ECNP Consensus Meeting, March 2003. Guidelines for the investigation of efficacy in social anxiety disorder

S.A. Montgomery*, Y. Lecrubier, D.S. Baldwin, S. Kasper, M. Lader,
R. Nil, D. Stein, J.M. van Ree

P.O. Box 8751, London W13 8WH, UK

1. Introduction

The guidelines on the investigation of the efficacy of treatments in social anxiety disorder (SAD), also known as social phobia, presented in this paper are the outcome of a consensus meeting of experts on the disorder held under the auspices of the European College of Neuropsychopharmacology in Nice in March 2003. The guidelines address pharmacological treatments but the same general principles apply to non-pharmacological treatments.

1.1. Prevalence and burden of SAD

SAD is a disorder characterised by persistent and excessive fear of social or performance situations where embarrassment or humiliation may occur. There should be no confusion between this condition and mere shyness. Sufferers with SAD avoid the feared situations or endure them only with anxiety and distress.

SAD is a common disorder, generally estimated to have a lifetime prevalence of 6–8%. The high prevalence makes SAD the third most common psychiatric disorder after major depression and alcohol dependence (Magee et al., 1996; Weiller et al., 1996) The disorder has an early age of onset, reported as around 15 years of age, and a particularly prolonged duration of the disorder prior to treatment is reported both in epidemiological studies and in treatment studies. The prevalence of SAD tends to decline in the elderly.

The nature of the disorder is chronic and unremitting and this results in a high cumulative disability level. Disability associated with SAD is estimated to be as great as that observed in major depression (Sheehan et al., 1996). It has been estimated that sufferers with generalised social anxiety have a fourfold increased disability compared with the general population (Wittchen and Beloch, 1996).

The early onset of SAD has the effect of interfering with the normal acquisition of social and educational skills at a critical period of adolescence. Those with SAD have a lower educational achievement and the time spent in education is reduced by 2–3 years (Davidson et al., 1994; Wittchen and Beloch, 1996). Interference with educational opportunities is consistently rated by sufferers as an important source of disability but social disability inherent in the disorder must also be recognised. It is no surprise that this early impediment is reflected through life with higher levels of unemployment, poor work performance, high absenteeism, lower than expected income, and financial dependency on support from the state (Davidson et al., 1993b; Lecrubier et al., 2000; Schneier et al., 1994; Wittchen and Beloch, 1996).

The avoidance of social interaction, which is an essential part of social anxiety leads to social isolation, and higher than expected rates of single, divorced, or separated people are observed in the SAD population(Wittchen and Beloch, 1996). The social and functional impairment is reflected in a substantial reduction in the quality of life. Poor quality of life is made even worse by an apparent increase in comorbid physical illness, a complication which is increased further when concomitant psychiatric comorbidity is present.

Much of the considerable psychiatric comorbidity reported in SAD is secondary to the social anxiety. Many sufferers try to cope by using alcohol or illicit drugs in attempts to control the symptoms by self-treatment (Lecrubier et al., 2000) and there is a consequent increased risk of the development of alcohol or substance abuse (Lecrubier

* Corresponding author.
E-mail address: stuart@samontgomery.co.uk (S.A. Montgomery).

and Weiller, 1997; Schneier et al., 1989). Secondary comorbid depression is common (Wittchen and Essau, 1989) and is estimated as 45% in community populations rising to 60–70% in clinical studies (Lepine and Lellouch, 1995; Van Ameringen et al., 1991). The risk of suicidality is also increased, even in the uncomplicated disorder, and the risk increases further when the complications of depression or alcoholism supervene (Lepine and Lellouch, 1995; Katzelnick et al., 2001).

1.2. Neurobiology of SAD

There appears to be a threefold increased risk of developing the disorder compared to the normal population if a relative has SAD (Merinkangas and Angst, 1995; Reich and Yates, 1988). Twin studies have established an increased risk of SAD in monozygotic twins which indicates that there is an underlying genetic component to the disorder (Kendler and Kessler, 1992; Kendler et al., 1993). Studies investigating the neurobiological associations of SAD have been undertaken more frequently in recent years focusing mainly on the serotonin and dopamine system but the results have been partly inconsistent (Stein et al., 2002c). MRI studies in SAD indicate abnormalities in signal to noise ratio in subcortical thalamic and caudate areas and a reduction of putamen volume with age (Davidson et al., 1993a; Furmark et al., 2002).

2. Current pharmacological treatment

There is evidence that cognitive behavioural treatments are effective in SAD and many clinicians believe that optimum treatment is achieved by a combination of pharmacological and psychological treatment. These guidelines are concerned with pharmacological treatment.

There is evidence of efficacy in SAD from placebo-controlled studies for a limited range of treatments and licences for only three medications have so far been granted in Europe for the treatment of the disorder. Demonstration of efficacy may be assumed on the basis of two or more positive placebo-controlled studies. The SSRIs, paroxetine (Allgulander, 1999; Baldwin et al., 1999; Liebowitz et al., 2002; Stein et al., 1999b), sertraline (Walker et al., 2000; Van Ameringen et al., 2001), escitalopram (Montgomery et al., 2003) and fluvoxamine (van Vliet et al., 1994; Stein et al., 1999a), have been shown to be effective. The SNRI venlafaxine, the RIMA moclobemide, and the MAOI phenelzine also have two or more positive placebo-controlled studies to their credit (Katschnig et al., 1997; Liebowitz et al., 1992; Schneier et al., 1998; Versiani et al., 1992). In Europe thus far only paroxetine, escitalopram and moclobemide have been licensed and in the USA paroxetine, sertraline and venlafaxine.

High-potency benzodiazepines, e.g. clonazepam, given in high doses show some evidence of efficacy (Connor et al., 1998; Davidson et al., 1991, 1993c; Versiani et al., 1997a), albeit with high levels of relapse within 2 weeks of discontinuation reported in some studies, though not in others. The results with alprazolam were disappointing as this drug failed to separate from placebo in a study where phenelzine was found to be effective (Gelernter et al., 1991).

Some preliminary data from open studies suggest that clomipramine may be effective but it is difficult to draw conclusions on the efficacy of tricyclic antidepressants in SAD in view of the absence of definitive studies. Data from single placebo-controlled studies indicate that the efficacy of the 5-HT antagonist odansetron and compounds such as gabapentin or pregabalin, which may exert a modulatory effect on neurotransmitter release, may be worth further investigation in the treatment of SAD (Van Ameringen and Mancini, 2001).

3. Population

3.1. Diagnosis

The studies that have demonstrated the efficacy of pharmacological treatments in SAD have investigated patients suffering from social phobia or SAD defined by diagnostic criteria according to the DSMIIIR or IV (American Psychiatric Association, 1987, 1994).

In DSMIV the essential feature is a marked and persistent fear, recognised as excessive, in social or performance situations in which humiliation or embarrassment may occur and where exposure almost invariably provokes an immediate anxiety response. The feared situations are avoided or suffered with intense anxiety or distress. In order to reach criteria for SAD there must be significant interference with occupational or social function or marked distress.

The ICD10 (World Health Organisation, 1992) criteria may also be able to define a treatment responsive population since there is reasonably close agreement between these criteria and DSMIV. However, there is no real experience with the ICD10 and applicability of the criteria for clinical trials remains to be established. The ICD10 diagnostic requirements for SAD lack a criterion of functional impairment and, if the ICD10 is used in efficacy studies, a separate evaluation of function would be required to quantify the initial severity. The assay sensitivity of a population defined by the ICD10 criteria has still to be demonstrated.

It would be sensible to document the diagnosis with the possible help of a structured or semi-structured interview. In some positive studies a structured interview has been used to confirm the diagnosis (Baldwin et al., 1999; Stein et al., 1999b; Van Ameringen et al., 2001) but in others not. There are no data on the relative sensitivity of the studies that used or did not use a structured or semi-structured interview so that a recommendation is not possible.

Some confusion has arisen from the overlap between the definitions of SAD and avoidant personality disorder in the

DSMIV. The definition of avoidant personality disorder in DSMIV uses SAD illness descriptors. The use of illness criteria to define a personality disorder may be misleading. Some studies have shown that the criteria for avoidant personality disorder may resolve with treatment, showing a similar response to SAD itself (Oosterbaan et al., 2002). The avoidant personality disorder diagnosis based on DSMIV may be misleading in studies in SAD.

DSMIV is the recommended diagnostic criterion because it has been widely used in SAD. It should be possible to use other internationally recognised diagnostic criteria; however, a criterion of loss of function should be included in order to identify the disorder of social phobia, which is associated with disability.

3.2. Generalised or non-generalised SAD

SAD may be generalised, where the individual suffers multiple fears and social avoidance, or non-generalised, where the range of situations is restricted. SAD must not be confused with specific or simple phobia where there is marked and persistent fear of a specific object or situation such as flying, heights, etc.

A clearer response to pharmacological treatment has been reported in the more pervasive generalised form of the disorder which affects larger areas of the individual's life and may, therefore, lead to greater dysfunction. There are also indications that the severity score on disease specific severity scales at entry to the studies is higher in generalised SAD than non-generalised patients. There are data showing that non-generalised social phobia responds to pharmacological treatment though it may be more difficult to show a drug placebo difference in this group.

The generalised form affects about half the SAD population and this group has been the target for treatment in some studies which have used a definition of having fear and anxiety in at least four different social situations (Liebowitz et al., 2002). The evidence from a number of studies suggests that the generalised form of the disorder identify more clearly a significant drug placebo difference compared to the non-generalised SAD.

If an effect is shown in generalised social phobia a generalised labelling for social phobia would be appropriate. Studies in a single social situation such as performance anxiety do not necessarily imply an effect in the more generalised version of the disorder.

It is recommended that studies investigating efficacy should concentrate on generalised SAD with symptoms of avoidance in at least four distinct social situations.

3.3. Severity

The available data from subanalyses of efficacy in different categories indicate that in SAD, as in other psychiatric disorders, there is a larger drug placebo difference in the more severe compared with the less severe subgroup (Montgomery, 1998). This suggests that the severe and moderate subgroups respond to treatment and that the benefit is more clearcut in the more severe subgroup. The efficacy of treatments in the mild subgroup has not yet been clearly established. It is, therefore, appropriate to require a minimum severity on entry to the study in order to identify a treatment sensitive population. A variety of severity scores have been used to define the initial minimum entry score. For example, scores of 50, 60 and 70 on the LSAS at entry to a study have all been used successfully to define a population in whom drug placebo differences can be demonstrated, with a score of 70 appearing to be the most widely used and validated.

On the basis of these data a minimum entry score of at least 70 on the LSAS or the equivalent on other scales is advisable.

The presence or absence of generalised SAD will affect the LSAS scores since the scale gives higher scores to those who have fears and anxiety or avoidance in multiple distinct situations. For practical purposes, those with a score of 70 or more on the LSAS would almost inevitably have generalised SAD.

3.4. Stability of SAD

The mean duration of prior illness in the pivotal placebo-controlled studies in SAD is remarkably long, ranging between approximately 15 and 20 years. Some data from subanalyses within studies suggest that patients with a longer prior duration of SAD may have a lower placebo response. The selection for studies of only those patients having long term stability in symptoms and behaviours has not been used as a formal entry criterion though in practice it may have been applied as an unpublished selection criterion in single centre studies. No recommendation can be made at the present.

3.5. Comorbidity

In studies investigating the efficacy of a treatment in a particular disorder it is usual to exclude or control the confounding variables of other comorbidities which may affect the result. For example, if a known antidepressant were being tested in SAD it would be wise to exclude comorbid major depression in order to establish a direct therapeutic effect on the uncomplicated condition rather than an effect that may be secondary to the drug's antidepressant effect. In all cases the primary diagnosis should be SAD and patients with other recent or current psychiatric diagnoses should be excluded.

In studies that include a putative or potential antidepressant, patients suffering from concomitant major depression, as well as those with a history of major depression over the previous 3–6 months, should be excluded. Some "depressive" symptoms are part of SAD. However, current depressive symptoms should nevertheless be restricted to a mild level, with a maximum permitted score on a depression

rating scale below that normally used to include patients into depression studies. The results of these studies may then be generalisable to the population with SAD without concerns of an indirect effect via depression.

Substance abuse is normally excluded from clinical trials to avoid this confounding variable and in SAD, where drugs and alcohol are commonly used as a coping mechanism and abuse becomes a secondary complication, care will be needed to exclude these patients.

It is recommended that significant comorbidity that is likely to complicate the assessment of direct efficacy in SAD be excluded. Comorbidity that is difficult to separate from SAD, for example dysthymia, should be kept to a low level wherever possible. If low levels of comorbid conditions are included these should be documented and quantified.

The primary goal of establishing efficacy in SAD leads necessarily to examining response in a group without comorbidity. The response of SAD with comorbidity is not needed to establish efficacy but nevertheless is of considerable interest. These studies in a wider population are usually carried out after efficacy is established.

4. Design of acute studies

4.1. Design

To establish the efficacy of a potential treatment for SAD the conventional double-blind placebo-controlled randomised group comparison study is recommended.

Crossover studies are difficult to interpret because of the well known carryover effects coupled with a typically slow response and a slow relapse in SAD. Crossover studies are thought to be more valid in other disorders where there is a rapid response and a rapid full relapse back to pre-treatment levels.

There is no persuasive evidence that the single blind run-in period is useful in eliminating placebo responders and some evidence that it may be counterproductive in SAD studies (Oosterbaan et al., 2002). The placebo run-in period is, therefore, not recommended.

4.2. Choice of comparator

4.2.1. Placebo

The most scientific and best-accepted evidence of efficacy comes from a direct comparison of the efficacy of a new treatment with placebo in a double blind randomised group comparison study. A placebo control is, therefore, recommended.

A variable and rising placebo response rate is reported in SAD, as it is with other psychiatric conditions, which complicates the estimations of required study size. Early single centre studies were associated with relatively low placebo responses, e.g. 8%, 12% and 23% (Liebowitz et al., 1992; Versiani et al., 1992; van Vliet et al., 1994). Placebo responses as high as 50% are seen in studies which included large numbers of patients with non-generalised SAD (Noyes et al., 1997). Placebo response in multicentre controlled studies of SSRIs varies from 23% to 41% (Stein et al., 1999a,b; Van Ameringen et al., 2001; van Vliet et al., 1994).

Attempts to control and minimise the placebo responder rate by excluding non-generalised SAD or by including only patients with a minimum defined entry score on the pivotal severity scale have been partially successful. Other methods which, have been tried include the reduction of supportive treatment during the study and limiting the number of assessment instruments, all aimed at restricting the contact time between the patient and the investigator.

4.2.2. Active control

An active comparator is sometimes included in a placebo-controlled study to give some indication that the study population is sensitive to a standard treatment. It may also be useful in discussing the clinical relevance of the response observed with the investigational treatment. The comparison of the reference compound with placebo should be secondary to the comparison of the investigational compound with placebo in order to avoid weakening the power of the study in achieving its primary objective. The size of the groups in this type of placebo-controlled study makes a valid direct comparison of the active treatments unlikely.

It may be possible to establish efficacy of a treatment if it can be shown to be significantly better than an established licensed treatment under conditions of fair comparison. This is likely to be difficult and require large numbers for an adequately powered study. A positive outcome with this strategy in SAD is, however, currently considered unlikely.

The choice of comparator drugs is limited to those that are licensed for treatment for SAD with paroxetine being the most widely accepted.

Fair comparisons with behavioural psychotherapy or cognitive behavioural therapy are difficult to achieve for methodological reasons. There are concerns that the studies supporting the efficacy of psychotherapies in SAD have not always been conducted to the same rigorous level required for establishing the efficacy of licensed pharmacological treatments. Randomisation, blinding of treatment, adequate blinding of raters or adequate reporting of data using intent to treat populations and last visit carried forward analysis have not been standard in these studies. Psychotherapy cannot readily be defended as a comparator in pivotal placebo-controlled studies because of the difficulty of blinding in the psychotherapy arm in contrast to the blinded placebo drug comparison. This creates an inherent bias in such a study.

As evidence is produced of the efficacy of new pharmacological treatments for SAD the range of choice of comparators may increase. Whichever comparator is selected should be justified.

4.3. Concomitant treatment

It is recommended that concomitant psychotropic treatments, including benzodiazepines, be excluded to allow correct attribution of efficacy to the treatment under investigation. Likewise, the exclusion of concomitant formal psychotherapy is recommended since this is likely to raise the placebo response rate and the drug response and may make it more difficult to detect efficacy.

It is recommended that self-exposure to feared situations should not be actively or explicitly encouraged between visits.

4.4. Duration of acute studies

The duration of treatment must be sufficient to allow a significant separation from placebo to emerge in order to establish efficacy. The recommended duration of a study needs to balance the chance of establishing efficacy against the disadvantages of receiving placebo.

A duration of 12 weeks has been used in the majority of the acute treatment investigations to date. However, studies with shorter, 8 weeks, and longer durations, 20 and 24 weeks, have been conducted and these have also been able to establish efficacy. A period of 12 weeks for an acute treatment study appears to be widely used and is realistic clinically. A substantial number of non-responders at 8 weeks go on to become responders at week 12 (Stein et al., 2002c). The point at which a drug placebo difference is most likely to be seen and where the discontinuation rate remains acceptable is 12 weeks. This is the duration recommended for short-term studies. In view of the long duration of SAD prior to treatment that is currently seen, it appears ethically acceptable to expose individual patients to placebo for 12 weeks. Studies with duration shorter than 12 weeks may risk a higher chance of failing to find a drug placebo difference unless they are adequately powered.

All the studies that have continued for longer periods (Lader et al., in press; Versiani et al., 1996, 1997b) show that there is continuous further improvement, both in the responders and the non-responders with further treatment, SAD is clearly a chronic disorder where further improvement is observed with prolonged treatment.

The 12 week duration of the short term studies is, therefore, recommended. Placebo-controlled studies of longer duration, say 24 weeks, may be able to investigate further improvement in the longer term.

4.5. Justification of dose

To establish an effective dose it is usual to compare the drug with placebo given in a dose regime, the dose regime being fixed for a large part of the study before efficacy is established. Identifying an appropriate dose is often undertaken by comparing two or three fixed dose regimens with placebo and identifying which is associated with the best efficacy safety ratio.

Flexible dose studies provide only limited information about the appropriate dose particularly in studies of SAD where response to any dose tends to be slow. Titration to a higher dose may under these circumstances reflect the impatience of the investigator rather than the lack of efficacy of the lower dose. Flexible dose regimes also tend to accumulate non-responders on the higher doses, which makes it difficult to compare the responses achieved on different doses achieved. Fixed dose studies rather than flexible dose studies are recommended to obtain the most useful assessment of the efficacy of different doses.

4.6. Severity scales

The pivotal scale chosen should be sensitive, validated, internationally recognised and have demonstrable ability to separate active treatment from placebo reliably.

A variety of scales have been developed for quantifying the severity of SAD. The most widely used of these is the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987). This scale has been able to establish efficacy in a large number of placebo-controlled studies and is currently viewed as the gold standard.

The Brief Social Phobia Scale (Davidson et al., 1997) has also been widely used and shown to be able to establish efficacy (Van Ameringen et al., 2001). Both of these observer scales are able to quantify the fear and avoidance components separately and these have been used in secondary analysis.

The Social Avoidance and Anxiety Inventory (Beidel et al., 1989), the Brief Standard Self-rating for Phobic Patients (Marks and Matthews, 1979), and the Social Avoidance and Distress Scale (Watson and Friend, 1969) have also proved useful. The SPIN (Connor et al., 2001) has also proved to be a simple but useful efficacy scale.

The Clinical Global scales, CGI Improvement and CGI Severity, have been used as both primary and secondary efficacy scales and as categorical scales to define responders. These global scales are not recommended as primary scales but are most useful as secondary scales to help judge the clinical relevance of the finding.

It is recommended that disorder specific scales are used as primary efficacy measures. The scales used should be justified and the pivotal scale for the analysis defined in advance.

5. Analysis

In placebo-controlled studies differential discontinuation rates are usual, particularly related to lack of efficacy on placebo and analysis of results needs to take account of missing values. Where there are significant differential discontinuation rates the observed case analysis (OC) is not appropriate and estimation of the contribution of the

missing values is needed. The last observation carried forward analysis (LOCF) on an intention to treat population is regarded as a conservative estimate of missing values and may be supplemented by additional sensitivity analyses including repeated measures analyses. Whichever method is chosen will need to be specified in advance.

6. Clinical relevance

The clinical relevance of the results seen in a study can be assessed in a number of ways. A commonly used method relates the response observed with the medication under investigation to that seen with an established reference treatment, preferably in the same study. In other therapeutic areas responders have been assessed by a defined percentage change (usually 50%). This has proved useful also in SAD. Reference to effect sizes observed in other studies might be helpful but this approach makes a number of assumptions relating to the similarity of the trial design used, and the populations investigated in different studies. For this reason historical controls are considered potentially unreliable. A defined change on one of the disease specific scales offers a simple measure. For example a 10 point change in the LSAS score registered a clinically relevant difference (Katzelnick, personal communication) in a large study of managed care (Katzelnick et al., 1995). This is in line with the clinically relevant difference between drug and placebo in a pivotal placebo-controlled study leading to licensing (Liebowitz et al., 2003).

The clinical relevance of an observed change is often indicated by the registration of efficacy on Clinical Global Scales, particularly in an analysis of the number of patients reaching defined criteria of response.

6.1. Responders and remitters

It is helpful to classify patients on the basis of the observed response in the study as responders or remitters and for this purpose the CGI scales have often been used as secondary categorical measures of efficacy.

6.1.1. Responders
Responders, who have improved but have not yet reached remission, have been identified on the CGI Improvement scale as having a score of 1 or 2, much or very much improved. Defining responders, as having a reduction in the initial score on the severity scale of 50%, used in other psychiatric conditions and which seems reasonable, has been reported to be useful in some studies in SAD. However, SAD tends to respond more slowly than the conditions where the 50% criterion has proved most useful. The studies indicate that at 12 weeks a 35% reduction in initial severity appears to be a useful measure with approximately half the patients achieving this criterion.

6.1.2. Remitters
A remitter is someone who has achieved the level of symptomatology close to or in line with the general population. The CGI Severity Score of 1 or 2, normal, not at all ill, or borderline illness, has been used to define remitters but the level of remission represented by these scores remains controversial. A cut off on a severity scale would be desirable, but generally accepted cut offs to indicate mild, moderate or severe illness, or to define remitters, have not yet been clearly established on the LSAS.

Indeed, the continuous further improvement in SAD observed in long term studies indicates that the concept of remission is over-optimistic and currently out of place in acute studies of SAD. This is similar to the situation in another chronic disorder, obsessive compulsive disorder, where improvement with treatment but not remission is the norm. In long term studies remission may be a more acceptable target.

Whichever criteria of response and remission are adopted should be specified in advance.

6.2. Functional measures

Improvement in function may be a useful measure of the clinical relevance of a change measured on a disease specific severity scale. The most widely used functional measure is the Sheehan Disability Scale (SDS) (Sheehan et al., 1996), which is a simple self-rated 10-point assessment in the areas of work, social and family function. This scale has proved robust in most studies and provides evidence of an improvement in disability in almost all the studies where it was used. The SDS has been able to distinguish an effective treatment from placebo, both in the short and long term studies. Other validated scales can also be considered.

7. Long term treatment

Until standard treatments become better established and a reasonably precise prediction can be made about their long-term efficacy a placebo control is necessary in long term studies.

7.1. Designs for long-term treatment

Two different approaches to establishing long-term efficacy have been adopted: prolonging treatment for an extended period in comparison with a control, and discontinuation on to placebo or active drug following response, the relapse prevention or randomised withdrawal design. The two approaches investigate different aspects of long-term treatment efficacy. In both cases care is needed to reduce the influence of non-drug treatments, formal or self applied.

The relapse prevention design is recommended to establish sustained efficacy of the treatment in responders and the prolonged efficacy design to establish the further symptom-

atic gains with prolonged treatment. The randomised withdrawal design does not investigate whether longer treatment than the 12 weeks of an acute treatment study is required to achieve response.

In either design a 6 months long-term treatment period is considered sufficient and is recommended.

7.1.1. Prolonged treatment

Studies of prolonged treatment are not affected by potential discontinuation symptom effects and mimic the use of the treatment in clinical practice. However, interpretation of the results is not straightforward because of the possible influence in this type of study, as in acute studies, of discontinuation of non-responders, with a bias in favour of the responders. The further improvement in the response to treatment on the pivotal scale between 12 and 24 weeks seen in several studies suggests that the 12 weeks short-term efficacy results underestimate the fuller response to treatment observed with prolonged treatment to 6 months. There are to date only limited trials but the available evidence indicate further mean improvement in the symptoms of SAD as registered on the LSAS total score over 6 months (Lader et al., in press; Stein et al., 2002a,b, 2003; Versiani, 2000) similar to the response seen in generalised anxiety disorder and obsessive compulsive disorder.

7.1.2. Relapse prevention

The alternative design for investigating long-term treatment, which has been widely used in major depression, is the relapse prevention or randomised withdrawal design. The design is more appropriate in a disorder where patients who are well suffer a relapse when treatment is discontinued. The data on SAD suggest it is a chronic disorder with continued improvement on treatment and deterioration on discontinuation that tends to be gradual so that patients may discontinue before formal relapse criteria are met. The definition of relapse should be able to capture these patients. A further problem that needs to be given attention in this design is differentiating possible discontinuation symptoms from relapse of the disorder.

Patients entering randomised withdrawal studies should have responded to treatment. The only entry criteria validated in positive relapse prevention studies have been based on the CGI scales. A CGI Improvement score of 1 or 2 (much or very much improved) and a CGI Severity score of 3 (mildly ill) have both been used successfully (Montgomery et al., 2003; Stein et al., 2002b). Other criteria may be possible but will need validation.

Several criteria for declaring a relapse have been used. A relapse criterion of an increase of 10 points on the LSAS which was proposed as a clinically relevant change score has been used successfully and accounted for some 90% of the relapses observed in one study (Montgomery et al., 2003). A deterioration of two points on the CGI-severity has also been used but is not reported as successful used on its own.

A certain proportion of patients withdraw from placebo-controlled studies because of clinical deterioration which does not meet a more severe protocolled relapse criterion such as CGI increase of one or two points. Adding these relapses to the relapses that meet the protocolled criteria has been shown to be a sensitive definition of relapse in placebo-controlled studies (Stein et al., 1999b). It is recommended that in relapse prevention studies the criteria for responders eligible for inclusion should adequately quantify the response and should be defined in advance. Criteria for relapse should take account of the judgement of the clinician and also be quantified with reference to a pivotal rating scale defined in advance.

8. Discontinuation symptoms

All drugs currently licensed for SAD are established antidepressants with a more or less known discontinuation/dependence profile. The data presented at this meeting suggest that the discontinuation symptoms are similar for particular antidepressants whether they are being studied for major depression or for different anxiety disorders. The symptoms appear to be compound-specific and to arise within a period of three to five half lives following the discontinuation of the treatment.

Discontinuation symptoms seem to increase with length of treatment with benzodiazepines but this does not appear to be the case with antidepressant-like treatments for SAD (Lader et al., in press). Data are now becoming available in SAD indicating that discontinuation symptoms do not appear to increase with a prolonged 6 months exposure compared to short-term exposure. Since the available data indicate that discontinuation symptoms are compound specific pertinent discontinuation data for a medication used in another indication may be sufficient.

A similar body of information would not be available to potential new drugs applying for SAD as the first indication and a study investigating discontinuation symptoms is important and is recommended.

The most widely used measures 26 May 2004 to register discontinuation symptoms are the 43-item self-rated Discontinuation Emergent Symptoms and Signs (Rosenbaum et al., 1998) and the Physician Withdrawal Checklist (PWC) (Rickels et al., 1999). Discontinuation symptoms are also registered as treatment emergent adverse events (TEAE) on the routine safety assessments. Each system has its drawbacks. The DESS and the PWC are checklists and produce inherent extra noise. Caution is needed in evaluating the multiple analysis of these data. The clinical relevance of findings produced with a checklist rating is more difficult to establish than with the clinician rated TEAEs.

The duration of a discontinuation study will depend on factors such as the half life of the treatment of concern. With most current treatments for SAD that have an antidepressant like action and a short or conventional half life the discon-

tinuation symptoms appear to be maximal in the first week and then to reduce in the second week, with symptoms generally registered as mild or moderate.

9. Adolescents

On the basis of existing data it appears that the diagnostic issues are much the same in adolescents and adults. The symptoms, fears, and avoidance patterns are reported to be very similar in adults and adolescents so that the same recommendations for study designs and scales (appropriately validated) should apply.

In children, developmentally relevant issues need to be considered. Medication may have effects on physical and cognitive growth and development. The adverse event profile may differ in adolescents compared to adults, and the particular issues of safety in adolescents need to be addressed.

There are as yet too few formal studies in adolescents so that efficacy has not been formally established and there are insufficient data to make recommendations.

10. Elderly

The prevalence of SAD is reported to decline in the elderly but this may in many cases reflect the adjustment of the individual to an isolated, asocial life rather than a diminution of the disorder. Assessment of dysfunction required for case recognition is difficult in the elderly, which may account for an apparently lower incidence.

Special efficacy studies in the elderly are not recommended and efficacy established in adults may be assumed on clinical grounds to apply to the elderly. While separate efficacy studies on the basis of age ranges are not indicated, it is advisable to include a range of ages in the studies in order that any signals of potential differences may be identified.

The safety of potential treatments is of concern in the elderly as they are likely to suffer more comorbid physical illnesses and age-related changes in metabolism of drugs is also more likely. Exposure to more concomitant treatments is likely and the pharmacokinetic aspects of treatment and potential drug interactions will need to be investigated.

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