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Guidelines for Investigating Efficacy in GAD

Chair: Stuart Montgomery, Barbara van Zwieten-Boot


Rapporteur D. Montgomery

1. Introduction

The guidelines on the investigation of the efficacy of treatments in generalised anxiety disorder (GAD) 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 2000. The guidelines address principally the investigation of pharmacological treatments but the same principles apply to non-pharmacological treatments.

The investigation of treatments for generalised anxiety disorder (GAD) has been held back to some extent by the slow evolution of the concept of GAD as a specific disorder. Once the concept of anxiety neurosis was eliminated in DSMIII, resulting in a separation of panic disorder and generalized anxiety, it became possible to study and attempt to define GAD more carefully.

The definition of GAD in DSMIII lacked adequate detail concerning the explicit criteria for the core elements of this disorder. In particular, insufficient attention was paid to the prior duration of the disorder and consequently the distinction was blurred between the often self-limiting short term forms of anxiety disorder on the one hand and the persistent condition of generalised anxiety, which appears to be more homogenous and to have a much higher level of impact on normal function. This was recognised in later versions of the DSM criteria, which established a minimum prior duration of 6 months. The symptom criteria were refined in DSMIV to reduce some of the diagnostic overlap with other anxiety disorders. There has been a shift of focus regarding the specific cognitive, behavioural and somatic symptoms that are characteristic for generalised anxiety. The largely nonspecific autonomic anxiety symptoms have been reduced in importance in DSMIV (American Psychiatric Association, 1994) with more weight given to nervous tension and chronic worrying. Further, the criteria of distress and impairment in function consequent on the disorder were specified.

2. Burden of the disorder

GAD is a very common disorder with similar high prevalence rates reported in both the US and Europe. The mean onset of GAD has generally been reported as relatively late at around 35 years compared with most forms of anxiety disorders that usually start in adolescence. This may reflect to some extent the delay in recognition of GAD. GAD in children and young adolescents is recognised in the DSMIV criteria, which include the diagnosis of “overanxious anxiety disorder of childhood”, but the prevalence of DSMIV GAD among subjects younger than 20 is comparatively very low with estimates well below 1%. The early onset GAD has an almost equal gender distribution, but this separates sharply after the age of 20 when the female predominance becomes obvious (Pigott, 1999).

The estimates of lifetime prevalence of DSMIIIIR and DSMIV GAD reported in various population surveys around the world have been generally in accord with the 5.1% rate reported in the National Comorbidity Survey (Wittchen et al., 1994). The reported 12 month prevalence rates vary between 2 and 4% and the high ratio of current to lifetime rates indicates that GAD mostly runs a very chronic course. When the important levels of subthreshold GAD are also taken into account it becomes evident that GAD is among the more frequent mental disorders. Because those with GAD are frequent attenders GAD is the most frequent of all anxiety disorders in primary care with rates in the range from 7–9%, almost three times higher than the rates reported in the community (Wittchen and Hoyer, 2001; Maier et al., 2000).

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indicating that GAD mostly runs a very chronic course. This is reflected in the mean duration of 20 years reported in epidemiological studies (Yonkers et al., 1996). Clinical experience also suggests that those who develop GAD are likely to still have the disorder twenty or thirty years later.

The level of disability associated with GAD appears to be higher than other anxiety disorders (Massion et al., 1993) and is reported to be the same as with pure major depression (Kessler et al., 1999) though in GAD the number of days’ work lost per month is slightly higher (Wittchen et al., 2000). This increase in impairment may well relate to the more chronic nature of GAD compared to major depression. In comorbid cases where both major depression and GAD were present, a frequent pattern, measures of disability were found to be in excess of those associated with pure disorders (Kessler et al., 1999; Wittchen et al., 2000).

GAD is frequently associated with physical symptoms and disorders. These are mostly of a chronic nature and include somatic conditions associated with pain, such as arthritis and chest complaints. Sufferers attend their primary care doctor twice as frequently as would be expected in contrast to depression (Katon et al., 1990; Wittchen et al., 1994). The co-existence of both GAD and depression in the same patient drives this attendance rate even higher. GAD is often not recognised and the high level of treatment provided is mostly inappropriate.

Due to the high prevalence of GAD, its chronic nature, the impairment of social function, and reduced productivity, the disorder places a heavy burden on sufferers, their relatives and on society at large. There have been few health economic studies focusing on the anxiety disorders and none that have addressed GAD specifically (Shah and Jenkins, 2000). The studies that have been carried out indicate a very high cost for the anxiety disorders particularly in the morbidity costs which reflect the loss of productivity (Rice and Miller, 1998) and specific pharmacoeconomic studies in GAD should therefore be encouraged.

### 3. Current treatment of GAD

Although sufferers with GAD seem very willing to attend their primary care practitioner their treatment is often inadequate or no treatment is offered. This is not surprising since so few treatments are licensed for the disorder.

Benzodiazepines were introduced for the treatment of anxiety neurosis and were undoubtedly useful. However, studies in patients suffering from GAD according to DSMIII criteria, which permitted a short, one month, prior duration of illness, produced equivocal results and a substantial number of failed studies. This was due in part to the high placebo response rates, which probably reflect the natural remission of short-term anxiety states.

Benzodiazepines have nevertheless been found to be effective in the short-term treatment of GAD, though possibly for the somatic symptoms rather than the psychic symptoms (Rickels et al., 1993), but there are no double blind placebo-controlled studies providing data on whether this effect is maintained in the long term. Benzodiazepines are also associated with some dependence problems and moderate to severe withdrawal phenomena, particularly after long-term treatment, and are restricted to short-term treatment in Europe.

Buspirone has been licensed for the treatment of anxiety largely on the basis of studies that used the early DSMII criteria of anxiety neurosis to select patients. Some studies have found efficacy for buspirone in anxiety that fulfilled a short prior duration criterion. Although a meta-analysis of randomised clinical trials indicated the efficacy of buspirone (Gammans et al., 1992) results have been disappointing from more recent studies that adopted the DSMIV criteria. There is no evidence of long term efficacy for buspirone in GAD.

Antidepressants are increasingly seen as potential treatments for GAD. Imipramine was found to be effective in placebo-controlled studies in patients who fulfilled DSMIIIR criteria for GAD, the best effect being seen on the psychic rather than the somatic symptoms (Rickels et al., 1993). Efficacy in long-term treatment with tricyclic antidepressants has however not been adequately investigated.

Of the newer antidepressants venlafaxine has been shown in several placebo-controlled studies to be effective over an 8-week period in GAD using DSMIV criteria, and a significant advantage in mean improvement has also been shown for venlafaxine compared with placebo in 6 month studies (Allgulander et al., 2001; Gelenberg et al., 2000; Rickels et al., 2000). The SSRIs are currently being investigated for the treatment of GAD and efficacy has been shown for some (Pollack et al., 2001).

A number of studies of psychological treatments, for example cognitive behaviour therapy, have been reported as positive but they have not been adequately designed and are sometimes poorly reported. They are therefore difficult to interpret and they do not provide an adequate basis for a judgement of efficacy since some studies failed to use the basic minimum criteria of randomisation, blinded raters or intention to treat analysis.

### 4. Diagnostic Criteria

The DSMIV criteria are the most widely used and there can be no doubt that these criteria identify a group of patients who are sensitive to treatment.

The diagnosis requires that the patient suffer from excessive anxiety and worry that is distressing and difficult to control with the presence of three out of a list of six symptoms which includes restlessness, feeling on edge,
being easily fatigued, concentration difficulties, irritability, muscle tension, sleep disturbance. The anxiety is not confined to features of another Axis I disorder, is not the direct physiological effect of substance abuse, or a physical condition. The chronicity of the disorder is emphasised with the requirement that symptoms must have occurred more days than not during a period of at least six months. This criterion must be specifically addressed. The population of GAD thus defined is more homogenous, chronic, stable and has a high level of functional impairment compared with GAD as defined in the earlier DSMIII criteria.

The ICD10 (World Health Organisation, 1992) criteria are largely consistent with the DSMIV criteria, although the ICD-10 general guidelines use a more “flexible” phraseology. ICD10 has not been tested sufficiently in pivotal placebo-controlled studies for a judgement to be made of the responsivity of the population identified. On current information the DSMIV criteria seem to have advantages favouring their use in pivotal studies.

The presence of GAD for a period of at least 6 months needs to be clearly established for patients entering efficacy studies to meet DSMIV criteria. Clinically significant distress or social or occupational impairment over this period due to the disorder has also to be established unequivocally and distress and impairment therefore need to be adequately documented. Even an experienced clinician may find the use of a good structured interview helpful.

5. Comorbidity

As with other anxiety disorders GAD is associated with high levels of lifetime comorbidity with other psychiatric disorder (Kessler, 2000). Nevertheless a sizeable proportion of those with GAD suffer from GAD alone and GAD is recognized in DSMIV as a distinct entity.

The most commonly reported lifetime comorbidity with GAD is major depression, estimated in the National Comorbidity Study as present in 17% of GAD (Wittchen et al., 1994). More recent studies using a much wider scope of mental disorders in the assessment strategy have found a higher prevalence of comorbidity of 40% (Wittchen et al., 2000). These studies indicate that GAD is an independent disorder and should not be considered as either a prodrome or a consequence of major depression. Other less frequent comorbid conditions include dysthymia, PTSD, and social phobia.

Where a proposed treatment for GAD is already established for a disorder that is frequently comorbid with GAD it is important to demonstrate that the effect of the agent on GAD is specific and not due to secondary therapeutic effects on other comorbid conditions. Comorbid conditions therefore need to be controlled in pivotal efficacy studies.

In studies to establish efficacy in GAD, patients meeting criteria for an episode of major depression, the commonest comorbidity, either current or within the last six months, should be excluded. The severity of any symptoms with depression-like features, even if considered to be part of GAD, should be kept to a mild level of severity. The rationale for this approach is that mild major depression does not normally show a reliable antidepressant placebo difference. Double depression, where major depression overlaps with dysthymia, should be excluded on the same basis. The presence of potential comorbid depressive (subthreshold) symptomatology should be documented.

Similarly, other disorders with significant but lower comorbidity, for example, PTSD, social phobia, OCD, and panic disorder, need to be excluded if they are concurrent. Patients with bipolar disorder or schizophrenia in the history should also be excluded. The use of a structured diagnostic interview may help to assess comorbidity systematically and help achieve a homogenous sample.

For purposes of licensing, studies in a relatively pure, non-comorbid, group are needed to justify the claim of a direct treatment effect in GAD. However in a condition where substantial comorbidity is the norm further studies in a population with comorbid conditions might be a helpful addition later in the post marketing—development programme.

6. Trial Design

To establish efficacy the conventional parallel group double-blind randomised placebo-controlled trial is necessary. Although a placebo run in period prior to randomisation is not considered necessary it may be helpful in reducing the confounding effects of initial exacerbation of anxiety as a previous treatment is discontinued. There is no evidence to date that crossover studies play any part in the investigation of efficacy in GAD, probably because of the difficulty in assessing carry-over effects in a condition where the speed of response and deterioration may be variable. At least two positive placebo-controlled, well-designed, well-conducted studies of sufficient power, using the intent to treat population, are needed to establish efficacy.

In general, greater efficacy has been shown in patient populations suffering from moderate or greater levels of severity. There is evidence that a larger drug placebo difference is seen with increasing severity of GAD. As with other disorders a minimum severity entry criterion is recommended. This may be a predetermined minimum score on a pivotal scale such as the Hamilton Anxiety Scale (HAMA) (Hamilton, 1959). Minimum entry scores of 18 and 22 on the HAMA have been successful in identifying an appropriate study population and these cut off scores have been used to separate the mild from the moderate levels of anxiety. A severity criterion at entry is
needed but there are insufficient published data to choose a definitive cutoff point.

7. Dose

The clinical trial programme should provide evidence to justify the selection of a recommended dose. The best evidence supporting the choice of a particular dose would come from a study comparing three fixed doses where the lowest dose did not separate from placebo but the higher one or two doses were found to be effective. Studies that are able to establish a dose response relationship are welcome since this of itself may be taken as evidence supporting efficacy.

Unfortunately, dose response relationships are established in psychotropic drug development only infrequently. The sensitivity of current trials is such that a treatment versus placebo effect is sometimes demonstrated only with difficulty and the designs may lack the sensitivity to detect reliably a difference between two active treatments.

Higher doses are generally associated with greater side effects, particularly at the start of treatment, so that a period of slow fixed titration is usually undertaken before achieving the full dosage. The titration regime adopted will need to be determined according to the side effects observed preferably before the design of the pivotal efficacy studies. The recommendation of the appropriate dose will be based on the best efficacy to side effect or safety ratio, which generally would favour the lowest dose at which a significant, clinically relevant drug versus placebo effect is seen.

8. Control Group

For the unequivocal demonstration of efficacy it is necessary to establish a significant difference between the proposed drug and placebo on predefined pivotal measures. In general, 3-way studies using a comparator reference control as well as a placebo control are the preferred design. An additional advantage of this design is that it might distinguish between a failed study, where the comparator also fails, and a negative result.

Insufficient studies have been carried out in GAD defined according to DSMIV to determine the comparators that can be regarded as established and there is no general agreement as to which is preferred. Nevertheless three-arm trials, including an active control are useful and may be needed from a regulatory perspective.

Benzodiazepines have been the comparator most commonly used in short-term trials in order to provide a comparison with experience gained from older studies, as well as to validate the population studied and to determine the relevance of the drug placebo difference. However, benzodiazepines are thought to exert a greater effect on the somatic symptoms than the psychic anxiety symptoms of GAD and are therefore not the most appropriate comparator agent. The choice of the dose of individual benzodiazepines is compromised by lack of studies to justify that choice. As long-term use might induce dependence, benzodiazepines may only be used as a comparator in short-term trials.

Venlafaxine has a strong body of data indicating efficacy in GAD in both placebo and reference controlled studies with adequate studies identifying the appropriate choice of dose. Some SSRIs have been shown to be effective in GAD, for example paroxetine, where the effective dose appears to be the same as for major depression. Comparative data with venlafaxine and paroxetine are of interest, though it may be too early at this stage for their use as a single comparator.

Buspirone is not thought to be the most useful reference agent because of the lack of data establishing appropriate dose and the general failure of buspirone in recent placebo-controlled studies where other agents were found to be effective.

For efficacy studies the choice of the particular comparator and the dose need to be justified on the basis of placebo-controlled evidence of efficacy.

9. Scales for Severity

The scale selected should be internationally recognised, established as valid, reliable, and sufficiently sensitive to test a drug placebo difference. Currently available symptoms scales used for assessing severity of GAD were largely developed prior to the delineation of the disorder in DSMIV. Many of the scales aimed to measure a broad construct to capture the different dimensions of anxiety as a heterogeneous disorder. As a result there is no available specific measure for GAD. The total scores of the scales are problematic as measures of GAD as many of the items are non-specific and only selected items cover DSM-IV GAD.

The Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) has been used as the gold standard but has many shortcomings. The core features of GAD according to DSMIV are the nervous tension and chronic worrying, which are difficult to control. These are more important than the autonomic or somatic symptoms prominent in earlier definitions. These psychic symptoms are captured in part in the HAMA but the scale has a serious over-representation of autonomic symptoms and equal weight is given to the two types of symptoms.

To address this problem some studies have used the HAMA but have concentrated on specific items that contribute to the psychic anxiety factor as being more relevant to DSMIV GAD. Anxious mood (item 1) and psychic tension (item 2) have been used together as a pivotal subscale in placebo-controlled studies. Similarly
the items of inner tension and worrying over trifles of the Comprehensive Psychopathological Rating Scale (Asberg et al., 1978) capture these complaints directly as does the self rated anxiety subscale of the Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983). Experience with their use as pivotal scales is limited. There is a need for a new sensitive scale that captures the core symptoms of GAD according to DSMIV.

10. Outcome Measures

The choice of pivotal scales and outcome measures and the method of analysis need to be specified in advance. The recommended primary efficacy analysis is the analysis of change scores on the pivotal scale, on the basis of intention to treat with the last observation carried forward. Placebo-controlled studies analysed on this basis have been able to establish efficacy in GAD. The number of dropouts from all causes should be kept to a minimum to reduce potential problems with missing data.

For an analysis of responders the definition of responder should be specified in advance. Various definitions have been used, the 50% reduction in the pivotal scale being the most widely accepted criterion. The choice of criterion will depend largely on the predicted responsiveness of the population studied, and on the sensitivity to change of the particular scale. The CGI-S (severity) or CGI-C (change) (Guy, 1976) have been used for responder analyses but the CGI-S is not a sensitive measure and the CGI-C score of 1 or 2, much or very much improved, is rather insensitive and tends to focus on recent change.

The remission rate is a useful measure of efficacy, particularly in long-term treatment studies. Recommended measures based on the HAMA include a score of less than 10, and less than 8. A score of 1 or 2 on the CGI-C scales has also been used but this is a measure of improvement rather than a criterion of remission.

In relapse prevention studies the most sensitive criterion of relapse appears to be the withdrawal of an individual from the placebo-controlled study for efficacy reasons. This measure has the advantage of being independent of pivotal scales but lacks objectivity and consideration may be given to a prespecified increase on a severity scale to define an event. Survival analysis (Kaplan Meier), which takes both the number of withdrawals and the time to withdrawal into account, is the most sensitive analysis of these data.

11. Clinical Relevance

A significant difference registered on a pivotal scale between a treatment and placebo may not necessarily be clinically relevant. A separate judgement of the clinical relevance of this difference needs to be made and a variety of approaches have been used. The most frequently applied method has been to establish a significant difference between the treatment and placebo on an outcome measure identified as clinically relevant.

This is essentially the main justification for the analysis of responders who reach a defined reduction on the pivotal severity scale. A reduction of 50% is a commonly used and widely accepted measure for clinically relevant response. A responder analysis on the CGI is also widely used for this purpose. The CGI has the advantage of being an independent clinical global judgement of the blinded investigator, which is likely to be clinically relevant.

The magnitude of difference between the improvement on treatment and on placebo has been used to make a judgement of clinical relevance. However, difference in improvement varies with such factors as the degree of treatment resistance in the population studied, the number of dropouts, particularly those occurring early, and the extent of the overall placebo response, and may be unreliable. This would apply particularly to judgements in relation to expected magnitude of difference extrapolated from potentially misleading historical controls. A better assessment of clinically relevant differences can be made where a comparator reference treatment of established efficacy included in the same placebo-controlled study provides a yardstick for the differences observed between the candidate treatment for GAD and placebo.

A measure of social and occupational function that is independent of the disorder-specific scales may also be helpful in indicating the relevance of improvement. The Sheehan Disability Scale (SDS) (Sheehan et al., 1996) has been shown to be efficient in demonstrating significant differences in improvement in function from the patients’ perspective. Since GAD is associated with considerable impairment of function the SDS may provide a useful comment on the functional relevance of the treatment.

12. Duration of Acute Studies

GAD is a chronic condition and this is reflected in the very long prior duration of the disorder, a mean of 10 or more years, reported in recent studies. Response may be seen within an 8-week time period in most individuals but is rather slow in others. A considerable number of studies in GAD that had a duration of four to six weeks have failed. Where the duration was of 8 weeks placebo-controlled studies have generally been successful and the number of early discontinuations has not compromised the demonstration of efficacy. Based on this experience the recommendation is that efficacy studies in GAD should have a minimum duration of 8 weeks.

The significant expected proportion of slow responders creates additional complications for study design. The six-month studies show that remission may be delayed until towards the end of the six-month period, particularly
in those who are more severe. There is, therefore, a case to be made for longer acute treatment studies and placebo-controlled studies with duration of six months could be useful to examine remission.

13. Long Term Treatment

In Europe evidence of both short-term and long-term efficacy is required for chronic disorders. The evidence in GAD suggests that we can expect to establish efficacy at 8 weeks. Long-term treatment begins when short-term treatment ends.

The conventional approach to establishing long-term efficacy in Europe is the standard relapse prevention design. In the treatment discontinuation study responders to acute treatment at 8 weeks are rerandomised (after a suitable taper period) to investigational treatment or placebo. This classical design provides information on the number of relapses on drug and placebo over this period. It also provides an assessment of the number of responders whose response persists over the normal 6 month relapse prevention assessment period.

Relapse should ideally be defined as a clinically meaningful deterioration measured on a standard severity scale. Unfortunately there are too few data on which to base a firm recommendation of the specific score, which should lie somewhere between definitions of moderate severity and remission. An alternate sensitive measure in designs of this nature is the withdrawal of the patient from a placebo-controlled study because of deterioration. The use of multiple criteria for deterioration has been shown to reduce sensitivity and increases the size of study. Survival analysis comparing drug and placebo, using predefined deterioration criteria of events, is likely to provide the clearest demonstration of efficacy.

Another design to establish efficacy in long-term treatment is to continue the treatment double blind beyond the 8-week acute study period. The design has the advantage that possible drug discontinuation effects do not impinge on the results. However, it carries the disadvantage of unequal groups and assumptions have to be made concerning the comparability of the populations in the different treatment arms.

14. Discontinuation Symptoms

There is concern that a number of drugs used for GAD or depression are associated with withdrawal symptoms on discontinuing the active treatment. In view of the debate about potential dependence with some anxiolytics such as benzodiazepines it is helpful to investigate possible discontinuation effects and to quantify the severity, the timing and the duration of such discontinuation symptoms.

The timing of the emergence of such discontinuation symptoms would be expected to vary according to the elimination half life and other properties of each compound, symptoms being expected after between 3 and 5 multiples of the half-life of the active drug. A two-week discontinuation study at the end of both an acute and long-term study would help to answer the question and provide useful data from comparisons generally at weeks 1 and 2 would help to address the question and provide useful data on discontinuation phenomena following placebo, active comparator, and test drug.

15. Special populations

The mean age of onset of GAD is reported to be later than other anxiety disorders. Based on our present knowledge GAD, as defined in DSMIV is extremely rare in children and uncommon in adolescents with an incidence well below 1%. Separate efficacy studies in this group would therefore be difficult to complete and difficult to justify.

There are at present few data on which to base a judgement as to whether GAD differs between older patients and the elderly. The available data indicate that treatment efficacy in those above and below the age of 60 is similar so that separate placebo-controlled efficacy studies according to age group are not justified.

The safety of potential treatments is of greater concern in the elderly since elderly patients are known to be more frail, to have more comorbid physical illnesses, and sometimes to have an altered metabolism of drugs. Since the elderly are likely to be exposed to more concomitant treatments the safety and pharmacokinetic aspects of treatment and potential drug interactions will need to be explored.

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.

16. Conclusions

GAD is very common and is associated with substantial suffering and impairment similar to, or even greater than, major depression. Modern diagnostic criteria for GAD emphasise the chronic nature of the disorder, which should not be confused with the short term, largely stress-induced anxiety states that seem to have a high spontaneous remission rate.

Despite the high level of health seeking behaviour of GAD sufferers there are few treatments thought to be effective and even fewer that have been licensed to treat GAD.

The methodology for investigating GAD has now been developed to a level where consensus positions are possible to justify.

The efficacy of treatments for GAD needs to be investi-
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gated compared to placebo under the usual randomised double-blind group comparison conditions. At least two positive placebo controlled studies will be needed to establish efficacy, though the whole database, including negative studies, would need to be taken into account. It is not possible to infer efficacy by comparing with established treatments for GAD without the inclusion of placebo because of the relatively high and variable placebo response seen both between and within studies. The inclusion of a comparator reference treatment within a placebo-controlled study is the preferred strategy to allow blinded judgements of clinical relevance in the population studied.

The choice of the comparator treatment and the selected dose need to be justified on the basis of placebo-controlled evidence of efficacy.

DSMIV are the preferred diagnostic criteria and using a minimum severity entry criterion should further refine the population. In order to investigate the direct effect of the treatment in GAD comorbidity of other relevant disorders such as major depression needs to be controlled or excluded.

The recommended duration of acute treatment studies is at least 8 weeks and the duration of long-term studies at least 6 months.

The HAMA scale is the most widely used but over-emphasises somatic anxiety symptoms of little relevance to GAD, which is more clearly defined by the anxious worrying and tension. Scales derived from the HAMA concentrating on these symptoms are more sensitive to treatment. The development of new scales is encouraged.

The choice of dose recommended for the new treatment needs to be justified. The best data are likely to be obtained from a multiple fixed dose efficacy and safety comparison with placebo following the appropriate initial fixed titration for the higher doses.

The long-term efficacy of treatments for GAD needs to be investigated in placebo-controlled studies. Possible designs include both placebo-controlled studies lasting 6 months and randomised withdrawal designs where responders to acute treatment are randomised to placebo or continued on treatment for 6 months.

References


