the short-term studies was maintained with continued treatment. Irrespective of whether they had been treated with Seroxat/Paxil or placebo during the short-term study, all patients were given Seroxat/Paxil (20-50 mg/day) for 24 weeks (open-label phase). At the end of this phase, patients were re-randomised to treatment with Seroxat/Paxil or placebo for 16 weeks (double-blind phase). The double-blind phase of the study was designed to assess prevention of relapse, which was defined as a score of greater than 2 on the CGI Global Improvement item on two consecutive study visits.

Long-term efficacy study: LSAS, SADS and SDS scores (open-label phase)

Patients who participated in study 382 formed two populations; those treated with Seroxat/Paxil and those treated with placebo. The subgroup of patients with social anxiety disorder who had received Seroxat/Paxil during study 382 experienced continued improvement in the symptoms of the disorder during the 24-week extension, as measured by further decreases in their LSAS and SADS scores. Furthermore, the resultant disability of the disorder on the personal and professional lives of this subgroup of patients progressively improved, as demonstrated by SDS work, social life, and family life items.

Long-term efficacy study: results from the double-blind phase

Only half the required number of patients entered the double-blind phase of study 470 (55 patients as opposed to the required 98). This precludes any firm statistically based conclusions being drawn on relapse rates.

Long-term efficacy study: LSAS, SADS, and SDS scores (double-blind phase)

During double-blind treatment for a further 16 weeks, LSAS, SADS, and SDS scores all demonstrated a greater deterioration in the placebo group than the group continuing paroxetine treatment. The detrimental changes in SADS total score and SDS work and family life items over the double-blind phase were statistically significantly greater in the placebo group than in the paroxetine group.

Long-term efficacy study: conclusions

Continued treatment with Seroxat/Paxil for up to 1 year maintained the improvement in symptoms and disability associated with social anxiety disorder observed during the short-term treatment studies. The benefit of treatment with Seroxat/Paxil for up to 6 months

has also been shown in a study by Stein[18] in patients with generalised social anxiety disorder. Seroxat/Paxil also has sustained long-term effects in the treatment of depression, panic disorder, and OCD.[62,63]

Tolerability of Seroxat/Paxil

Adverse experiences in short-term studies

The tolerability of treatment with Seroxat/Paxil in social anxiety disorder was assessed in the 522 patients who took part in the three short-term studies. This was a total exposure to Seroxat/Paxil of 106.9 patient-years. A similar proportion of patients treated with Seroxat/Paxil or placebo reported adverse experiences (84% versus 72%). The most common side effects reported were abnormal ejaculation, nausea, somnolence, insomnia, asthenia and headache. It should be noted that the majority of the reports of abnormal ejaculation came from study 454. In this study, a relationship to dose was apparent with more reports occurring at the 60 mg dose level. The adverse event profile seen in the social anxiety disorder studies was similar to that seen in for Seroxat/Paxil in patients with depression, panic disorder, and OCD. No new side effects were noted.

Severity of adverse experiences in short-term studies

Most of the adverse experiences were mild-to-moderate in severity. The number of severe adverse experiences was low in both the Seroxat/Paxil and placebo groups (9.3% and 6.4%). Importantly, the adverse experiences which had been reported most commonly for Seroxat/Paxil (eg abnormal ejaculation and nausea) were mostly mild-to-moderate in severity (78% and 92%, respectively), and led to few patients stopping therapy (with withdrawals due to abnormal ejaculation and nausea being 4.9% and 4.0%, respectively).

Adverse experiences during the long-term study (open-label phase)

The most common adverse events reported in the open-label phase of study 470 were similar to those reported in short-term studies; headache, abnormal ejaculation, somnolence, and asthenia. The long-term safety of treatment with Seroxat/Paxil has already been shown during studies in patients with depression, panic disorder, and OCD.

Tolerability of Seroxat/Paxil: conclusions

The overall side-effect profile in patients with social anxiety disorder treated with Seroxat/Paxil was the same as that seen in patients with depression, panic disorder, and OCD, treated with Seroxat/Paxil. No new adverse experiences were noted and the majority of side effects were of mild-to-moderate severity.

Summary of Seroxat/Paxil in social anxiety disorder / social phobia

Overall conclusions

Seroxat/Paxil is an effective and well-tolerated treatment for patients with social anxiety disorder. The recommended starting dose is 20 mg/day. Some patients may benefit from increasing their dose in increments of 10 mg/day to a maximum of 50 mg/day. However, there appears to be no additional benefit to increasing the dose greater than 50 mg/day. The benefit in treatment with Seroxat/Paxil is maintained when treatment is continued in the long term for up to one year.

Overall conclusions

Seroxat/Paxil was well tolerated in patients with social anxiety disorder in both short- and long-term studies. The side effects reported by patients were characteristic of the effects of Seroxat/Paxil which have already been observed in extensive safety and tolerability studies in patients with depression, panic disorder, and OCD. Seroxat/Paxil is an established treatment for depression, panic disorder, and OCD. These conditions - depression in particular - are commonly comorbid in patients with social anxiety disorder. Seroxat/Paxil is, therefore, a good first-line choice for monotherapy in patients with social anxiety disorder.

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