Clinical Guidelines for the Management of

Anxiety

Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder)

in adults in primary, secondary and community care

This work is undertaken by ScHARR, University of Sheffield which received funding from the Royal College of General Practitioners on behalf of the National Institute for Clinical Excellence. The views expressed in this Publication are those of the authors and not necessarily those of either the Royal College of General Practitioners or the National Institute for Clinical Excellence.

Citation:

McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, Feetam C, Hague J, Hughes I, Kelly J, Kosky N, Lear G, Owens L, Ratcliffe J, Salkovskis P (2004) *Clinical Guidelines and Evidence Review for Panic Disorder and Generalised Anxiety Disorder* Sheffield: University of Sheffield/London: National Collaborating Centre for Primary Care

Quick Reference Guide

An abridged version of this guidance (a 'quick reference guide') is also available from the NICE website (www.nice.org.uk/CG022quickrefguide). Printed copies of the quick reference guide can be obtained from the NHS Response Line: telephone 0870 1555 455 and quote reference number N0763.

Information for the Public

Information for the Public is available from the NICE website or from the NHS Response Line (quote reference number N0764 for a version in English and N0765 for a version in English and Welsh).

Contents

1. Key priorities for implementation

General management

- Shared decision-making between the individual and healthcare professionals should take place during the process of diagnosis and in all phases of care.
- Patients and, when appropriate, families and carers should be provided with information on the nature, course and treatment of panic disorder or generalised anxiety disorder, including information on the use and likely side-effect profile of medication.
- Patients, families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate.
- All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly.

Step 1: Recognition and diagnosis of panic disorder and generalised anxiety disorder

- The diagnostic process should elicit necessary relevant information such as personal history, any self-medication, and cultural or other individual characteristics that may be important considerations in subsequent care. (See also 'Which NICE guideline', page 12)

Step 2: Offer treatment in primary care

- There are positive advantages of services based in primary care practice (for example, lower drop-out rates) and these services are often preferred by patients.
- The treatment of choice should be available promptly.

Panic disorder

- Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.
- Any of the following types of intervention should be offered and the preference of the person should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order, are:
  - psychological therapy (cognitive behavioural therapy [CBT])
  - pharmacological therapy (a selective serotonin reuptake inhibitor [SSRI] licensed for panic disorder; or if an SSRI is unsuitable or there is no improvement, imipramine[a] or clomipramine[a] may be considered)

[a] Imipramine and clomipramine are not licensed for panic disorder but have been shown to be effective in its management.

- self-help (bibliotherapy – the use of written material to help people understand their psychological problems and learn ways to overcome them by changing their behaviour – based on CBT principles).

Generalised anxiety disorder

- Benzodiazepines should not usually be used beyond 2–4 weeks.
- In the longer-term care of individuals with generalised anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalised anxiety disorder should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order, are:
  - psychological therapy (CBT)
  - pharmacological therapy (an SSRI)
  - self-help (bibliotherapy based on CBT principles).

Step 3: Review and offer alternative treatment

- If one type of intervention does not work, the patient should be reassessed and consideration given to trying one of the other types of intervention.

Step 4: Review and offer referral from primary care

- In most instances, if there have been two interventions provided (any combination of psychological intervention, medication, or bibliotherapy) and the person still has significant symptoms, then referral to specialist mental health services should be offered.

Step 5: Care in specialist mental health services

- Specialist mental health services should conduct a thorough, holistic, re-assessment of the individual, their environment and social circumstances.

Monitoring

- Short, self-complete questionnaires (such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder) should be used to monitor outcomes wherever possible.

Important messages to share with people with generalised anxiety disorder or panic disorder

- Anxiety disorders are
  - common
  - chronic
  - the cause of considerable distress and disability
  - often unrecognised and untreated
- If left untreated they are costly to both the individual and society.
- A range of effective interventions is available to treat anxiety disorders, including medication, psychological therapies and self-help.
- Individuals do get better and remain better.
- Involving individuals in an effective partnership with health care professionals, with all decision-making being shared, improves outcomes.
- Access to information, including support groups, is a valuable part of any package of care.

2. Panic disorder and generalised anxiety disorder

2.1 Introduction

Anxiety disorders are neither minor nor trivial. They cause considerable distress and are often chronic in nature.

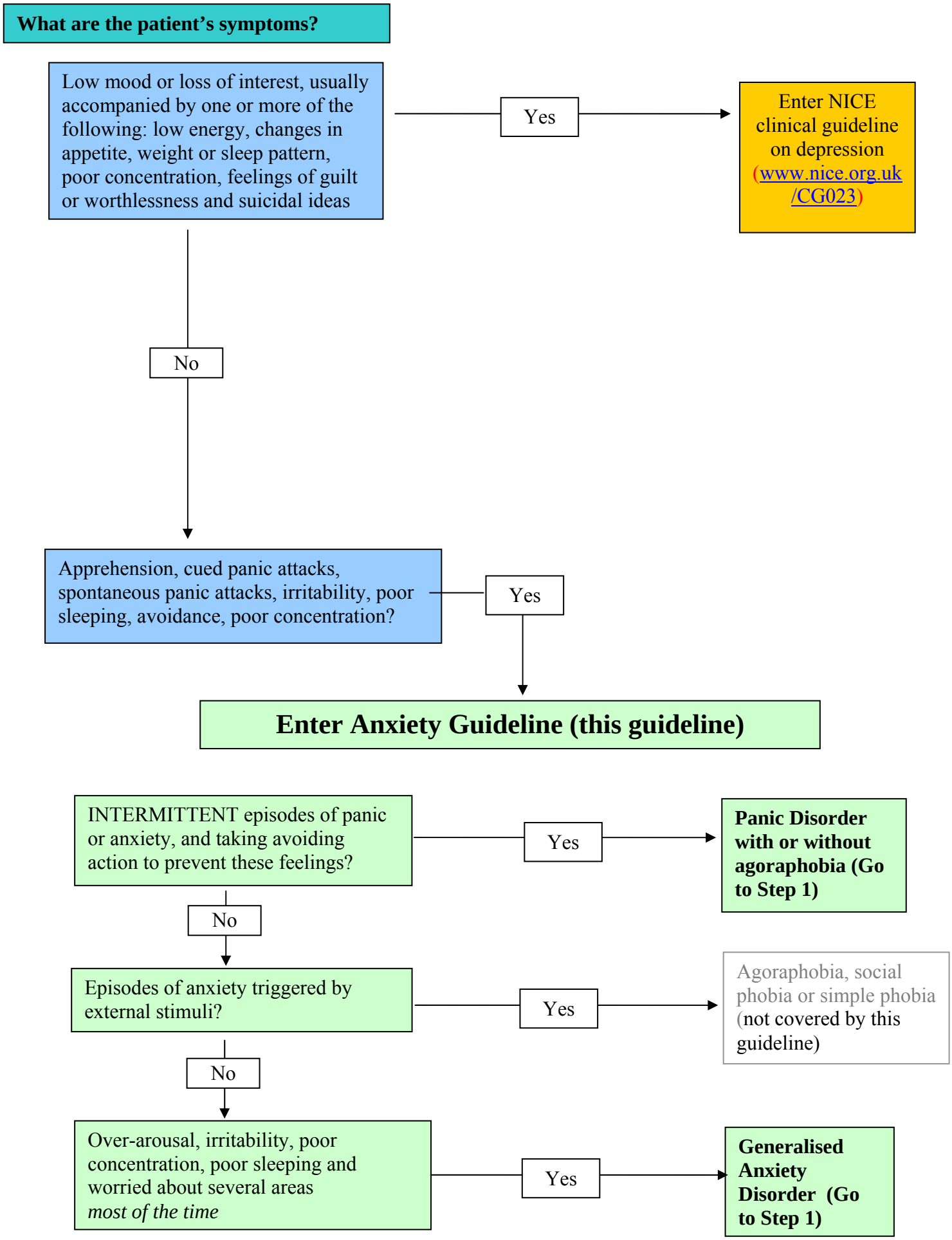
Both panic disorder and generalised anxiety disorder, are one subtype of several anxiety disorders, including:

- generalised anxiety disorder (GAD)
- panic disorder (with or without agoraphobia)
- post traumatic stress disorder
- obsessive compulsive disorder
- specific phobia (e.g. of spiders)
- social phobia (social anxiety disorder)
- acute stress disorder

In some instances it is difficult to distinguish the different disorders, and co-morbidity is very common, with other anxiety disorders, depression and other mood disorders.

This guideline is one of several that NICE will produce to address common mental health problems. To help guide health care professionals to the most appropriate NICE guideline, the algorithm overleaf may be of use.

Which NICE guideline?



2.2 Panic disorder and generalised anxiety disorder

The introduction of DSM IV (1980) marked significant changes in the way that anxiety disorders were considered, identified and categorised. For example, generalised anxiety disorder had often been viewed as a residual category to be used only when an individual did not fit into other defined conditions. The advent of DSM IV meant that it became a well defined condition in its own right with diagnostic criteria. The developments in DSM IV were later reflected in ICD 10, although the descriptions in ICD 10 (at least in terms of the phraseology) are considered more flexible.

DSM IV criteria are those most often used in the USA and therefore are the criteria most often used in research studies, due in large part because of where much of the research is both undertaken and funded (for both GAD and panic disorder).

DSM IV has quite comprehensive descriptions of the conditions and these are presented below.

2.2.1 Panic disorder defined

DSM-IV-TR states that the essential feature of panic disorder is the presence of recurrent, unexpected panic attacks followed by at least one month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks, or a significant behavioural change related to the attacks.

The panic attacks are not due to the direct physiological effects of a substance or general medical condition. The panic attacks are not better accounted for by another mental disorder. Depending on whether criteria are also met for agoraphobia, panic disorder with or without agoraphobia is diagnosed.

At least two unexpected panic attacks are needed for diagnosis of the disorder.

Individuals with the disorder display characteristic concerns or attributions about the implications or consequences of the panic attacks. Some individuals fear that they indicate the presence of an undiagnosed, life-threatening illness (such as cardiac disease). They may remain frightened and unconvinced that they do not have a life-threatening illness despite repeated medical testing and reassurance. Other individuals may fear that they are ‘going crazy’, losing control or are emotionally weak.

2.2.1.1 Panic attacks

An unexpected (spontaneous or uncued) panic attack is one that is defined as one that an individual does not immediately associate with a situational trigger. These situational triggers can be external (e.g. phobic object or situation) or internal (physiological arousal).
The frequency and severity of panic attacks varies widely.

2.2.1.2 Agoraphobia

The essential feature of agoraphobia is anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a panic attack. This anxiety is said to typically lead to a pervasive avoidance of a variety of situations that may include: being alone outside the home or being home alone; being in a crowd of people; travelling by car, bus or place, or being on a bridge or in a lift.

2.2.1.3 Associated features and disorders (from DSM-IV-TR)

In addition to the worry about panic attacks and their implications, many individuals also report constant or intermittent feelings of anxiety that are not focused on any specific situation or event. Some may become excessively apprehensive about the outcome of routine activities, in particular those associated with the health of or separation from loved ones. Some individuals often anticipate a catastrophic outcome from a mild physical symptom or medication side effect. Demoralisation is said to be a common consequence, with many individuals becoming discouraged, ashamed and unhappy about the difficulties of carrying out their normal routines.

2.2.1.4 Associated physical examination findings

Transient tachycardia and moderate elevation of systolic blood pressure may occur during some panic attacks. It is also reported that significant comorbidity between panic disorder and general medical conditions including dizziness, cardiac arrhythmias, hyperthyroidism, asthma, chronic obstructive pulmonary disease, irritable bowel syndrome. (American Psychiatric Association, DSM-IV-TR, 2000, code 300.01 – panic disorder without agoraphobia, 300.21 panic disorder with agoraphobia, pp430-441)

2.2.2 **Generalised anxiety disorder defined**

DSM –IV-TR states that the essential feature of generalised anxiety disorder is excessive anxiety and worry (apprehensive expectation), occurring more days than not for a period of at least 6 months, about a number of events or activities. It goes on to say that the individual finds it difficult to control the worry. The anxiety and worry must be accompanied by at least three additional symptoms from a list that includes:

- restlessness
- being easily fatigued
- difficulty concentrating
- irritability
- muscle tension
- disturbed sleep

The focus of the anxiety and worry is not confined to features of another disorder (e.g. being embarrassed in public [as in social phobia], having panic attacks [panic disorder]). The definition from DSM-IV-TR goes on to say that although individuals with generalised anxiety disorder may not always identify the worries as excessive, they report subjective distress due to constant worry, have difficulty controlling the worry, or experience related impairment in social, occupational or other important areas of functioning. To meet a diagnosis of generalised anxiety disorder, their experiences must not be due to the direct physiological effects of a substance or a general medical condition, and the symptoms must not occur exclusively during a mood, psychotic or pervasive developmental disorder.

DSM-IV-TR goes on to say that the intensity, duration or frequency of the anxiety and worry is out of proportion to the actual likelihood or impact of the feared event. With generalised anxiety disorder the individual finds it difficult to keep worrisome thoughts from interfering with attention to tasks being undertaken. The manual states that adults with generalised anxiety disorder often worry about everyday, routine life circumstances (such as possible job

responsibilities, finances, health of family members, misfortunes that may befall their children) or minor matters (such as household chores, car repairs or being late). The focus of worry may shift from one concern to another during the course of the event.

2.2.2.1 Associated features and disorders (from DSM-IV-TR)

DSM-IV-TR states that individuals with generalised anxiety disorder may experience the following:

- muscle tension
- trembling
- twitching
- feeling shaky
- muscle aches
- soreness

In generalised anxiety disorder, according to DSM-IV, somatic symptoms, such as:

- sweating
- nausea
- diarrhoea

may also be experienced.
For individuals with generalised anxiety disorder, symptoms of autonomic hyperarousal (such as accelerated heart rate, shortness of breath and dizziness) are less prominent than in other anxiety disorders.

Generalised anxiety disorder is said to be frequently occur alongside mood disorders such as depression and other anxiety disorder such as panic disorder, social phobia and specific phobias. Substance related disorder are also said to co-occur quite frequently. DSM-IV TR also points out that other conditions associated with stress, such as irritable bowel syndrome, frequently accompany generalised anxiety disorder. (American Psychiatric Association, DSM-IV-TR, 2000, code 300.02, pp.472-6)

2.2.3 Incidence and prevalence

Accurate information about the incidence and prevalence of anxiety disorders is difficult to obtain. Relevant, key findings from the recent survey by the Office of National Statistics (ONS 2000) entitled Psychiatric Morbidity among Adults living in Private Households are presented here to give an indication of the extent to which anxiety disorders exists.

ONS found that there were 164 cases per 1,000 of neurotic disorder in the week before interview, which represents about 1 in 6 of all adults. They found that the most prevalent neurotic disorder among the population as a whole was mixed anxiety and depressive disorder (88 cases per 1,000). They report that this is a ‘catch-all’ category, in that it included people with significant neurotic psychopathology who could not be coded into any of the other five neurotic disorders. The next most common disorder found was that of generalised anxiety

disorder (44 adults per 1,000). They reported that the remaining disorders (depressive episode, phobias, obsessive compulsive disorder and panic) were less prevalent, ranging from 26 to 7 cases per 1,000.

The ONS survey found that prevalence rates were higher among women than men for all disorders except panic (7 cases per 1,000 for both men and women), although the differences were only statistically significant for phobias and mixed anxiety and depressive disorder.

2.2.3.1 Characteristics of individuals affected

The ONS survey found that generalised anxiety disorder affected 5% of adults in the week before interview. They reported that, compared with adults with no neurotic disorder, those with generalised anxiety disorder were:

more likely to be:

- aged between 35 and 54 (55% compared with 38%);
- divorced or separated (20% compared with 7%); and
- living as a one person family unit (22% compared with 16%) or as a lone parent (11% compared with 4%).

less likely to be:

- aged between 16 and 24 (5% compared with 15%) or between 65 and 74 (6% compared with 12%); and
- married or cohabiting (61% compared with 67%).

They also found that women with generalised anxiety disorder were particularly likely to be living as lone parents, 17% compared with 8% among women with no neurotic disorder. They also reported that men with generalised anxiety disorder were less likely than those with no neurotic disorder to be single, 19% compared with 27%.

One per cent of adults were assessed as having a panic disorder in the survey. As the number of people with panic disorder in the survey was very small, differences between those with panic disorder and no neurotic disorders did not reach statistical significance. They did note, however, that it was equally likely to occur in men and women, whereas all other disorders, occurred more frequently in women.

2.2.4 Impact of panic disorder and generalised anxiety disorder

The impact of panic disorder and generalised anxiety disorder are considerable, in terms of the NHS, such as GP consultations (often multiple consultations), on society as a whole in terms of sickness and absence from work, labour turnover and reduced productivity; and on in individuals and families. The impact in any of these spheres is difficult to measure accurately and estimates may underestimate the impact.

For the individual, the impact can be considerable both in terms of their economic well being as well as their health. Individuals may report severe and enduring physical sensations. There may be considerable concern that they have something physically and this may be very difficult to provide adequate reassurance that this is not the case.

3. Guideline development methods

3.1 Introduction

This guideline is aimed at all health care professionals providing care to individuals who have panic disorder (with or without agoraphobia) or generalised anxiety disorder.

The guideline provides recommendations to help health care professionals in primary and secondary care.

Guideline development methods are NICE development process, which are described in three NICE Guideline Development Process Manuals, available on the NICE website (www.nice.org.uk).

Key features of the guideline are that:

- it is evidence based, where evidence is available
- in areas where evidence is lacking this is made clear, and the consensus methods used are clearly described
- recommendations are explicitly linked to evidence where it is available
- the recommendations, methods and conclusions in the guideline are explicit and transparent.

The full scope of the guideline is presented in Appendix 17.

3.2 Using guidelines

Guidelines are only one type of information that health care professionals may use when making decisions about patient care. It is assumed that this guideline, like all guidelines, will be used by health care professionals who will also bring to bear their clinical knowledge and judgement in making decisions about caring for individual patients. It may not always be appropriate to apply either specific recommendations or the general messages in this document to each individual or in every circumstance. The availability of resources may also influence decisions about patient care, including the adoption of recommendations.

3.3 Responsibility and support for the guideline

The guideline was commissioned by NICE. The development of the guideline was undertaken by ScHARR, a provider partner in the National Collaborating Centre for Primary Care (NCC-PC). The guideline development group (GDG) was convened by the NCC-PC. The guideline development group consisted of relevant health care professionals, patient representatives and guideline developers, including a systematic reviewer. The membership of guideline development group is shown in Appendix 16.

3.4 Scope of the guideline

The scope of this guideline is the management of adults (aged 18 years or older) with a working diagnosis of panic disorder (with or without agoraphobia) or generalised anxiety disorder. The guideline does not cover the care of the following: children (people younger than 18 years); people with major depression; people with mixed anxiety and depression; people with bipolar depression; people with seasonal affective disorder (SAD); people with combat disorder; people with anxiety disorders associated with dementia; people with phobic disorders other than panic disorder with agoraphobia; people with organic brain disorders. The guideline also does not cover the care of people with post-traumatic stress disorder or obsessive–compulsive disorder, for which other NICE guidelines are being developed. The full scope can be seen in Appendix 17.

3.5 Key clinical questions

The guideline development group identified the potential pathways that people with panic disorder or generalised anxiety disorder might take in accessing and moving though health care services. From these pathways they identified potential interventions that might be available and also the decision points where these interventions might have to be considered by individual patients and those involved in their care. This provided the key clinical questions that the guideline would try and address.

When referring to pharmacological treatments, NICE guidelines will normally recommend use within licensed indications. Exceptionally, and only where the evidence supports it, the guideline may recommend use outside a treatment's licensed indications. In this guideline the tricyclic antidepressant, imipramine, was considered to be a pharmacological intervention that although not licensed for panic disorder should be considered. We did therefore look at the research literature for this preparation and made recommendations about its use in panic disorder. The decision to examine imipramine was also influenced by the consideration that it was a drug that had been available before current licensing practices existed and was considered by some guideline development group members to be used in clinical practice.

These key clinical questions are presented in Appendix 18.

3.6 Evidence identification

3.6.1 Search strategies

3.6.1.1 Diagnosis

The search strategies attempted to locate meta-analyses, systematic reviews and diagnostic papers for generalised anxiety disorder and panic disorder (with or without agoraphobia). Searches were limited to English language citations.

ICD-10 and DSM-IV classifications were used to identify relevant studies. Although in the development process, papers considered were limited to those that discussed tools/instruments that could be used as screening and diagnostic tools, rather than instruments that might be used for examining outcomes in studies, the literature search did not impose these limits.

Other papers that might be useful in the process of diagnosis, such as papers that discussed patient or clinician characteristics that might influence prognosis were also searched for.

3.6.1.2 Interventions

The search strategies attempted to locate meta analyses, systematic reviews and randomised controlled trials of interventions for generalised anxiety disorder and panic disorder (with or without agoraphobia). Searches were limited to English language citations.

The search strategies are presented in Appendix 19.

3.6.2 Sifting and reviewing the evidence

Studies retrieved were assessed for their quality and relevance in answering the key clinical questions identified by the guideline development group.

For studies where our concern is that of what intervention seems to be most effective, then in our assessment of those studies our key concern was the quality of the study in terms of the various aspects of study validity. Firstly, if a study can credibly demonstrate the causal relationship between treatment and outcome then it can be said to have internal validity. Secondly, if the findings can be generalised from the specific study sample to a wider population then it is said to be generalisable or to have external validity. Thirdly, if the study actually measures what it says it measures then it is said to have construct validity.

3.6.2.1 Outcomes used

The issue of outcomes in panic disorder and GAD is problematic and often controversial. The following approach was used in the development of this guideline.

<u>3.6.2.1.1 Panic disorder</u>

Outcomes for Panic disorder are defined in terms of panic attacks with the primary outcomes to do with changes in panic attacks including

- The number of people per treatment group who did not show a remission in the panic attacks
- The number of people per treatment group who did not show a clinical improvement in the panic attacks
- Number of people reporting panic-related phobias (including agoraphobia and body-sensation phobia)
- Number of people reporting anticipatory anxiety relapse rates among panic-free or symptoms-free patients receiving treatment
- The number of people per treatment group who had any adverse effect (other than deterioration in panic symptoms)

- The average change in the panic symptoms or their severity at the end of the trial

Other outcome measures of interest listed included outcomes concerning comorbidity. Such outcomes will not be isolated as the scope of this review specifies non-inclusion of studies concerning comorbid conditions.

Otherwise, the third group of outcomes that will be recorded, is, as with GAD, the acceptability of the treatment. These were measured by the number of people dropping out during the trial.

Also measured are suicide attempts, use/misuse of substances, use of health services and death.

It is also noted that all of the above outcomes are, where possible, grouped according to time periods (short-term: less than three months; medium-term: between three and six months; long-term: more than six months).

3.6.2.1.2 GAD

Generalised anxiety changes at the end of the trial, (including absence of treatment effect or response, improvement rate in the symptoms of GAD on any anxiety scale, group mean score on Hamilton Anxiety scale or other scales as provided by original studies), acceptability of treatment as measured by the number of people dropping out during the trial and post randomisation exclusions; numbers of patients reporting at least one side-effect during the trial; specific side effects, relapse, quality of life measure changes at the end of the treatment.

3.6.3 Synthesising the evidence

Extraction tables were used to provide the basis for conclusions about the findings of the body of evidence.

3.6.4 Areas without evidence

The guideline development group used informal consensus methods to derive evidence statements and recommendations in areas where research literature was not available, drawing upon their clinical knowledge and experience. The research recommendations reflect some of the areas that lacked research evidence that would have been useful in developing recommendations.

3.7 Evidence grading

Once individual papers had been assessed for methodological quality and relevance in terms of our key clinical questions, they were graded according to the levels of evidence. We have used the following grading which differentiates in level I between meta-analyses and RCTs and in level II different types of experimental design. These distinctions are not used by NICE (where Ia and Ib are not differentiated nor are IIa or IIb).

Classification of Evidence

Evidence level	Description
Ia:	evidence from meta-analysis of randomised controlled trials
Ib:	evidence from at least one randomised controlled trial
IIa:	evidence from at least one controlled study without randomisation
IIb:	evidence from at least one other type of quasi-experimental study
III:	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV:	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Adapted from Eccles M, Mason J (2001) How to develop cost-conscious guidelines. *Health Technology Assessment* 5(16)

This classification is most appropriate for questions of causal relationships, and is usually used to assign studies, dealing with causal relationships, to levels of evidence.

Other types of evidence may, however, have been used in this guideline. In some areas of management, studies looking at causation may not be available or may not be the appropriate study type. Therefore different types of study design will also have been assessed for quality and graded according to the classification outlined, even though the classification is most appropriate for causal relationship studies.

The literature was synthesised, using a qualitative narrative approach, to produce an evidence report. This also included health economics information. This evidence report, with summary evidence statements, was presented to the guideline development group.

3.8 Health economic review and analysis

The search strategy to identify health economics papers is included in Appendix 19, which contains all search strategies. From a health economics perspective the available evidence relating to the cost effectiveness of pharmacological and/or non-pharmacological treatments for generalised anxiety disorder or panic disorder is scant. The majority of studies which have been undertaken to assess cost effectiveness issues in this area suffer from methodological weaknesses in that these studies have been undertaken upon small numbers of patients and often not in an RCT or controlled before and after study format. Given the paucity and general poor quality of available evidence from a health economics perspective it was decided that it would not be possible to undertake an economic modelling exercise as a component of this guideline.

The literature relating to cost effectiveness has been reviewed and considered under three main headings:

1. Studies relating to the cost effectiveness of pharmacological agents

2. Studies relating to the cost effectiveness of non-pharmacological agents
3. Studies relating to the costs of cognitive behavioural therapy (CBT).

These reviews have been included in the relevant sections of the guideline where effectiveness of the interventions have been discussed. The evidence tables for the health economics studies are presented in Appendix 12.

3.9 Derivation and grading of recommendations

The derivation of recommendations usually involves assessment of evidence, processes of interpretation and consensus to arrive at recommendations. The mix of evidence, interpretation and consensus will vary between topic areas. The grading of recommendations takes account of this and therefore variation may occur between different groups presented with the same evidence. Whilst evidence statements can be formulated without reference to the context in which clinicians practise, this is not always the case with recommendations.

Recommendations were graded A to D, using the current NICE approach.

Grading of Recommendations

A	directly based on category I evidence
B	directly based on category II evidence, or extrapolated recommendation from category I evidence
C	directly based on category III evidence, or extrapolated recommendation from category I or II evidence
D	directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence

Adapted from Eccles M, Mason J (2001) How to develop cost-conscious guidelines. *Health Technology Assessment* 5(16)

The grading system used was not a mechanistic process where a recommendation derived from an evidence statement with a particular level of evidence had one, and only one, corresponding recommendation grading. The development of recommendations draws upon both the research evidence and expertise of the Guideline Development Group. Therefore a lower strength of recommendation could be given than its evidence level might suggest. Furthermore the available evidence may only partially cover an important clinical area, so again a gap in the evidence would occur. Thus to cover the areas identified by the key clinical questions it is likely that inferences from the available evidence will have to be made, which are beyond the empirical data.

The recommendation grading indicates only the level of evidence upon which it is based. It does not indicate the level of clinical importance or clinical practice relevance.

3.9.1 Consensus in recommendations

There may be areas where the group was unable to reach consensus on an area, no matter whether evidence is available or not. Where this may happen, there is scope to report that a consensual recommendation could not be reached, to present the opposing views, and leaving the final view to the user of the guidelines. Consensus was achieved on all recommendations presented in the guideline.

3.10 Update of evidence searches

Due to the delay in publication of the guideline, searches were repeated for MEDLINE and Cochrane Library in November 2004. The search period had a 6 month overlap with previous searches. One thousand, six hundred and eighty one hits were found. The abstracts for these were looked at and the same selection criteria as previously used were applied. Once duplicates and those already included in the guideline (e.g. because of overlapping time period) were excluded, forty two papers remained.

It was considered that nothing was found in the updated searches that necessitated any changes in evidence statements or guideline recommendations.

3.11 Guideline review

The process of reviewing the evidence is expected to begin 4 years after the date of issue of this guideline. Reviewing may begin earlier than 4 years if significant evidence that affects the guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

4. Diagnosis and decision making

4.1 Recognition and diagnosis of panic disorder and generalised anxiety disorder

Consultation Skills

1. **All healthcare professionals involved in diagnosis and management should have a demonstrably high standard of consultation skills so that a structured approach can be taken to the diagnosis and subsequent management plan for panic disorder and generalised anxiety disorder. The standards detailed in the video workbook Summative Assessment For General Practice Training: Assessment Of Consulting Skills – the MRCGP/Summative Assessment Single Route (see www.rcgp.org.uk/exam) and required of the Membership of the Royal College of General Practitioners are a good example of standards for consulting skills. (D)**

Diagnosis

The accurate diagnosis of panic disorder or generalised anxiety disorder is central to the effective management of these conditions. It is acknowledged that frequently there are other conditions present, such as depression, that can make the presentation and diagnosis confusing. An algorithm has been developed to aid the clinician in the diagnostic process, and to identify which guideline is most appropriate to support the clinician in the management of the individual patient

2. **The diagnostic process should elicit necessary relevant information such as personal history, any self medication, and cultural or other individual characteristics that may be important considerations in subsequent care. (D)**

3. **There is insufficient evidence on which to recommend a well-validated, self-reporting screening instrument to use in the diagnostic process, and so consultation skills should be relied upon to elicit all necessary information. (D)**

Comorbidities

4. **The clinician should be alert to the common clinical situation of comorbidity, in particular, anxiety with depression and anxiety with substance abuse. (D)**

5. **The main problem(s) to be treated should be identified through a process of discussion with the patient. In determining the priorities of the comorbidities, the sequencing of the problems should be clarified. This can be helped by drawing up a timeline to identify when the various problems developed. By understanding when the symptoms developed, a better understanding of the relative priorities of the comorbidities can be achieved, and there is a better opportunity of developing an effective intervention that fits the needs of the individual. (D)**

6. **When the patient has depression or anxiety with depression, the NICE guideline on management of depression should be followed. (D)**

Presentation in A& E with panic attacks

It is important to remember that a panic attack does not necessarily constitute a panic disorder and appropriate treatment of a panic attack may limit the development of panic disorder. For people who present with chest pain at A&E services, there appears to be a greater likelihood of the cause being panic disorder if coronary artery disease is not present or the patient is female or relatively young. Two other variables, atypical chest pain and self-reported anxiety, may also be associated with panic disorder presentations, but there is insufficient evidence to establish a relationship.

7. If a patient presents in A&E, or other settings, with a panic attack, they should:

- **be asked if they are already receiving treatment for panic disorder**
- **undergo the minimum investigations necessary to exclude acute physical problems**
- **not usually be admitted to a medical or psychiatric bed**
- **be referred to primary care for subsequent care, even if assessment has been undertaken in A&E**
- **be given appropriate written information about panic attacks and why they are being referred to primary care**
- **be offered appropriate written information about sources of support, including local and national voluntary and self-help groups. (all D)**

Shared decision-making and information provision

People who have panic disorder or generalised anxiety disorder and their carers need comprehensive information, presented in clear and understandable language, about the nature of their condition and the treatment options available. Such information is essential for shared decision-making between patients and healthcare professionals, particularly when making choices between broadly equivalent treatments. In addition, given the emotional, social and economic costs that generalised anxiety disorder or panic disorder usually entail, patients and their families may need help in contacting support and self-help groups. Support groups can also promote understanding and collaboration between patients, their carers and healthcare professionals at all levels of primary and secondary care.

8. Shared decision-making should take place as it improves concordance and clinical outcomes. (C)

9. Shared decision-making between the individual and healthcare professionals should take place during the process of diagnosis and in all phases of care. (D)

10. Patients and, when appropriate, families and carers should be provided with information on the nature, course and treatment of panic disorder or generalised anxiety disorder, including information on the use and likely side-effect profile of medication. (D)

11. To facilitate shared decision-making, evidence-based information about treatments should be available and discussion of the possible options should take place. (D)

12. Patient preference and the experience and outcome of previous treatment(s) should be considered in determining the choice of treatment. (D)

13. Common concerns about taking medication, such as fears of addiction, should be addressed. (D)

14. In addition to being provided with high-quality information, patients, families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate. (D)

Language

15. When talking to patients and carers, healthcare professionals should use everyday, jargon-free language. If technical terms are used they should be explained to the patient. (D)

16. Where appropriate, all services should provide written material in the language of the patient, and appropriate interpreters should be sought for people whose preferred language is not English. (D)

17. Where available, consideration should be given to providing psychotherapies in the patient's own language if this is not English. (D)

Evidence statements

1. *Shared decision making improves concordance and clinical outcomes. (III)*
2. *There is no evidence that specifically links people with GAD or PD to consultation skills of health care professionals or outcomes. (IV)*
3. *There is some general evidence that links outcomes and patient satisfaction with consultation style. (III)*
4. *There is no evidence that links patient satisfaction with outcome when treating people with GAD or PD. (IV)*
5. *Involving patients in the decision making process improves patient satisfaction with the consultation. (III)*
6. *There is considerable variability as to the amount that individual patients wish to be involved in the decision making process in general medical practice. (III)*
7. *There is no evidence that describes the most effective way of involving the patient in the decision making process. (IV)*
8. *Patients need information about treatment options to engage in shared decision making. (IV)*
9. *Primary care can provide effective treatment for GAD and PD. (Ia/b)*
10. *In most cases, people with anxiety disorders can be effectively cared for in primary care. (III)*

4.1.1 Introduction

The process of the consultation, how the doctor, nurse, or other health care professional interacts with the patient, is thought to be central to the successful management of people with anxiety disorders. The consultation process covers four different stages:

Stage

1. discovering why the patient has attended,
2. defining the clinical problem,
3. exploring solutions to the problem, and
4. agreeing an effective outcome (RCGP 2003).

These four stages are integral to all consultations, but there is little evidence that demonstrates absolutely that these steps lead to improved clinical outcome (Ford et al 2003a,b, 2002).

These four stages, and the clinical competencies associated with each stage, are required of all new general practitioners. They must be able to demonstrate that they possess these skills and are assessed by means of video assessment (RCGP 2003). Since these skills are a requirement for all general practitioners, it can be considered good practice to be able to utilise these skills when consulting with individuals with anxiety disorders.

4.1.2 Making the Diagnosis of GAD or PD:

The diagnosis of both of these conditions is dependent on the presence or absence of certain symptoms and signs. However the clinical picture at presentation can be extremely variable, and the question of the presence of GAD or PD may only become an issue after several other medical conditions have been excluded, or that the management of other medical conditions have been unsuccessful.

It is the skill of the primary health care professional, to whom the person first presents, to be able to disentangle "the chaos of the first presentation" into a clinical syndrome that allows a management plan to be developed.

The diagnostic criteria have been discussed earlier (see 2.2.1 and 2.2.2). The clinical features of GAD and PD are:

GAD	PD
Symptoms of anxiety, fear, avoidance and increased arousal	Symptoms of anxiety, fear, avoidance and increased arousal
6 month period of excessive anxiety and worry plus anxiety symptoms	Recurrent unexpected panic attacks, plus a month of worry, concern about attacks or a change in behaviour

The constellation of symptoms and signs are nebulous, and to be able to separate out the reason for presentation, and then define the clinical problem (stages 1 and 2 above) may take several consultations.

There are a number of questionnaires that are used in research papers to clarify the diagnosis of GAD or PD, but there are no simple questionnaires that can be used routinely during the primary care consultation. However there is increasing evidence (Freedman 2003) from the United States of America that administering a questionnaire in the waiting room prior to the consultation is both acceptable to the person, and improves the outcome of the consultation. There is a need to develop the research base for this approach in the UK.

Once the clinical picture is clearer, exploring solutions with the individual can take place. To do so requires that the clinician will provide information on different interventions to allow the person to make an informed decision as to which is most appropriate. Such information might include the availability of particular types of talking therapies, the effects of stopping medication, whether or not certain complementary interventions have been shown to be effective. In individual cases there may be specific reasons why one intervention or another is inappropriate.

Using the information discussed in exploring the solution, the best available intervention can be agreed between the individual and the healthcare professional.

These four steps take time to complete, and it is unrealistic to expect that they will all occur within one ten minute consultation. However the presence of this structured approach to the diagnosis of GAD or PD is likely to improve concordance, and hence improve the ultimate outcome.

4.1.3 Cultural variations in presentation

Kirmayer 2001

This paper presents a review (not systematic) of cultural variations in the clinical presentation of depression and anxiety. Somatic symptoms are common and clinicians must be aware of this to avoid unnecessary diagnostic procedures and inappropriate treatment. Four domains are necessary to consider: the ethnocultural identity of the patient, the patients' explanations of illness, culturally distinctive dimensions of the psychosocial environment and levels of functioning and the relationship between individual and clinician. Also important to take into account include social class, socio-economic disparity, power and racism.

4.1.4 Physician characteristics

Robbins 1994

This Canadian study took data from this study from a larger study of symptom experience. The study included 55 physicians who had treated 600 patients. All patients were attending a general hospital family medicine clinic on a self-initiated visit. Only 51% of subjects agreed to participate in this study. Each patient completed the Center for Epidemiologic Studies Depression Scale and the Diagnostic Interview Schedule (CES-D). Physicians completed measures of attitudes toward psychosocial problems, emotional sensitivity and psychological mindedness. They took a brief test of sensitivity to nonverbal expression of emotion. Medical charts were reviewed by a physician blinded to DIS diagnosis and CES-D scores.

On the basis of CES-D, 192 patients (32% of sample) were defined as a case. The DIS definition identified 62 patients (10%) as having either a major depressive episode or an anxiety disorder within the last month. Of all 600 patients, physicians identified 45 (7.5%) as depressed or anxious following the initial clinical visit and 115 patients (19%) as depressed or anxious at some time during the following 12 months. The main findings were as follows: physicians who were more sensitive to nonverbal expressions of emotion made more psychiatric or psychosocial assessment of their patients and appeared to be over-inclusive in their judgements of psychosocial problems; physicians who tended to blame depressed patients made fewer psychosocial assessments and were less accurate in detecting psychiatric distress; false positive labelling of patients was rare.

Van den Brink 2001

This paper describes a study in the Netherlands of consecutive attenders to 18 GPs. There were two stages in the sampling process. In the first stage, patients (18-65 years) were asked to complete the GHQ-12 while waiting to see their GP. In the second stage, a stratified random sample of patients were invited for a baseline psychiatric interview within two weeks of their visit to the GP. This consisted of the CIDI-PHC in order to allow generation of diagnoses according to ICD-10 criteria. The study focused on patients with a diagnosis of depressive episode or GAD (exclusion criteria for absence of panic disorder for GAD was omitted). Patients with four or more symptoms in a section were invited for a 1 year follow-up interview with the CIDI-PHC.

At baseline, 119 patients had GAD, 27 (23%) of whom were not recognised by their GP, 2 (2%) were recognised but no prognosis was given and 25 (21%) did not complete the follow-up interview. Therefore the results of only 65 cases of GAD are reported in the paper.

There was modest agreement between GP prognosis and course for GAD (κ=0.11). Conclusions were that GPs' prognosis of common mental disorders may be too inaccurate to fulfil its important functions in patient management. There is scope for improving the accuracy of prognosis. Finally, GPs were felt to be pessimistic about the 1- year course of depression and generalised anxiety.

4.1.5 Presentation at A&E departments with panic attacks

The nature of some symptoms of panic attacks, such as palpitations, tachycardia, shortness of breath and chest pain, may lead some individuals to think that they are experiencing a potentially life threatening event, such as a heart attack. This often results in presentation to A&E departments. It has been estimated that between 18% and 25% of patients who present to

emergency or outpatient cardiology settings meet the criteria for panic disorder (Huffman and Pollack 2003), which is often not recognised.

A review by Huffman and Pollack (2003) looked at the prevalence of panic disorder among people who seek treatment for chest pain in emergency or outpatient cardiology settings. They reviewed papers published between 1970 and 2001, identified from PubMed. The search terms used were given in the paper. They undertook statistical analyses comparing the rate of panic disorder in subjects with coronary artery disease compares with the rate of panic disorder in people without coronary artery disease. They employed two methods of analysis: first, they summed the total number of patients in all studies and used chi squared to compare panic disorder prevalence between the two groups (which essentially weighted studies on the basis of number of patients enrolled in each study); second, they averaged proportions of patients with panic disorder in each study (giving equal weight to each study regardless of number of patients, to account for the possibility that larger studies may have had methodological or setting-related differences that could have skewed the analysis). They used different papers and different numbers of papers to examine different variables. For patients presenting with chest pain, they found a number of variables associated with a greater prevalence of panic disorder. They found statistically significant associations between panic disorder and, absence of coronary artery disease, female gender and younger age. They also report that atypical chest pain and self-reported anxiety also appeared to be associated with panic disorder, but further studies were needed to confirm this.

The guideline development group thought it important that awareness of panic presentations to A&E was raised, and that for most individuals, reassurance and information should be provided and referral to primary care would allow ongoing care to be initiated.

4.2 Screening tools

Recommendation

1. **There is insufficient evidence on which to recommend a well-validated, self-reporting screening instrument to use in the diagnostic process, and so consultation skills should be relied upon to elicit all necessary information. (D)**

Evidence statements

1. *Recognition of an anxiety disorder is only the beginning of caring for that individual. (IV)*

2. *The ONS survey found that, compared with adults with no neurotic disorder, those with generalised anxiety disorder were:*

   more likely to be:

   - *aged between 35 and 54 (55% compared with 38%);*
   - *divorced or separated (20% compared with 7%); and*
   - *living as a one person family unit (22% compared with 16%) or as a lone parent (11% compared with 4%).*

   less likely to be:

   - *aged between 16 and 24 (5% compared with 15%) or between 65 and 74 (6% compared with 12%); and*
   - *married or cohabiting (61% compared with 67%).*

   and that

   - *women were more likely to be living as lone parents (17% compared with 8%)*
   - *men were less likely to be single (19% compared with 27%)(III)*

4.2.1 Introduction

There are many instruments/tools that are used in measuring outcomes in terms of interventions for anxiety. Many of these instruments may also be used as screening tools (at the individual rather than population level) to identify the level of anxiety/panic that an individual is experiencing. In the development process it was decided that for the considerations relating to diagnosis, only instruments that could be used in the diagnostic process to help confirm a diagnosis would be reviewed. The role that these may have in assisting health care professionals in identifying or confirming panic or generalised anxiety disorder was examined in the review of papers. Their role in case finding was not part of our scope and therefore not addressed The instruments considered were:

- Becks Anxiety Inventory (I and II)
- General Health Questionnaire (GHQ)
- Hamilton Anxiety Scale (HAM-A)
- Hospital Anxiety and Depression Scale (HAD)
- Sheehan Disability Scale
- Sheehan Patient-Related Anxiety Scale (SPRAS)
- Twenty one studies were identified that dealt with screening, diagnosis or measurement of anxiety or panic disorder. The studies are summarised in Table 1. Data on depression, social phobia etc was often presented in the papers but is not reported here unless it was directly related to the findings regarding anxiety screening or diagnosis.

4.2.2 Panic Disorder

Four papers dealt with panic disorder only (Ballenger 1998, Bech 1992, Bouchard et al 1997, Leon et al 1999). Of these, Ballenger 1998, Bech 1992 and Bouchard provided information on measurement of panic disorder only while Leon et al (1999) presented trial data on screening for panic disorder.

4.2.3 Anxiety

Fifteen studies of anxiety were identified. Of these, Barlow & Wincze et al (1998), Maier et al (2000) and Slade & Andrews (2001) dealt with diagnosis only. Kessler et al (1999) dealt with both screening and diagnosis, van den Brink et al (2001) with diagnosis and measurement and Robbins et al (1994) with diagnosis and physicians' characteristics.

With regard to screening, Ballenger et al (2001) presented some information on screening as did Bjelland et al (2002), who also provided information on measurement, and Kessler et al (1999) as mentioned above. Other studies dealing with the measurement of anxiety included Gilbody et al (2001), Kvaal et al (2001) and Dunbar et al (2000), who also presented factor analysis.

Bech et al (1990) and Okun et al (1996) provided theoretical data only, Kirmayer (2001) presented a review of cultural variations in anxiety (see previous section for discussion of study) and Labelle & Lapierre (1993) presented a general review (not systematic) of anxiety.

Two studies were identified that dealt with both panic disorder and anxiety. One (Brown et al 2001b) dealt with diagnosis and McQuaid et al (2000) with screening.

4.2.4 Overviews and use of instruments

4.2.4.1 The use of questionnaires in non-psychiatric settings

Gilbody et al (2001)

This systematic review examined the effect of routinely administered psychiatric questionnaires on the recognition, management and outcome of psychiatric disorders in non-psychiatric settings. Details of search strategies, databases searched, inclusion criteria, outcomes, validity assessment

and data extraction and synthesis were all given in this systematic review, ensuring reproducibility. Nine studies were identified, six of these in primary care and three in general medical outpatient settings. Questionnaires included the Beck depression inventory, the general health questionnaire (versions 12 and 28), the Zung self rated depression scale and an anxiety questionnaire (anxiety scores from symptom check list 90) combined with the SF-36. Of the nine studies, six dealt mainly with depression, two with mental illness or psychological problems and only one with anxiety problems. Therefore the results relate to the recognition of depression. The study dealing with anxiety employed the routine measurement of outcome in addition to the active education of clinicians (including the nature and management of untreated anxiety). This approach increased the rate of recognition of anxiety disorders (defined as "chart notations") from 19% to 32% in the intervention arm (relative risk of recognition 1.72, 1.25 to 2.37). This study also showed increased mental health referrals (10% versus 3%, relative risk of outside referral 2.94, 1.33 to 6.51).

The overall conclusions of the review are that the recognition of emotional disorders seems to be increased only when there is some form of screening procedure, whereby an instrument is administered, scored by someone other than the clinician and the results of those with high scores only fed back to the clinician. There is little evidence to show that routine measurement of outcome is of benefit in improving psychosocial outcomes of those with psychiatric disorder managed in non-psychiatric settings.

4.2.4.2 General instruments

Many instruments can be used to identify anxiety in different presentations (including GAD and PD) as well as being used as outcome measures in studies. This section presents papers that discussed instruments concerned with anxiety which might have had a role in helping health care professionals reach a diagnosis of either GAD or PD.

Anxiety Disorders Interview Schedule

Brown et al 2001b

This paper describes a study of 362 out patients who were assessed and treated at two anxiety research centres in the USA. These patients were randomly selected from 1,400 consecutive admissions meeting eligibility criteria. The Anxiety Disorders Interview Schedule for DSM-IV, Lifetime version (ADIS-IV-L) was administered twice independently to each patient. Interrater reliability of DMS-IV diagnoses was calculated by kappa coefficients. The findings show the ADIS-IV-L to provide good to excellent reliability for the majority of DSM-IV categories. Higher kappas were observed for all principal DSM-IV anxiety and mood disorders relative to reliability findings for the corresponding DSM-III-R categories. Most improved reliability was for panic disorder and GAD. There were potential boundary problems for some disorders (GAD and major depressive disorder). Sources of unreliability included disagreements on whether constituent symptoms were sufficient in number, severity or duration to meet DSM-IV diagnostic criteria.

Hamilton Anxiety Scale

Bech et al 1992

An overall history of the development of the Hamilton scales for depression and anxiety is presented in this paper. The Hamilton Anxiety Scale was originally used on patients with "anxiety neuroses". The Hamilton scales are considered to be a method for standardising a

clinical interview. Factor analysis and latent structure analysis were used to illustrate the relationship between the primary dimension of anxiety and the many second order dimensions. In the Ham-A scale there are two main factors in which the psychic anxiety factor includes items relevant for mild depression or dysthymia.

Hospital Anxiety and Depression Scale

Bjelland et al 2002

This paper presents a literature review of the Hospital Anxiety and Depression Scale. Three questions were addressed: (1) How are the factor structure, discriminant validity and the internal consistency of HADS? (2) How does HADS perform as a case finder for anxiety disorders and depression? (3) How does HADS agree with other self-rating instruments used to rate anxiety and depression?

In total 747 papers were reviewed and from these, 71 relevant papers were identified. In the included studies, most of the patients had cancer or other somatic illnesses and only three studies used samples selected from the general population. With regard to factor analyses, most factor analyses demonstrated a two-factor solution in good accordance with the HADS subscales for Anxiety (HADS-A) and depression (HADS-D). The correlations between the two subscales varied from 0.40 to 0.74 (mean = 0.56). Cronbach's alpha for HADS-A ranged from 0.68 to 0.93 (mean= 0.83).

With regard to identifying cases of anxiety and depression, the sensitivity and specificity of both HADS-A and HADS-D were both approximately 0.80, with 8+ as the optimal cut off point. This threshold was found in the general population samples as well as in the somatic patient samples.

When HADS-A was compared to other instruments, correlations between the GHQ-28 (for two studies) were 0.50 and 0.68. Correlations with the Clinical Anxiety Scale were 0.69 and 0.75 (for two studies). Five studies examined correlations between STAI and HADS and the correlations ranged from 0.64 to 0.81. Two studies examined the correlation between the SCL-90 subscales of Anxiety and Depression and HADS. Correlations for anxiety were 0.49 and 0.73. Low correlations (0.34 to 0.44) were found between the Hamilton Anxiety Rating Scale and HADS-A (one study). The authors conclude that HADS performs well in screening for the separate dimensions of anxiety and depression.

Dunbar et al 2000

This paper describes a community based study in Scotland of 2547 participants who completed a survey including the HAD scale. Three age cohorts were included (approximately 18, 39 and 58 years). Confirmatory factor analysis was used to compare competing models for the structure of the HAD scale. Four models were compared to another model derived from a tripartite theory of anxiety and depression. The model derived from the tripartite theory produced the closed fit to the data. This model included factors labelled negative affectivity, anhedonic depression and autonomic anxiety. These three factors appear to underlie the HAD scale. The authors suggest that the HAD scale contains only a few items regarding negative affectivity and autonomic anxiety and that additional markers of these should be used to supplement the HAD scale.

General Health Questionnaire

Kessler et al 1999

This paper reports a study of a single GP practice within the UK. A total of 305 consecutive patients completed the GHQ (12 items). A score of 3 or more on this questionnaire was adopted as definition of a case of psychological disorder. Patients also completed the symptom interpretation questionnaire. GPs were blind to the results and were asked to report any diagnosis of depression or anxiety they made. For the symptom interpretation questionnaire three explanations were attached to each symptom: psychologising (psychological explanation), somatising (physical explanation) or normalising (explanation for symptoms from life circumstances). Patients were asked to choose one explanation for each symptom. Patients were then classified as predominantly normalisers, psychologisers or somatisers if they scored 7 or more on that scale.

On the GHQ, 157 (52%, CI: 46%-57%) scored 3 or more. A diagnosis of depression was made by GPs in 57 patients (19%, CI: 15%-24%) and a diagnosis of anxiety in 14 (5%, CI: 3%-8%). Measured against the GHQ threshold of 3 or more, GPs showed a specificity of 80% (69% to 89%0 and a sensitivity of 57% (50% to 63%). There were also 14 false positive results (diagnosed by GP as depressed or anxious but scored less than 3 on GHQ).

With regard to the symptom interpretation questionnaire, the normalising attribution was most often selected. Subjects with a normalising attributional style were less likely to be detected as cases. In the 46 patients (85%, 73% to 93%) who had high questionnaire and high normalising scores, doctors did not make any psychological diagnosis. The more normalising attributions patients choose, the less likely are GPs to diagnose depression or anxiety and the association remains after adjustment for age, sex, GHQ score and which doctor saw the patient.

Spielberger State Trait Anxiety Inventory

Kvaal et al 2001

This study was undertaken to investigate the observed high scores for the state part of the STAI among geriatric inpatients. The study was undertaken in a hospital in Oslo, Norway. A total of 101 patients who were 60 years or over and suffered from one or more chronic somatic disease took part in the study. Also, 68 healthy controls took part in the study. The key findings were that the STAI “absence of anxiety” items were scored significantly higher than that for the ten “presence of anxiety” items. Factor analysis produced two correlated factors: well-being and nervousness. The most important cause for the observed high score on the STAI state instrument in geriatric patients relates to a reduced well-being.

Symptom-Driven Diagnostic System for Primary Care

Leon et al 1999

In this study, 1001 primary care patients in California completed the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) (screens for alcohol dependence, drug dependence, GAD, MDD, OCD, panic disorder and suicidal ideation) and the Sheehan Disability Scale (to assess functional impairment). Patients were randomly chosen from those with scheduled appointments with primary care clinicians. The study dealt with the screening of depression and panic disorder only. There were 78 false positive and 18 false negative results on the panic disorder screen. This represents 61.9% of the positive panic disorder screens. The positive predictive value (proportion of positive screens who have the disorder) for panic

disorder was 38.1%. False negative rate, among those meeting criteria for the disorder, was 27.3% for panic disorder. Sensitivity for panic disorder was 72.7%.

With regard to functional impairment, those with false positive results and false negative results had similarly moderate functional impairment. A substantial number of patients with either false positive or false negative screen results met diagnostic criteria for other mental disorders.

Multiple instruments compared

McQuaid et al 2000

A total of 213 primary care patients in California, USA took part in this study. This site was one of several that took part in a larger study. Participants were asked to complete the screening instruments and a structured diagnostic interview. Screening instruments included the Center for Epidemiological Studies-Depression (CES-D), the Autonomic Nervous System Questionnaire (ANS) used to diagnose panic disorder, the Beck Anxiety Inventory (BAI) and the Social Phobia Questionnaire (SPQ), in which separate total scores for anxiety and avoidance were calculated. The diagnostic interview was the Composite International Diagnostic Interview, short form (CIDI). The ANS screening instrument was developed by the authors.

With regard to frequency of diagnosis, there were 184 screener positive patients, and of these 29 (15.8%) met criteria for GAD and 18 (9.8%) met criteria for panic disorder. For those 29 patients not meeting screening criteria, one (3.5%) participant met CIDI criteria for GAD. For those patients with a diagnosis, 38 (43.7%) participants had multiple diagnoses. All screening measures were significantly correlated at $p<0.05$.

Logistic regression analyses were used to investigate the relationship between screening measures and diagnosis of psychiatric disorders. Depression diagnosis was related to CES-D score as well as ANS score. GAD diagnosis was not related to BAI but was related to CES-D. Panic disorder was related to ANS as well as CES-D. Both the CES-D and the SPQ anxiety scale were related to the presence of any diagnosis. Additional logistic regression analyses for both GAD and panic disorder were conducted and any relationship between the CES-D and anxiety disorders was not accounted for solely by the comorbidity of depression diagnosis and anxiety. Sensitivities and specificities are presented for the CES-D, SPQ-Anxiety and the ANS. For the CES-D, standard cut off score of 16 provides a sensitivity of 0.79 and a specificity of 0.77 when identifying depression. For the ANS, a cut off of 4 gives a sensitivity of 0.94 and a specificity of 0.76 for panic disorder. For any diagnosis and a cut off score of 15 on the CES-D there is a sensitivity of 0.72 and a specificity of 0.80. The authors therefore conclude that the CES-D is not necessarily specific for depression but is a useful tool for screening for psychopathology, the ANS is highly sensitive and reasonably specific for panic disorder and the BAI is a relatively poor screening tool for GAD.

Okun et al 1996

This paper describes a comparison of the item content of the Psychiatric Symptom Index with two other scales, the Center for Epidemiologic Studies (CES)-Depression Scale and the STAI using the DSM-IV criteria to diagnose major depressive episode and GAD. The Psychiatric Symptom Index contains 29 items and was designed for use in a community sample to measure stress and coping. The CES-Depression Scale was designed to measure depressive symptoms in a community sample and includes 20 items. Finally the STAI has two separate 20 item scales. In the state scale, the respondent indicates how he/she feels right now and on the trait scale the respondent indicates how he/she generally feels.

DSM-IV contains six criteria used to define GAD. The Psychiatric Symptom Index and the STAI each measured 5 of the 8 domains for GAD. Although the authors conclude that the Psychiatric Symptom Index achieves comparable content validity to the STAI, the comparison is theoretical only and no actual trial data is presented. No items from the Psychiatric Symptom Index covered excessive anxiety and worry or difficulty in controlling worry.

4.2.4.3 Panic disorder

Panic Disorder Severity Scale

Ballenger et al 1998

A consensus statement on the management of panic disorder is presented in this paper. The clinical course of panic disorder is detailed, as well as the impact of comorbidity and the clinical implications. Treatment options are described. In order to measure improvement the Panic Disorder Severity Scale (PDSS) is recommended, as it is a single measure of the five principal domains of PD. However this is a new instrument and further research is recommended to validate its use in the long term follow-up of patients and to determine scores in the normal population and in a primary care setting.

Multiple instruments compared

Bech et al 1992

Patients from 14 countries took part in this study of patients with panic disorders. A total of 1128 patients, who had at least one attack per week and had three symptoms (rather than the four required by DSM-III) were included. Patients were randomly assigned to three treatment groups: alprazolam, imipramine or placebo, although this paper reports the findings of the imipramine and placebo groups only. The Hamilton rating scales (HRSD and HRSA) and the Hopkins Symptom Checklist (SCL-90) were used in this study. Factor analysis and latent structure analysis were used to test the construct validity of the two measures.

The latent structure analysis on the HRSA showed that the whole scale is not homogenous. Also, high concurrent validity was found between the subscales of depression, anxiety and discomfort.

Bouchard et al 1997

This paper presents a “comprehensive survey” using some systematic review methods of validated self-report instruments for the diagnosis of panic disorder. Fourteen instruments with published information on reliability and validity are described both global and specific measures.

Four global measures are described; the National Institute of Mental Health Panic Questionnaire (NIMH PQ), the Panic and Agoraphobia scale (P & A), Panic-Associated Symptoms Scale (PASS), Panic Attack Questionnaire (PAQ DMSM-III-R version). Ten specific measures are described; Agoraphobic Cognitions Questionnaire (ACQ), agoraphobic cognitions Scale (ACS), Anxiety Sensitivity Index (ASI), Body Sensations Questionnaire (BSQ), Castastrophic Cognitions Questionnaire-Modified (CCQ-M), Panic Appraisal Inventory (PAI), Panic Attack Cognition Questionnaire (PACQ), Panic Attack Symptoms Questionnaire (PASQ), Panic Belief Questionnaire (PBQ) and the Self-Efficacy to Control Panic Attacks Questionnaire (SE-CPAQ). They all appear to be measures for use in trials rather than screening tools.

The overall conclusions are that global assessment questionnaires are preferable to specific measures and that it is difficult to compare instruments because of the variable amount of information available.

4.2.4.4 GAD

Ballenger et al 2001

This paper presents a consensus statement on the management of GAD. Four members of the International Consensus Group on Depression and Anxiety took part and based the statement on six review articles. GAD is often associated with somatic symptoms such as muscle pain, headache, irritability, insomnia, fatigue and restlessness. Typically GAD patients suffer symptoms for 5 to 10 years before diagnosis and treatment. The use of two screening questions was endorsed "During the past 4 weeks, have you been bothered by feeling worried, tense or anxious most of the time?" and "Are you frequently tense, irritable and having trouble sleeping?" If yes to either question the physician can explore further symptoms. Examples of self-report measures include Penn State Worry Questionnaire and diagnostic instruments using DSM criteria.

The consensus statement goes on to recommend treatment options.

4.2.4.5 Criteria

Barlow & Wincze 1998

This paper compares and contrasts the DSM-III, DSM-III-R and DSM-IV diagnostic criteria for GAD. DSM-III allowed GAD to be diagnosed only if patients did not meet the criteria for any other anxiety or affective disorder. It also separated generalised anxiety disorder from panic disorder. This was considered to create confusion because GAD was a residual category.

With the development of DSM-III-R, the cardinal feature of GAD became apprehensive expectation, thus basing classification on a cardinal symptom not necessarily present in other anxiety disorders. In addition 6 of 18 symptoms from the three clusters of DSM-III criteria (motor tension, autonomic hyperactivity and vigilance and scanning) needed to be present with this diagnostic criteria. Finally, the threshold was changed from one month to six months duration. GAD has traditionally been associated with the highest rates of comorbidity among DSM-III-R anxiety disorders. These criteria are associated with diagnostic unreliability with kappa coefficients only in the fair range.

DSM-IV criteria include a reduction of associated (somatic) symptoms from 18 (in DSM-III-R) to 6. Preliminary results show that the DSM-IV criteria are associated with improved kappa coefficients. GAD is still associated with extremely high rates of comorbidity. Problems remain with the diagnostic criteria and considerably more research is needed as diagnosis of GAD using these criteria remains controversial.

Maier et al 2000

The objectives of this study were to determine whether or not symptoms of GAD (especially as an isolated condition) are occurring with substantial prevalence in primary care, are associated with substantial social impairment in primary care, whether GAD is a valid diagnostic category and whether the ICD-10 definition of GAD is appropriate in primary care. Patients with GAD were identified among primary care patients of the WHO study on "Psychological Problems in Primary Care". Identical techniques and tools in primary care settings in 14 countries were used. This study used the GHQ (12 item version) as a first stage screening instrument.

All data for diagnosis was based on the ICD-10 (6 months minimum duration and at least 4 associated symptoms). This allowed the exploration of core symptoms and associated symptoms (mainly somatic hyperactivity). One month prevalence rates of anxiety varied considerably between centres (mean 7.9%). About 25% of cases presented with GAD and no other comorbid psychiatric disorder. Marked social impairment was observed in up to 55% of primary care patients with generalised anxiety syndrome (symptom criteria according to ICD-10 but without any time criteria). The ICD-10 definition of GAD was not found to be completely appropriate as the diagnostic threshold was too restrictive. Therefore some patients are remaining undetected.

Slade & Andrews 2001

This paper compares the ICD-10 with the DSM-IV for the diagnosis of GAD. The data comes from the Australian National Survey of Mental Health and Well-Being, which was designed to assess the prevalence of the major psychiatric disorders and their associated disability and health service utilisation. At total of 10,641 people participated (response rate 78%). The computerised version of the Composite International Diagnostic Interview (version 2.0) allowed both the DSM-IV and ICD-10 diagnoses of GAD to be determined. Disability was measured by the SF-12. Of the 10,641 people in the sample, 123 received a positive diagnosis and 10,166 received a negative diagnosis of GAD on both classifications. Chance corrected agreement between the systems was only fair (kappa = 0.39, 95% CI = 0.34-0.45). Multiple linear regression analysis was undertaken. When DSM-IV was positive and ICD-10 was negative, this was due to the requirement in ICD-10 that the respondent endorse symptoms of autonomic arousal and the requirement that ICD-10 GAD does not co-occur with panic-agoraphobia, social phobia or OCD. When ICD-10 was positive and DSM-IV was negative, this was due to the requirement in DSM-IV that the worry be excessive and that it causes clinically significant distress or impairment.

DSM-only GAD cases had significantly higher levels of disability than ICD-only cases of GAD (controlling for demographic variables and presence of comorbid psychiatric disorders). The authors conclude that prevalence rates of GAD with either DSM-IV or ICD-10 are almost identical, these systems are diagnosing different groups of people.

Table 1. Summary of studies describing screening tools

Study	Tools; use	Summary
Ballenger et al, 1998	PDSS; measurement	Consensus statement on panic disorder in general
Ballenger et al, 2001	Two screening questions for GAD; screening	Consensus statement on GAD in general
Barlow & Wincze, 1998	DSM-III, DSM-III-R and DSM-IV, diagnosis of GAD	DSM-IV is an improvement over earlier versions but extremely high rates of comorbidity associated with GAD
Bech et al, 1990	HRSA; measurement of anxiety	History and theoretical analysis of HRSA scale
Bech et al, 1992	HRSD, HRSA, SCL-90; measurement of panic disorder	Study used factor analysis and latent structure analysis to compare the Hamilton scales to the SCL-90 for the treatment of panic disorders
Bjelland et al, 2002	HADS; measurement and screening of anxiety	Literature review showing that HADS performs well for screening
Bouchard et al, 1997	14 tools for PD; measurement	Comprehensive survey of 4 global measures and 10 specific measures for validated self-report instruments. Global assessment questionnaires preferable but comparisons are difficult.
Brown et al, 2001b	ADIS-IV-L; diagnosis of GAD and PD	US study looking at reliability of DSM-IV criteria. The ADIS-IV-L provided good to excellent reliability for the majority of DSM-IV categories. There were potential boundary problems and disagreement on number, severity and duration of symptoms.
Dunbar et al, 2000	HADS; factor analysis/measurement	Community based Scottish study using confirmatory factor analysis. Three factors underlie the HADS scale and additional markers made be need to supplement the scale.
Gilbody et al, 2001	9 studies of routinely administered questionnaires including BDI, GHQ, Zung Self rate depression scale, SCL-90; measurement of anxiety.	Systematic review mostly relating to diagnosis of depression. Recognition of emotional disorders is increased only when there is some form of screening procedure, an instrument is administered, scored by someone other than the clinician and the results of high scores only are fed back to clinician.
Kessler et al, 1999	GHQ (12 items), symptom interpretation questionnaire; screening/diagnosis	Single UK GP study showing that normalising attributional style is predominate in GP attenders and an important cause of low rates of detection of depression and anxiety.
Kirmayer, 2001	None	A review of cultural variations in presentation of anxiety and depression.

Kvaal et al, 2001	STAI; measurement of anxiety	A study of geriatric inpatients in Norway. The high scores on the STAI state instrument for geriatric patients was thought to be related to reduced well-being.
Labelle & Lapierre, 1993	None	A review of anxiety disorders suggesting that many anxious patients do not meet the strict diagnostic criteria for GAD
Leon et al, 1999	SDDS-PC and Sheehan Disability Scale; screening for PD	US study dealing with screening of depression and panic disorder. Sensitivity for panic disorder was 72.7%, positive predictive value 38.1% and false negative rate was 27.3%
Maier et al, 2000	ICD-10, GHQ-12; diagnosis of GAD	WHO study of 14 countries, ICD-10 definition of GAD not completely appropriate as diagnostic threshold was too restrictive
McQuaid et al, 2000	CES-D, BAI, ANS, SPQ; screening for PD and GAD	A US study of primary care patients using CIDI for diagnosis. BAI was found to be a poor screening measure, but the CES-D was found to be useful for detecting psychiatric disorders, ANS was sensitive and reasonably specific for panic disorder.
Okun et al, 1996	PSI, CES-D, STAI; theoretical factor analysis	A comparison of the item content of the three scales. PSI found to achieve comparable content validity to STAI but theoretical only
Robbins et al, 1994	CES-D and Diagnostic Interview Schedule; diagnosis of anxiety	The study explores various characteristics of physicians and how this affects their ability to diagnose anxiety and depression in a primary care setting.
Slade & Andrews, 2001	DSM-IV and ICD-10; diagnosis of GAD	Compares the DSM-IV and ICD-10 diagnostic criteria for GAD, and found that different groups of people are being diagnosed
Van den Brink et al, 2001	GHQ-12, CIDI-PHC; diagnosis and measurement of GAD	Looked at ability of GPs to recognise depression and GAD and ability to predict prognosis over a one year period

HRSD Hamilton rating scale for depression, HRSA Hamilton rating scale for anxiety, ADIS-IV-L anxiety disorder interview schedule for DSM-IV, HADS hospital anxiety and depression scale, SDDS-PC symptom-driven diagnostic system for primary care, PDSS Panic Disorder Severity Scale' SCL-90 symptom check list, GHQ general health questionnaire, STAI Spielberger State Trait Anxiety Inventory, CES-D Center for Epidemiological studies depression scale, PSI Psychiatric Symptom Index, BAI Beck Anxiety Inventory, CIDI-PHC Composite International Diagnostic Interview-Primary Health care version, ANS autonomic Nervous System Questionnaire, SPQ Social Phobia Questionnaire.

5. Introduction to evidence review of interventions

5.1 Presentation of recommendations and evidence statements

There are many different ways to present the recommendations and the evidence base for interventions, none of them necessarily better than any other. In this guideline we have presented all recommendations, concerned with interventions, for each condition at the start of the sections concerned with those conditions (that is an overview of all intervention recommendations). We then present the evidence for each type of intervention, as well as the evidence statements and the recommendations for that type of intervention.

The evidence has been arranged by nature of comparison of intervention, and in this guideline we have presented the evidence in the following order:

Panic disorder interventions

- pharmacological versus psychological versus combined interventions
- pharmacological versus combined
- psychological versus combined
- pharmacological versus psychological interventions
- pharmacological versus pharmacological
- pharmacological versus placebo, and other
- psychological versus psychological
- psychological versus placebo, and other
- other e.g. exercise

Generalised anxiety disorder

- pharmacological versus psychological versus combined interventions
- pharmacological versus combined
- psychological versus combined
- pharmacological versus psychological interventions
- pharmacological versus pharmacological
- pharmacological versus placebo, and other
- psychological versus psychological
- psychological versus placebo, and other
- other e.g. exercise

There is also a section that presents papers that are not specifically for either panic or generalised anxiety, but which have been used as the basis for extrapolation by the guideline development group.

In each evidence section, we have presented papers in the following order:

- meta-analyses
- systematic reviews
- RCTs
- other study types

(note: not all evidence sections will necessarily have papers of every kind in them)

5.2 The nature of evidence considered

There is lack of research evidence for many interventions. This lack of effectiveness data does not necessarily mean that it is not effective, but does mean that the guideline development group could not make evidence based recommendations about interventions where research literature is lacking.

The introduction of DSM IV (1980) marked significant changes in the way that anxiety disorders were considered, identified and categorised. For example, generalised anxiety disorder had often been viewed as a residual category to be used only when an individual did not fit into other defined conditions. The advent of DSM IV meant that it became a well defined condition in its own right with diagnostic criteria. The developments in DSM IV were later reflected in ICD 10, although the descriptions in ICD 10 (at least in terms of the phraseology) are considered more flexible.

DSM IV criteria are those most often used in the USA and therefore are the criteria most often used in research studies, due in large part because of where much of the research is both undertaken and funded (for both GAD and panic disorder). This obviously has had an impact on the studies that were examined for the development of this guideline. In these guidelines, we have used studies that used DSM IV criteria wherever possible, DSM III where it was the latest available and papers that used ICD criteria were also looked at (covering the same time periods). Papers that were covering earlier time periods were not looked at.

The nature of psychological therapies have also changed and what was described in the 1970s as cognitive behavioural therapy and that described in the 1980s and onwards, may have been describing quite different interventions. We have tried therefore to find as recent as possible papers for psychological therapies, and have looked at papers from 1979 onwards, but recognising that papers from 1999 onwards are more likely to describe what is now considered, for example, cognitive behavioural therapy.

5.3 Medication issues

There are several issues associated with medications that are relevant to the care of individuals with panic disorder or generalised anxiety disorder. These are briefly discussed below.

Placebo response

The use of a placebo is an integral part of clinical trial design. Demonstration of a difference in response or outcome, such as a measurement on the HAM-A scale, between an active intervention compared with a placebo is seen as the gold standard of efficacy of a new treatment such as a new anxiolytic. The placebo response rate may range from 20% to over 50% and what contributes to this is not always clear in the report of a study.

Placebo response was reported to be low in the early trials of treatments for panic disorder with the result that the effect size for active compounds was large. Thus only small samples were required for the studies to be adequately powered. More recent trials have observed increasing placebo response rates with smaller effect sizes which has lead to greater difficulty in demonstrating efficacy. Large trials are now needed and the clinical relevance of small although statistically significant drug-placebo differences has been questioned.

In order to reduce the degree of placebo response many trials have used placebo run-in periods which are meant to identify individuals who respond to placebo (placebo responders) before randomisation. These are then excluded from the trial. This practice has been questioned. If the placebo response is short lived and the trial is long enough, those who initially improve on placebo will deteriorate during the course of the trial. This would then lead to a larger difference being observed between the active and placebo groups.

Placebo response has been observed to be affected by a number of variables such as severity and duration of the illness and may differ between centres. Recent trials have attempted to correct for this but it may lead to unrepresentative samples. One study however has confirmed comparable efficacy between venlafaxine and diazepam in the short term treatment of GAD in study centres able to distinguish the efficacy of diazepam from placebo response. This clearly demonstrates a significant effect size.

Discontinuation syndromes

Discontinuation reactions have been associated with all the major classes of antidepressants. They are reported to occur particularly with compounds with short elimination half lives.

Discontinuation syndromes can cause morbidity and can be misdiagnosed, leading to inappropriate treatment, and can adversely affect anti-depressant adherence. There is very little robust, systematic research on discontinuation syndromes in generalised anxiety disorder and panic disorder.

A discontinuation syndrome has been defined as having the following characteristics:

- onset shortly after stopping a drug or, less commonly, reducing the dosage – symptoms generally appear within a few days of stopping or reducing dosage, onset more than 1 week later is unusual
- treatment length – symptoms rarely occur with treatment of less than 5 weeks duration
- short duration – if untreated most discontinuation reactions are short-lived – resolving between 1 day and 3 weeks
- rapid reversal on restarting the original drug
- distinct from a re-appearance of the underlying disorder for which the drug was prescribed

- not attributable to other causes

The symptoms vary and they also vary in their severity. Different symptom clusters can also occur and add to the complexity of the issue. Tapering of antidepressant use is the most common preventative strategy. (Haddad, 2001)

Benzodiazepine dependence

The risk of benzodiazepine dependence is something that both patients and prescribers worry about. Two types of dependence on benzodiazepines are possible, "substance dependence" that is closely related to barbiturate dependence and the so-called "therapeutic dose dependence".

Substance dependence and the benzodiazepines

The DSM-IV definition of substance dependence emphasises the following aspects:

- tolerance/dose escalation
- withdrawal syndrome
- priority of using/obtaining substance over all other pursuits
- loss of control over the drug-taking

Underlying the last two points is the development of a specific 'craving' or 'drug appetite' which many believe to be at the core of the problem. Although benzodiazepines are capable of causing this type of dependence it is rare.

Therapeutic dose benzodiazepine dependence

This is very different from classic substance dependence in that there is:

- no dose-escalation (although tolerance may be present, especially to the hypnotic action)
- no specific craving giving rise to priority of usage or loss of control over the drug-taking

Instead, any attempt at withdrawal or dose-reduction leads to an intolerable rebound of anxiety symptoms. It is controversial whether the anxiety is more severe than it was before treatment, but patients have reported having panic attacks for the first time during benzodiazepine withdrawal. This form of benzodiazepine dependence only occurs in a minority of patients.

A withdrawal syndrome may be associated with all benzodiazepines, but the shorter acting ones appear to present more of a problem in this respect. It has been known to occur even after short-term treatment and can begin up to three weeks after stopping a long acting benzodiazepine but may happen almost immediately when a shorter acting one is discontinued if it has been taken for a long time

6. Care of individuals with panic disorder

Recommendations: care of people with panic disorder

Step 2: Offer treatment in primary care

The recommended treatment options have an evidence base: psychological therapy, medication and self-help have all been shown to be effective. The choice of treatment will be a consequence of the assessment process and shared decision-making.

There may be instances when the most effective intervention is not available (for example, cognitive behavioural therapy [CBT]) or is not the treatment option chosen by the patient. In these cases, the healthcare professional will need to consider, after discussion with the patient, whether it is acceptable to offer one of the other recommended treatments. If the preferred treatment option is currently unavailable, the healthcare professional will also have to consider whether it is likely to become available within a useful timeframe.

1. Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder. (A)
2. Sedating antihistamines or antipsychotics should not be prescribed for the treatment of panic disorder. (D)
3. In the care of individuals with panic disorder, any of the following types of intervention should be offered and the preference of the person should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order are:
   - psychological therapy (A)
   - pharmacological therapy (antidepressant medication) (A)
   - self-help (A)
4. The treatment option of choice should be available promptly. (D)
5. There are positive advantages of services based in primary care (for example, lower rates of people who do not attend) and these services are often preferred by patients. (D)

Psychological interventions

6. Cognitive behavioural therapy (CBT) should be used (A)
7. CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols (A)
8. CBT in the optimal range of duration (7–14 hours in total) should be offered. (A)
9. For most people, CBT should take the form of weekly sessions of 1-2 hours and should be completed within a maximum of 4 months of commencement. (B)
10. Briefer CBT should be supplemented with appropriate focussed information and tasks (A)
11. Where briefer CBT is used, it should be around 7 hours and designed to integrate with structured self-help materials (D)
12. For a few people, more intensive CBT over a very short period of time might be appropriate (C)

Pharmacological interventions

13. The following must be taken into account when deciding which medication to offer:
    - the age of the patient (D)
    - previous treatment response (D)
    - risks
        - the likelihood of accidental overdose by the person being treated and by other family members if appropriate (D)
        - the likelihood of deliberate self-harm, by overdose or otherwise (D)
    - tolerability (D)
    - the preference of the person being treated (D)
    - cost, where equal effectiveness is demonstrated (D)
14. All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. (C)
15. Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (D)
16. Unless otherwise indicated, an SSRI licensed for panic disorder should be offered. (A)
17. If an SSRI is not suitable or there is no improvement after a 12-week course and if a further medication is appropriate, imipramine or clomipramine (which are not licensed for panic disorder but have been shown to be effective in its management) may be considered. (A)
18. When prescribing an antidepressant, the healthcare professional should consider the following
    - Side effects on the initiation of antidepressants may be minimised by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. (D)
    - In some instances, doses at the upper end of the indicated dose range may be necessary and should be offered if needed. (B)
    - Long-term treatment may be necessary for some people and should be offered if needed. (B)
    - If the patient is showing improvement on treatment with an antidepressant, the medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. (D)
19. If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy should be offered. (D)
20. Patients should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. (C)
21. Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over an extended period of time. (C)

22. All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly. (C)
23. Healthcare professionals should inform patients that the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. (D)
24. Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (D).
25. If discontinuation/withdrawal symptoms are mild, the practitioner should reassure the patient and monitor symptoms. If severe symptoms are experienced after discontinuing an antidepressant, the practitioner should consider reintroducing it (or prescribing another from the same class that has a longer half-life) and gradually reducing the dose while monitoring symptoms. (D)

Self-help

26. Bibliotherapy based on CBT principles should be offered. (A)
27. Information about support groups, where they are available, should be offered. (Support groups may provide face-to-face meetings, telephone conference support groups [which can be based on CBT principles], or additional information on all aspects of anxiety disorders plus other sources of help.) (D)
28. The benefits of exercise as part of good general health should be discussed with all patients as appropriate. (B)
29. Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. [NICE 2002]

Step 3: Review and offer alternative treatment if appropriate

30. If, after a course of treatment, the clinician and patient agree that there has been no improvement with one type of intervention, the patient should be reassessed and consideration given to trying one of the other types of intervention. (D)

Step 4: Review and offer referral from primary care if appropriate

31. In most instances, if there have been two interventions provided (any combination of psychological intervention, medication or bibliotherapy) and the person still has significant symptoms, then referral to specialist mental health services should be offered. (D)

Step 5: Care in specialist mental health services

32. Specialist mental health services should conduct a thorough, holistic, re-assessment of the individual, their environment and social circumstances. This reassessment should include evaluation of:
    - previous treatments, including effectiveness and concordance
    - any substance use, including nicotine, alcohol, caffeine and recreational drugs
    - comorbidities
    - day to day functioning
    - social networks
    - continuing chronic stressors
    - the role of agoraphobic and other avoidant symptoms

    A comprehensive risk assessment should be undertaken and an appropriate risk management plan developed (D)

33. To undertake these evaluations and to develop and share a full formulation, more than one session may be required and should be available. (D)

34. Care and management should be based on the individual's circumstances and shared decisions made. Options include:
    - treatment of co-morbid conditions
    - CBT with an experienced therapist if not offered already, including home based CBT if attendance at clinic is difficult
    - structured problem solving
    - full exploration of pharmaco-therapy.
    - day support to relieve carers and family members
    - referral for advice, assessment or management to tertiary centres

35. There should be accurate and effective communication between all healthcare professionals involved in the care of any person with panic disorder, and particularly between primary care clinicians (GP and teams) and secondary care clinicians (community mental health teams) if there are existing physical health conditions that also require active management. (D)

Monitoring and follow up

Psychological interventions

36. There should be a process within each practice to assess the progress of a person undergoing CBT. The nature of that process should be determined on a case-by-case basis. (D)

Pharmacological interventions

37. When a new medication is started, the efficacy and side-effects should be reviewed within 2 weeks of starting treatment and again at 4, 6 and 12 weeks. Follow the Summary of Product Characteristics (SPC) with respect to all other monitoring required. (D)

38. At the end of 12 weeks an assessment of the effectiveness of the treatment should be made, and a decision made as to whether to continue or consider an alternative intervention. (D)

39. If medication is to be continued beyond 12 weeks, the individual should be reviewed at 8- to 12-week intervals, depending on clinical progress and individual circumstances. (D)

Self-help interventions

40. Individuals receiving self-help interventions should be offered contact with primary healthcare professionals, so that progress can be monitored and alternative interventions considered if appropriate. The frequency of such contact should be determined on a case-by-case basis, but is likely to be between every 4 and 8 weeks. (D)

Outcome measures

41. Short, self-complete questionnaires (such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder) should be used to monitor outcomes wherever possible. (D)

7. Interventions for panic disorder

7.1 Pharmacological compared with psychological compared with combination interventions for panic disorder

Recommendations

1. In the care of individuals with panic disorder, any of the following types of intervention should be offered and the preference of the person should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order are:
   - psychological therapy (A)
   - pharmacological therapy (antidepressant medication) (A)
   - self-help (A)
2. The treatment option of choice should be available promptly. (D)
3. There are positive advantages of services based in primary care (for example, lower rates of people who do not attend) and these services are often preferred by patients. (D)

Evidence statements

1. *Psychological, pharmacological and combination interventions have been shown to be effective in panic disorder. (Ia)*
2. *Meta-analyses do not give consistent and firm evidence of whether talking therapies or combination therapies have better outcomes. (Ia)*
3. *CBT is superior to TCAs so far as tolerability and duration of cessation of symptoms is concerned. (Ib)*
4. *There is no difference between CBT with imipramine and CBT with placebo in the acute phase of the illness. (Ib)*
5. *There is some evidence that 3 months after stopping treatment, CBT with placebo was more effective than CBT with imipramine. (Ib)*
6. *There is no evidence that will allow the clinician to predict which of the three broad intervention groups (pharmacological, psychological or self help) will be effective for an individual patient, based on duration of illness, severity of illness, age, sex, gender, or ethnicity. (IV)*
7. *Evidence for effectiveness in different genders is lacking. (Ia)*
8. *Evidence for effectiveness in different ethnic groups is lacking. (Ia)*
9. *Evidence for effectiveness in different levels of severity in panic disorder is lacking. (Ia)*

7.1.1 Research literature evidence

Several meta-analyses, systematic reviews and RCTs looked at the relative effectiveness of pharmacological, psychological and combination treatments for panic disorder.

7.1.1.2 Meta-analyses, systematic reviews and other reviews

Van Balkom et al 1997

A meta-analysis of 106 studies comparing 222 treatment conditions was conducted on 5,011 patients suffering from panic disorder with or without agoraphobia. Search years were 1964 to 1995, specific search terms used were given. The quality of the individual study was not used as an inclusion criterion for the review, although quality aspects of the study were reviewed and recorded/coded. Details of the reasons for inclusion and exclusion of studies were given. Effect sizes were calculated within treatments of high-potency benzodiazepines, antidepressants, psychological panic management, exposure in vivo, pill-placebo combined with exposure, antidepressants combined with exposure, and psychological panic management combined with exposure in vivo. Compared with the control condition (either pill placebo, attention placebo or waiting list), antidepressants, psychological panic management, high-potency benzodiazepines and antidepressants combined with exposure in vivo were superior to the control condition for panic attacks. Exposure in vivo alone was found not be effective for panic attacks. All treatments were superior to control on agoraphobic avoidance. There were no significant differences between treatments in the control of panic attacks. This review found that the best treatment for agoraphobic avoidance and for panic attacks with agoraphobia was a combination of antidepressants with exposure in vivo.

Gould et al 1995

This paper presents a meta-analysis of 43 studies encompassing 76 treatment interventions for panic disorder. Treatment outcome studies for patients with panic disorder with or without agoraphobia that employed a control group were included. Randomisation was a requirement in the studies included. Databases searched were given as were search terms used. Further details about quality assessment of studies for inclusion is not given. Therefore it is difficult to draw firm conclusions about the appropriateness of combining studies. Mean overall effect sizes for all outcome (dependent) measures are calculated as well as individual effect sizes for outcomes specific to panic frequency for cognitive behavioural relative to pharmacological treatments and combined treatments. Outcomes were divided between short-term (i.e. less than 6 months) and long-term (greater than 6 months) findings. Studies were grouped according to comparator used. It was considered that those in a no-treatment comparator group would do worse than those in a pill-placebo condition or more active psychological placebo. Only 8 studies examined combination of pharmacotherapy and psychological therapy. However, some interesting results are presented on pharmacotherapy versus psychological therapy as well as that discussed on combined therapy. Both pharmacotherapy and CBT were found to be more effective than any control conditions. Antidepressants and benzodiazepines were found to be equally effective in the short term but dropout rates revealed that benzodiazepines were better tolerated. Results of CBT interventions showed very high effect sizes with good tolerability but the authors caution that this favourable result is likely due to the control condition, that being, wait-list rather than pill-placebo. Of all the CBT interventions, those that combine cognitive restructuring and exposure appear to be the most effective. The final finding that combined exposure therapy rather than pure CBT, is qualified by the statement that relatively few studies use the most current and comprehensive programmes of CBT for panic disorder. The authors also state that SSRIs could not be included because of the paucity of evidence for their use in PD even though they state that they have a more favourable side-effect profile. Only 12 studies were included in long-term follow-up and this is stated as due to the difficulty with maintaining patients in a control group.

Bakker et al 1998

This aim of this meta-analysis was to update the knowledge of long term efficacy of different treatments in panic disorder with or without agoraphobia. They reviewed all 106 studies included in the meta-analysis of van Balkom et al (1997) for the availability of long term data. This identified 59 studies for inclusion. They also undertook literature searches (databases and search terms given in paper) which provided another 9 studies. Selection and quality assessment of included studies is not given except to say that case studies that would not allow for calculation of an effect size are excluded. A total of 68 studies were included. These studies included 106 treatment conditions (benzodiazepines [n=8], antidepressants [n=5], psychological panic management [n=25], exposure in vivo [n=43], antidepressants combined with exposure in vivo [n-=4], psychological panic management combined with exposure [n=21]). Since no follow-up studies included a placebo or no-treatment control condition, it was only possible to make within treatment comparisons and effect sizes were calculated using Cohen's *d*. Kruskal-Wallis tests revealed non-significant differences between treatments and therefore, the different treatments could be considered together for all groups. A total of 2173 patients participated in the follow-up studies identified and 1862 was the final number at post-test during this follow-up period. Only 2 of the four outcome variables were included in the analysis, those being, panic and agoraphobia. Significant differences were found between combination therapy with antidepressants and exposure in vivo and psychological panic management, exposure in vivo and the combination of psychological panic management and exposure on agoraphobic measures used.

Clum et al 1993

This systematic review examined the literature on panic disorder from 1964 to 1990. This review only included treatment outcome studies that included a control group as well as a treatment group. The control groups could be in receipt of placebo (either drug or psychological therapy), no treatment or some combination of these. This review did not give sufficient detail to be confident that included studies were quality assessed or appropriately combined. Criteria for inclusion of studies into the review are not given. Pharmacological, psychological and combined treatments were examined and seven dependent variables recorded and effect sizes calculated for twenty-nine studies. Of the 29 studies included, 8 used combination treatments. The authors conclude that psychological coping strategies (effect size = 1.41) and flooding or exposure (effect size = 1.36) are the treatments of choice for panic disorder. These are closely followed by combination treatment (effect size = 1.09). The effect size of psychological treatment combined with antidepressants when compared with placebo (effect size = 1.17) is higher than that for psychological therapies combined with high-potency benzodiazepines (effect size =0.68). This conclusion is tempered with the acknowledgement that it is drawn from a pool of studies that do not offer direct comparisons of the most promising treatments that incorporate adequate follow-up periods.

7.1.1.3 RCTs

CBT versus imipramine versus combined imipramine + CBT

Barlow et al 2000

This study measured five comparisons: whether both CBT alone and imipramine alone performed better than placebo; if either CBT or imipramine performed better relative to each other; and if there was an advantage to combining CBT and imipramine as evidenced by superiority of CBT + imipramine to CBT + placebo, imipramine alone, and CBT alone. Of 326

randomised patients, 312 (as 13 were considered ineligible post-randomisation) were included in an intent-to-treat analysis that included a 3 month acute phase, a 6 month maintenance phase and a 6 month follow-up. Patients who went on to the maintenance phase continued in 'blind' and were considered responders: likewise with the follow-up phase. At the end of each phase, an intent-to-continue analysis was also performed. Numbers randomised to each group were divided in order to improve trial efficiency (6 CBT, 6 imipramine, 5 CBT + imipramine, 25 CBT + placebo, and 2 placebo per block of 24). Comparisons are therefore 5-fold. Overall, both active treatments, administered singly are better than pill placebo for treating panic disorder. Pairwise comparisons for active treatments versus placebo were significant (CBT alone, p=0.006, imipramine alone, p=0.007, CBT + imipramine, p=0.001 and CBT + placebo, p=0.004). Imipramine was judged to produce a better quality response. CBT, on the other hand had a more sustained response and was better tolerated than imipramine. However there was no significant difference between treatments alone but there were more dropouts due to adverse events in the imipramine group than there were with the CBT group. Study limitations are mentioned including the fact that the investigators only enrolled patients with limited degrees of phobic avoidance. Results are therefore only generalisable to this group of patients.

7.2 Combination compared with pharmacological interventions for panic disorder

7.2.1 Research literature evidence

7.2.1.1 RCTs

Psychoeducation + SSRI (paroxetine) versus SSRI (paroxetine)

Dannon et al 2002

The purpose of this double-blind randomised controlled trial was to evaluate the effectiveness of a self-information booklet (SIB) in reducing anxiety and panic attacks. Eighty four patients referred to a tertiary clinic in Israel were randomised to receive either paroxetine at 40mg per day and a self-education booklet or paroxetine alone. Outcomes measured were the HAM-A, the HRSD, the Panic Questionnaire and the Visual Analogue Scale (VAS). Tests were administered at baseline and at weeks 1, 3 and 12. Both groups improved significantly. The SIB group however, showed a significantly greater response than the paroxetine only groups. However, by week 12, there was no difference between groups and the non-SIB group had caught up with the SIB group.

The authors conclude that despite the fact that SIB effects do not endure it is stressed that it can increase overall well-being and compliance in patients with panic disorder.

7.3 Combination compared with psychological interventions for panic disorder

Evidence statements

1. *There is limited evidence that shows that CBT + pill placebo and CBT + imipramine were equally effective at the end of 3 months. (Ib)*

2. *There is limited evidence that shows that CBT + pill placebo was more effective than CBT + imipramine, 3 months after cessation of treatment. (Ib)*

3. *There is some evidence that people who fail to respond to CBT, may find SSRIs a helpful adjunct. (Ib)*

4. *One poor quality study showed that CBT with paroxetine is more effective than CBT plus placebo. (Ib)*

7.3.1 Research literature evidence

7.3.1.1 RCTs

CBT + SSRI (paroxetine) versus cbt + placebo

Kampman et al 2002

This double-blind randomised-controlled trial was designed to test whether patients who were considered nonresponsive to CBT for panic disorder, would respond to continued CBT plus either paroxetine or placebo. The sample was derived from 161 patients who had received 15 sessions of CBT in two outpatients clinic in the Netherlands. Sixty six of the 161 patients fulfilled the criteria for non-response. Successfully treated patients were those who reported no panic attacks for the previous 2 weeks, having a score of 1.9 or lower on the Agoraphobic Cognitions questionnaire (ACQ) and a score of 5.9 or lower on the Anxiety Discomfort Scale (ADS). Of the 66 eligible, 38 patients agreed to participate and were equally divided across treatments. Treatment consisted of 15 sessions of CBT and either paroxetine at first 20mg/day for the first 2 weeks increased to 40mg/day for the remainder of the study, or placebo. Outcome measures included the Mobility Inventory and the Agoraphobic Cognitions Questionnaire. Also measured were Dutch adaptation of the Body Sensations Questionnaire (BSQ)-fear and the BSQ-frequency. The global state of phobic symptoms was measured with the Fear Questionnaire (FQ-GA). Patients were assessed by the ADIS-IV prior to entry into the trial and this was 4 weeks from any treatment administered from the earlier study. Change scores from before and after trial treatment with either paroxetine or placebo revealed a significant change for CBT plus paroxetine condition ($F=5.35$, $df=6.13$; $p<.05$) but not for the CBT plus placebo condition ($F=2.09$, $df=6.13$; $p=.13$). This effect trend was also seen for symptoms reduction ($F=6.39$, $df=6.31$; $p<.0001$). Change scores on all the outcome measures were significantly larger for the CBT plus paroxetine groups. However a comparison of change in panic free status between the two treatment groups was not statistically significant ($\chi^2=2.75$, $df=1$, $p<.10$). Using the same criteria for treatment failure as was used to recruit patients to the study, 73% of the CBT plus placebo group were considered treatment failures compared to 37% of the CBT plus paroxetine

group. The authors conclude that the results suggest the usefulness of paroxetine as an adjunctive therapy in patients who fail to respond to CBT alone.

Stein et al 2000

In this double-blind randomised controlled pilot trial, a very brief form of cognitive behavioural therapy was administered to 33 patients suffering from panic disorder according to DSM-IV. Patients were newly referred sufferers of panic disorder in an Anxiety Clinical in Winnipeg, Canada. Groups were randomised to receive either paroxetine or placebo with the CBT. For the first 4 days, both groups received 10mg of paroxetine per day so that all patients experienced side effects. After that, from week two onwards, patients received either placebo or paroxetine (10mg) which increased throughout the study at each weekly visit up to week 4 if needed. At week 5, both groups received a 45 minute session of cognitive behavioural therapy and completed a battery of questionnaires. Then, at week 7, all participants had another 30 minutes of CBT. Throughout the study, the term very brief (vb) CBT is used. At week 10, the final week of the study, subjects completed the dependent measures once more. The primary outcome measure was the proportion of subjects judged to be responders according the Clinical Global Impression of Change Scale (CGI-C). Responders were those who were rated as very much improved or much improved according to the CGI-C and two versions were scored; the patient-rated (CGI-C-Pt) and the clinician rated (CGI-C-CI). Other secondary measures included the frequency of panic attacks as measured by a diary, the Fear Questionnaire, the Beck Anxiety Inventory, the Beck Depression Inventory, the Anxiety Sensitivity Index and the Sheehan Disability Scale. Due to missing data, only 12 subjects' measures could be analysed in each group. On the primary outcome measure, there was no statistically significant difference between groups on either the patient or clinician-rated scales. Using the more 'stringent' criteria of 'very much improved' according the CGI-C, there was a greater proportion of patients who achieved high end-state functioning although the difference between the paroxetine and placebo patients was not statistically significant on the Clinician-rated scale. On the patient-rated scale, the difference was significant. 13% of the placebo versus 60% of the paroxetine group achieved high end-state functioning (χ^2=5.70, d.f.=1, P<0.02). There were a significantly greater proportion of panic free patients in the paroxetine group versus the placebo group (80% versus 25%, χ^2=7.31, d.f.=1, P<0.007). The two groups did not differ on the magnitude of symptom change nor, when partial or full panic attacks were added together, on the proportion who reported zero attacks by the end of the study.

The authors conclude that this pilot study, although small in numbers, suggests the vbCBT can be an effective treatment for panic disorder. They recommend future research to replicate the utility of this treatment and to see whether it is generalisable to other clinical settings.

Paroxetine + CBT versus paroxetine versus placebo

Oehrberg et al 1995

This 12 week multi-centre double-blind randomised controlled trial compared the efficacy of paroxetine to placebo as well as a course of cognitive behavioural therapy. Patients were sufferers of panic disorder with or without agoraphobia. Following a 3-week single-blind washout period, patients were randomised to receive low (10-20mg/day), medium (20 to 40mg/day) or high (40 to 60mg/day) doses of paroxetine or placebo. Dose could be increased to the high dose according to efficacy and tolerability. Patients were assessed at weeks, 1, 2, 3, 4, 6, 9 and 12 and following the 2 week placebo wash-out period. Both groups also received standardised cognitive behavioural therapy. The primary efficacy measure was the reduction in the number of panic attacks recorded by patients in a daily diary and a reduction > 50% from baseline as well as a reduction to zero in the number of panic attacks within a 3 week period and

the mean change in the number of panic attacks from baseline. Also documented were the severity of each attack and whether there were precipitating factors. Adverse events were recorded at each assessment by open question or/and observation. One hundred and twenty patients were included in an intent-to-treat analysis. Significantly more patients in the paroxetine groups had a greater than 50% reduction in the number of panic attacks at 6, 9 and 12 weeks (p=0.006, p=0.001 and p=0.001 respectively). By week 12, 36% of paroxetine patients compared to 16% of placebo patients were panic free (p=0.024). The paroxetine group also showed a significantly greater reduction in the mean number of panic attacks from baseline (p=0.084). Significantly more patients in the paroxetine group reported at least one adverse event compared to placebo (77% versus 55%, p=0.012). Treatment emergent adverse events in the each group (paroxetine/placebo) were nausea, (23%/12%), sweating (23%/5%), headache (22%/23%), dizziness (17%/7%), asthenia (15%/3.3%), decreased libido (12%/2%) and dry mouth (10%/8%). No serious adverse event was attributed to the treatment group. In the two week placebo washout period, 34.5% of paroxetine and 13.5% of placebo patients reported adverse events upon discontinuation with dizziness reported the most in 4 of the paroxetine (7.3%) and one of the placebo patients. The authors conclude that there is a 'clear advantage' in combining paroxetine with cognitive therapy in the treatment of panic disorder.

This study added a version of CBT to either pill placebo or paroxetine. The absence of a CBT or medication alone condition renders it extremely difficult to interpret. CBT was not carried out according to any recognised protocol, as it was carried out on the basis of a generic CBT text in untrained therapists who were not supervised. The response of the CBT plus placebo group is unusually poor, consistent with the treatment quality issue.

7.4 Pharmacological compared with psychological interventions for panic disorder

7.4.1 Research literature evidence

7.4.1.1 RCTs

SSRI (paroxetine) versus TCA (clomipramine) versus cognitive therapy

Bakker et al 1999

This 12 week randomised controlled trial sought to measure the relative efficacy of paroxetine (20-60mg/day), clomipramine (15-150mg/day), a pill placebo and cognitive therapy based on Clark's method (sessions lasted 45 minutes over the trial duration) in the treatment of panic disorder with or without agoraphobia. Patients were included if they had a diagnoses of panic disorder according to DSM-III-R and a minimum of 3 panic attacks in the 3 week, single-blind run in period.

Patients were enrolled from two outpatient clinics in the Netherlands. Medication was titrated over the first 6 weeks of study participation according to the psychiatrists' judgement and then kept constant for the remaining 6 weeks of the study. No benzodiazepine was allowed during the course of the study.

All participants kept panic diaries. Patients were considered panic-free if no panic attacks were experience for the final three weeks of the study. Therapeutic effects were measured via the HAM-A, the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI Severity of Illness Score (CGI-S) and patients completed the marks-Sheehan Disability Scale (SDS). They also gave an Overall Phobia Score and an Anticipatory Anxiety Score.

One hundred and thirty one of 154 enrolled patients were included in an intention to treat analysis, although completer analysis is also presented by the authors. Four per cent of participants suffered panic disorder without agoraphobia and the remaining suffered agoraphobic avoidance. Eighteen patients dropped out during the treatment phase due to non-compliance (11 cognitive therapy condition; 8 paroxetine condition; 1 clomipramine and 1 placebo) lack of efficacy (3 cognitive therapy; 1 paroxetine; 2 clomipramine and 1 placebo) 2 in the clomipramine groups due to intolerable side-effects and 1 patient in the paroxetine group due to improvement.

In the intention to treat sample 65% of the paroxetine, 53% of the clomipramine, 40% of the cognitive therapy and 34% of the placebo sample were panic free. Significantly more were panic free in the paroxetine condition compared to the placebo condition. Paroxetine was also significantly better than placebo in terms of panic frequency and superior to cognitive therapy on all measure but panic frequency. Clomipramine was not superior to placebo on panic frequency and MADRS. There were no significant differences between cognitive therapy and placebo. Clomipramine was better than cognitive therapy on the HAM-A, MSPS anxiety, Anticipatory Anxiety and the SDS.

Effect sizes were calculated for all conditions as all conditions demonstrated significant time effects. The effect sizes for the active treatment were greater than those for placebo. Antidepressants had moderate to large effect sizes and cognitive therapy and placebo had

comparably low effect sizes. The Authors conclude that the two antidepressants, clomipramine and paroxetine were consistently superior to pill placebo, whereas cognitive therapy was superior on only a few measures.

7.4.1.2 Cost effectiveness studies

One study which emanates from the US which compared the cost effectiveness of CBT and pharmacotherapy for the treatment of PD (Otto et al 2000) reported favourable results in relation to CBT. However, the sample size was too small to make valid clinical and economic statements in relation to efficacy and cost effectiveness. From a health economics perspective there are a number of issues which require further investigation including the optimal format and/or number of sessions for CBT, assessment of the comparative cost effectiveness of CBT versus other non-pharmacological treatments and assessments of the comparative costs and effectiveness of pharmacological versus non-pharmacological treatments. The evidence relating to the cost effectiveness of non-pharmacological treatments is summarised in below.

Otto et al 2000

This study examined the cost effectiveness of CBT in relation to pharmacotherapy for panic disorder in a specialty outpatient clinic setting. The authors commence with a review of the results of comparative treatment trials and meta-analyses of the treatment outcome literature. These studies suggest that CBT is as effective as antidepressants or high potency benzodiazepines in short term treatment trials and that, in general, CBT patients maintain their treatment gains over time. In contrast, pharmacotherapy requires ongoing treatment to maintain its beneficial effects and discontinuation of either antidepressant or benzodiazepine treatment is associated with relapse rates that range from 54-70%. Although CBT is clearly more effortful than pharmacotherapy during the acute treatment phase, this greater effort appears to be tolerable to patients and may lead to the elimination of medication side effects and the monetary cost of pharmacotherapy in the longer term.

Participants in the study were 80 outpatients with a primary diagnosis of panic disorder confirmed with a semi-structured clinical interview. Four groups of patients were included: patients initiating pharmacotherapy who were already on medication with another provider (n=20) patients initiating pharmacotherapy who were medication free (n=20), patients initiating CBT who were already on medication (n=20) and patients initiating CBT who were medication free (n=20). Costs were calculated only for the 40 patients who initiated treatment whilst medication free and included visit costs, medication costs and alternative treatment costs (defined in terms of additional treatments). Outcome was assessed by a 7 point Clinician Global Impression of Severity Scale.

According to this scale the patients in the two CBT arms achieved significantly better outcomes than those patients who did not receive CBT. The most expensive treatment over the 1 year period of the study was psychopharmacology, with an average total cost per patient of $2,305. Individual CBT was the next most expensive treatment with an average cost per person of $1,357. The least most expensive treatment was group CBT with an average cost per patient of $523.

The cost benefit ratio over four months was $246 for group CBT, $565 for individual CBT and $447 for pharmacotherapy, for a 1.0 point change in the CGI rating. The total costs over 1 year for a maintained 1.0 point decrease in CGI were estimated to be $248 for group CBT, $646 for individual CBT and $1,153 for pharmacotherapy.

Study limitations

- study setting and items of resource use and cost are US based hence limited applicability for UK
- sample size is quite small hence clinical and economic statements in relation to efficacy and cost effectiveness must be interpreted with caution

Conclusions from study

Provides some evidence of cost effectiveness of CBT in relation to pharmacotherapy which appears to hold over the longer term (1 year) in addition to short term (4 months) period.

7.5 Pharmacological interventions for panic disorder

Recommendations

1. Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder. (A)
2. Sedating antihistamines or antipsychotics should not be prescribed for the treatment of panic disorder. (D)
3. The following must be taken into account when deciding which medication to offer:
    - the age of the patient (D)
    - previous treatment response (D)
    - risks
        - the likelihood of accidental overdose by the person being treated and by other family members if appropriate (D)
        - the likelihood of deliberate self-harm, by overdose or otherwise (D)
    - tolerability (D)
    - the preference of the person being treated (D)
    - cost, where equal effectiveness is demonstrated (D).

3. All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. (C)
4. Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (D)
5. Unless otherwise indicated, an SSRI licensed for panic disorder should be offered. (A)
6. If an SSRI is not suitable or there is no improvement after a 12-week course and if a further medication is appropriate, imipramine or clomipramine (which are not licensed for panic disorder but have been shown to be effective in its management) may be considered. (A)
7. When prescribing an antidepressant, the healthcare professional should consider the following
    - Side effects on the initiation of antidepressants may be minimised by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. (D)
    - In some instances, doses at the upper end of the indicated dose range may be necessary and should be offered if needed. (B)
    - Long-term treatment may be necessary for some people and should be offered if needed. (B)
    - If the patient is showing improvement on treatment with an antidepressant, the medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. (D)

8. If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy should be offered. (D)
9. Patients should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. (C)
10. Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over an extended period of time. (C)
11. All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly. (C)
12. Healthcare professionals should inform patients that the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. (D)
13. Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (D)
14. If discontinuation/withdrawal symptoms are mild, the practitioner should reassure the patient and monitor symptoms. If severe symptoms are experienced after discontinuing an antidepressant, the practitioner should consider reintroducing it (or prescribing another from the same class that has a longer half-life) and gradually reducing the dose while monitoring symptoms. (D)

Evidence statements

1. *Two types of medication have been shown to be effective in treating panic disorder; tri-cyclic anti-depressants and selective serotonin re-uptake inhibitors (SSRIs). (Ia)*

2. *SSRIs have been shown to be effective, although higher doses may confer increased effectiveness. (Ib)*

3. *SSRIs are as effective as tricyclics, however one paper indicates that tricyclics are unhelpful in panic disorder. (Ia)*

4. *The side effects of SSRIs and TCAs in treating panic disorder are those that would be expected for these classes of medication. (Ia)*

5. *Benzodiazepines in the long term are associated with a less good outcome than antidepressants. (Ia)*

6. *There is no clear evidence statement about what constitutes an adequate trial of treatment. (Ib)*

7. *There is no clear evidence statement about what is the optimal length of treatment with medication. (Ib)*

8. *There is no clear evidence about the withdrawal or discontinuation effects of many medications used for anxiety disorders. (Ib)*

9. *Discontinuation syndromes have been found with all the major classes of antidepressants (Ib)*

10. *Evidence of efficacy beyond the age of 65 years is difficult as most clinical trials have an age cut-off for entry between 65 and 70 years of age. (Ib)*

11. *The available evidence is that there are no differential effects across the different levels of severity in panic disorder. (Ia)*

7.5.1 Research literature evidence

7.5.1.1 Pharmacological interventions compared with pharmacological interventions

7.5.1.1.1 Meta-analyses, systematic reviews and other reviews

SSRIs versus TCAs

Otto et al 2001

This paper presents the results of a systematic review and meta-analysis of placebo-controlled trials examining the efficacy of SSRIs including paroxetine, fluoxetine, fluvoxamine, sertraline and citalopram. An effect size analysis was conducted on double-blind, placebo-controlled studies of SSRI for panic disorder with or without agoraphobia. Studies were obtained through searches done of PsychLit and Medline together with discussions with colleagues and examining of the reference sections of related articles. Search terms are given in the paper. The search period, was not specified but study paper dates were between the years 1993 and 1998. Intention to treat analysis in studies included is not given. Twelve placebo-controlled studies were pooled and an overall mean effect size was calculated from individual effect sizes. Weighted and unweighted (by samples) effect sizes were calculated. This review found that effect sizes were significantly inversely related to study sample size (R=0.72, F=10.9, df=1, 10, p<0.009). Mean overall effect sizes were d=0.55. Effect sizes from studies of SSRIs were compared with those obtained by Gould et al 1995. Using unpaired t tests, there were no significant differences between Imipramine and the SSRIs. Mean dropout for SSRIs = 19.9%, SD10.9. No significant difference with comparison conditions. When data was pooled across all studies, mean dropout rate for SSRIs was 24.6%. Year of publication was also examined and it was found that sample size confounded with the year of study publication (R)=0.76, F=13.4, df=1, 10, p<0.004). More recently published studies were associated with smaller SSRI effect sizes (R=0.82, F=20.1, df=1, 10, p<0.002). An examination of changes in sample responsivity over time using panic-free rate for patients in placebo did not show significant association between year of publication and treatment responsivity (R=0.41, F=1.40, df=1, 8 p<0.28). The authors conclude that this effect-size analysis of controlled studies of treatment for panic disorder revealed no significant differences between SSRIs and older antidepressants in terms of efficacy or tolerability in short-term trials. An inverse relationship was evident between sample size and effect size for SSRIs. Early studies of small samples may have led to initial over-estimations of the efficacy of SSRIs for panic disorder.

SSRIs (paroxetine, fluvoxamine, citalopram) versus TCAs (clomipramine, imipramine) versus benzodiazepines (diazepam, alprazolam)

Baldwin & Birtwistle, 1998

This paper is a systematic review of the literature from 1992 to 1997 examining placebo-controlled trials as searched in MEDLINE in peer-reviewed journals of trials of pharmacological treatments of panic disorder. Studies were included if they recorded side-effects of treatments. It is not stated whether all studies employed an intention to treat analysis. Results presented include some tabulation of the black-listed alprazolam and the unlisted clomipramine. For this guideline, comparisons with placebo rather than any non-included drug are of more interest. In all studies, significantly more side effects are experienced in the treatment groups in comparison to placebo. In head-to-head comparisons, there were significantly more side effects in imipramine compared to the un-listed clomipramine group in a 12-week study. Fluvoxamine in combination with a psychological therapy recipients experienced significantly more side effects than placebo plus psychological therapy recipients in another 12 week study but these side effects decreased within time although how much they decreased and within what timeframe is not stated. Fluvoxamine was considered better tolerated when compared to imipramine by the investigators. Paroxetine in a head-to-head with clomipramine was better tolerated. The same participants, in a long-term extension of this latter study recorded a decrease in side-effects over time in the paroxetine group. However, less than half the patients continued in this study. In head-to-head comparison between citalopram and clomipramine, patients in the citalopram group had significantly more side effects than the clomipramine patients. Finally, when diazepam was compared to (black-listed) alprazolam, it was recorded that there were no significant differences in treatment emergent side-effects. The reviewers conclude that SSRIs emerge most favourably in this analysis of side-effects. However, as no direct head-head comparisons were made between SSRIs and benzodiazepines or between TCAs and benzodiazepines, a conclusion such as that reached by the reviewers is very tentative.

SSRIs (paroxetine) versus TCAs (clomipramine)

Wagstaff et al 2002

This ADIS drug evaluation reviews the major pharmacological features of paroxetine and its use to treat depression, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder and post traumatic stress disorder. For the purposes of this review, it is possible to view data pertaining to both panic disorder and generalised anxiety disorder in isolation from the other disorders. Included studies, were large, well-controlled trials but available evidence was heavily weighted towards short-term placebo-controlled double-blind trials. Unless otherwise stated, included studies employed and intention to treat analysis and diagnostic criteria used was DSM-III-R.

Outcomes examined on studies on panic disorder were the percentage panic free for one to three weeks, the mean change from baseline in the number of full panic attacks (i.e. those with at least 4 symptoms defined by DSM-III-R and a CGI score for severity of illness). When paroxetine at dosages of between 20 and 60mg/day is compared with placebo, symptoms improved significantly across multiple assessment parameters in the short term (10-12 weeks) double blind randomised trials involving between 120 and 278 patients. Paroxetine was found to be efficacious in the domains of panic attacks, anxiety, phobia, well-being and disability. In a fixed dosage trial, results were significant for a higher dosage (40mg/day) only but not in 10-20 mg/day. In a double blind extension phase of one trial, at 20-60 mg/day, paroxetine reduced the occurrence of panic attacks relative to placebo for up to 36 weeks. When compared to

clomipramine, again at dosages of between 20 and 60 mg/day, paroxetine was at least as effective as clomipramine (50-150mg/day) in two 12-week trials. In one trial, significantly more paroxetine patients (50.9%) were panic free at the end of the study compared to 36.7% of clomipramine patients. When compared on all other efficacy measures, there was no significant difference between these drugs. In a 36 week extension of a phase one trial, paroxetine was as effective as cloimipramine in reducing symptoms of PD according to DSM-IV. Short-term (60 day) treatment with either paroxetine up to 50 mg/day or citalopram (up to 50 mg/day) appears to reduce the symptoms of PD in adults with DSM-IV PD symptoms equally. There were no significant differences on any of the primary efficacy parameters although a trend toward a higher proportion of the paroxetine group being panic free at then the end of the study was observed.

The most common adverse events recorded in all psychiatric disorders where paroxetine was administered were nausea, sweating, headaches, dizziness, somnolence, constipation, asthenia and sexual dysfunction. The incidence of abnormal ejaculation among patients with generalised anxiety disorder and panic disorder ranged from 21-28% with a dosage range from 10-60 mg/day. This is commonly associated with all SSRIs. All SSRIs have been implicated in the development of serotonin syndrome, a potentially life threatening complication. There have been reports of serotonin syndrome developing when paroxetine was coadministered with MAOIs or other SSRIs or after a switch from another SSRI without a washout period. A meta-analysis of 39 studies of treatment of depression showed a statistically significant lower proportion of patients receiving paroxetine (64%) experienced adverse events with an incidence of >1% than those receiving clomipramine (77%, p=0.02) or another TCA (77%, p<0.001). There was a trend toward a lower incidence of withdrawal due to adverse events with paroxetine compared to TCAs which reached significance with clomipramine. When compared to other SSRIs in studies of depression, it has been shown to have a similar tolerability profile. SSRIs also seem to be generally better tolerated than TCAs in the elderly with equal tolerance among the SSRIs based on depression studies.

The authors conclude that paroxetine is better tolerated than TCAs and, in relation to generalised anxiety disorder and panic disorder, it is an appropriate first-line therapy. They stated that given its success in the treatment of depression and anxiety, and the fact that there is a high degree of psychiatric comorbidity of depression and anxiety it is an important first-line option.

Benzodiazepines versus SSRIs versus tricyclics

Den Boer 1998

This review included controlled clinical studies from Medline 1966 to 1998 for panic disorder. Full details of reproducibility, expected with systematic reviews were not presented. Outcomes were freedom from panic attack, reduction of panic attack frequency and ability to attenuate global anxiety (HAM-A, SCL-90, Clinical Anxiety Scale), depressive symptomatology (HAM-D, Montgomery-Ashberg and Zung Self rating), agoraphobic avoidance (SCL-90, Overall Phobia Scale, Marks Matthews Phobia Scale, Fear Questionnaire and CGI)and overall impairment (Sheehan Disability Scale). Approximately 700 patients who had received paroxetine, treated from 10-36 weeks when compared to placebo, resulted in 36-86% of the treated group becoming panic free compared to 16-0% of the placebo. In studies comparing paroxetine compared to clomipramine, 51% of paroxetine and 37% of clomipramine were panic free. Reduction in global anxiety was demonstrated in studies of paroxetine comparable to that of clomipramine. SSRIs improved depressive symptoms compared with placebo. Comparative data between SSRIs (citalopram and paroxetine) and clomipramine showed no statistically significant difference in improvement of depressive symptoms. All were equally efficacious. Paroxetine and clomipramine produced similar reductions in overall phobia scores using Marks

Sheehan Phobia Scale during a 12-week acute phase and during the extension of the study. No differences between the two treatment groups were found. When compared to clomipramine, both paroxetine and clomipramine showed similar improvements in the short-term in work, social and family life compared to the placebo. Subjects continued to improve in the long term.

When citalopram was administered at 20-30 mg/day 58% of patients were panic free compared to 50% of the clomipramine group and 32% of the placebo group. Citalopram and clomipramine showed equal efficacy in reducing global anxiety in a large multi-centred study. Comparative data between SSRIs (citalopram and paroxetine) and clomipramine showed no statistically significant difference in improvement of depressive symptoms. All were equally efficacious.

The author concludes that anti-depressants have been shown to be more effective than benzodiazepines in reducing depression, and at least as effective in improving anxiety, agoraphobic avoidance and overall impairment. The author does not comment on comparison of freedom from panic attacks.

SSRIs

Baldwin & Birtwistle 2000

This paper describes the use of SSRIs in the treatment of anxiety disorders. Full details of reproducibility, expected with systematic reviews were not presented. A review of studies as elicited from Medline Express and Embase searches from January 1985 to June 1999 was conducted for citalopram, fluoxetine, paroxetine, sertraline and zimelidine (now withdrawn due to side-effects). Included studies were double-blind RCTs and also, recent published abstracts of studies. No studies were found for the treatment of patients with SSRIs who suffer from generalised anxiety disorder. Five different SSRIs were reviewed for panic disorder including fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram. Most, but not all of the studies of SSRIs, have shown efficacy of treatment but that magnitude of response varies. The percentage of patients that were free of panic attacks ranged from 36-86%. A meta-analysis of 27 placebo controlled trials completed in 1995, concluded that SSRIs were more effective than either imipramine or alprazolam, but this study is out of date. Another more recent systematic review by the authors indicates that SSRIs are better tolerated than other pharmacological treatments. There have been few comparisons of the efficacy of different SSRIs and the authors reach no conclusion on a preferred SSRI.

7.5.1.1.2 RCTs

SSRI(citalopram) versus TCA (clomipramine)

Wade et al 1997

In this multicentre, placebo and clomipramine controlled trial, the efficacy of 3 dose ranges of citalopram, an SSRI, were tested over 8 weeks, preceded by a 1 week washout period. The structure of the trial comprised of 5 study arms as follows: 1. placebo, 2. clomipramine 60 or 90 mg/day, or 3. citalopram 10mg/day with the option of increasing to 15 mg/day if efficacy not seen, or 4. citalopram titrated over 3 weeks to 20mg/day with the option of increasing to 30 mg/day if efficacy not seen, or 5. citalopram titrated over 3 weeks to 40 mg/day with the option of increasing to 60 mg/day day if efficacy was not seen. The primary efficacy variable was the number of patients responding at week 8 using the last observation carried forward in an intention to treat analysis. Panic attacks were measured using the panic attack item of the Clinical Anxiety Scale. Also measured were physicians' and patients' self-assessment using the Global Improvement Scale. Four hundred and seventy five patients were randomised from

specialist psychiatric clinics and two general practice centres. A total of 22 centres partook from Finland, Sweden, the Netherlands and the UK. Citalopram, taken at doses of 20 or 30mg, appears to be more efficacious than placebo. This mid-range dose is more effective than both the lower (10 to 15mg per day) and the highest (40 to 60mg/day group). These effects were recorded by the CAS, PHYGIS and PATGIS scales. The HAS mean total and mean psychic scores showed for the mid and high range citalopram and clomipramine groups, statistically significant improvement by the last assessment. Significant improvement on the somatic score was recorded for the high citalopram group only. MADRS final scores showed statistically significant improvement at the final assessment (i.e. decrease from baseline) in the mid and high range citalopram and clomipramine groups. Thirty six patients recorded adverse events that resulted in them withdrawing from the study. The most commonly experienced adverse events reported in 5% or more of patients were headache, nausea and dry mouth and also reported were increased sweating, dizziness, insomnia, abdominal pain, tremor and constipation. Anorgasmia was the only dose-related adverse event reported. There was one death from coronary atheroma, one patient was diagnosed with schizophrenia and a third developed depression after 46 days of treatment with placebo. These patients were withdrawn from the study. Adverse events were considered consistent with those seen in this class of drugs (i.e. SSRIs). The authors conclude that the most advantageous benefit/risk ratio for the treatment of panic disorder was associated with citalopram 20 or 30 mg/day.

Lepola et al 1998

This paper documents a one year elective follow-up study to an 8 week double-blind randomised controlled trial to test the efficacy and tolerability of 3 doses of citalopram (10-15mg/day, 20-30mg/day and 40-60mg/day) against clomipramine (60-90mg/day) and placebo in patients suffering from panic disorder. Of the 475 randomly assigned to one of the 5 study groups, 279 agreed to continue in the one year follow-up study. The primary outcome measures were the Clinical Anxiety Scale panic attack time with response defined as no panic attacks. Also measured were the Physician's Global Improvement Scale, the Patient's Global Improvement Scale and the HAM-A. In results analysis, 21 of the 279 had to be excluded due to the use of concomitant medication. Adverse events were either observed by the investigator or reported by the patients. According to the CAS, patients in the citalopram, 20-30mg/day and 40-60mg/day showed significantly better response then patients receiving placebo ($p=.001$ and $p=.003$ respectively). The low dose of citalopram and clomipramine also showed a smaller but still significant improvement over placebo ($p<.05$). No further improvement in the drug groups was seen from between months 6 and 9. A survival curve of patients retained in the study showed that the highest number of patients were retained in the citalopram 20 to 30 or 40 to 60mg/day groups. On the PHYGIS, PATGIS, month 3 and 6 showed greater gains than months 9 and 12. The placebo group improved after month 6. 8 of the citalopram, 4 of the clomipramine and 1 placebo patient discontinued due to adverse events. All patients reported at least one adverse event. Headache was higher in the citalopram and placebo groups than the clomipramine group. Tremor and dry mouth were reported significantly more frequently in the clomipramine group than the citalopram groups. The authors conclude that citalopram, within the dose range of 20 to 60mg/day is effective, well tolerated, and safe in the long-term treatment of patients with panic disorder.

Benzodiazepine (diazepam) versus beta blocker (propanol)

Noyes et al 1984

This study's aim was to measure whether symptoms of panic disorder with agoraphobia according to DSM-III could be relieved by use of propranolol, a beta-blocker or diazepam (DZ). The patient population were adults referred to the University of Iowa Hospital's clinics in the

US. Twenty seven patients were randomised to this 4 week cross-over trial (2 weeks on each medication). Patients underwent a 7 day washout. Six failed to complete and data analysed on completers revealed more patients were observed to improve at least moderately on DZ (18 versus 7 on propranolol). The response to DZ was shown to be significantly better on all self-rated scales also. Side-effects were experienced in both groups. Distressing side-effects in the DZ group most frequently reported were fatigue and insomnia in the propranolol group. In the DZ group, the only side effect to diminish in the second week of treatment was drowsiness where 16 reported drowsiness in the first week, 8 did so in the second weeks. This trial also measured whether illness severity predicted response. Patients diagnosed as suffering moderate severity of PDA had a better response to both drugs than those with severe PDA (t=4.00, p=.06 for relief; t=6.31, p=.02 for improvement). Mean improvement with both drugs was 1.94 for moderately severe illness compared with 1.25 for severe illness. A significant interaction effect was found between drugs employed and duration of illness (t=10.00, p<.01 for relief; t=5.18, p=.04 for improvement). As duration of illness increased, the response to diazepam improved while the response to propranolol declined.

7.5.1.2 Pharmacological interventions for panic disorder

7.5.1.2.1 SSRIs

RCTs

SSRI (paroxetine)

LeCrubier 1997

This trial was a multi-centre, 12 week double-blind randomised controlled trial measuring the efficacy of paroxetine versus placebo and clomipramine. Three hundred and sixty seven patients from psychiatric outpatients were randomised to receive the drugs or placebo for the study period preceded by a 3 week placebo washout period. Patients recorded panic attacks in diaries and noted the number, types and total symptoms experienced. This study specified full from partial attacks with full being the experience of at least 4 symptoms. The primary efficacy variables were the mean change in the number of full panic attacks between baseline and the 3-week intervals, the proportion of patients with zero full panic attacks at the 3-week intervals and the proportion of patients with a 50% reduction in the number of full panic attacks between baseline and 3-week intervals. A significant difference was observed in time to withdrawal between Paroxetine and placebo in favour of paroxetine (p=0.05, log-rank test). At the end point, paroxetine was shown to be significantly more effective than both placebo and clomipramine with 50.9% of the paroxetine group and 36.7% of the clomipramine group and 31.6% of the placebo group recording a reduction in the total number of full panic attacks to zero. Fisher's exact test recording this difference as significant from clomipramine (p=0.041) and placebo (p=0.004). Seventy six point one (76.1%) of the paroxetine group, 64.5% of the clomipramine group and 60% of the placebo group had a ≥50% reduction in total number of full panic attacks. Both active drugs were superior to placebo at week 9 on the CGI-S, HAMA total score, MSPS, PGE and SDS but there were no significant differences between drugs.

Seventy three (73.2%) per cent of the paroxetine group, 89.3% of the clomipramine group and 67.5% of the placebo group experienced treatment emergent side-effects. Significantly more patients in the clomipramine group experienced treatment-emergent side effects than the paroxetine group (*P*=0.002). The same trend is observed in the proportion of patients who

withdrew due to side effects with 7.3% of paroxetine patients, 14.9% of clomipramine patients and 11.4% of placebo patients withdrawing due to side effects. The most common side effects in the paroxetine and clomipramine groups were nausea. Two of the paroxetine patients, 3 of the clomipramine patients and 7 of the placebo patients reported serious adverse events. The authors conclude that paroxetine displayed statistically and clinically significant efficacy in patients with DSM-III-R-defined panic disorder with or without agoraphobia.

SSRI (paroxetine) – long term evaluation

Lecrubier & Judge 1997

One hundred and eighty patients who completed a 12 week RCT comparing the efficacy of paroxetine to clomipramine and paroxetine to placebo (see preceding study, Lecrubier et al 1997) could elect to enter in a 36 week, long-term follow-up study. The original RCT is described above by the same author. A total of 176 patients were included in the study and two assessments were made: the average reduction in panic attacks and the number of panic-free patients. Patients kept a panic attack diary and also completed a panic severity scale and completed measures that were included in the 12 week trial (i.e. the Clinical Global Impression Scale, the Hamilton Anxiety Rating Scale, the Marks Sheehan Phobia Scale and the Sheehan Disability Scale). Drug dosages were kept the same as they had been during the 12 week trial. An 'intent to treat' analysis was performed and 116 patients completed the study. Also assessed were numbers of patients that relapsed (with relapsed defined as a return to panic status as measured at baseline) and number of adverse events. At the end of the 48 weeks (i.e. 12 weeks study participation plus 26 week follow-up), 85% of paroxetine recipients, 72% of clomipramine recipients and 59% of placebo recipients were free from panic. There were no significant differences in efficacy between paroxetine and clomipramine but paroxetine was significantly better than placebo throughout the study and better than clomipramine at the 12th 3-week assessment period (84.6% versus 59.1%; Fisher's exact test, p=0.004; 95% CI for the difference, 6.6%, 44.4%). Relapse rate was highest in the placebo group (4 patients, 10.8% and lowest in the clomipramine group (3 patients, 6.0%) and 5 patients or 8.3% of paroxetine patients relapsed. Adverse events experienced during the study were highest in the clomipramine group with 1 adverse event experienced in 76.2% of clomipramine patients, 61.8% of paroxetine patients and 51.1% of placebo patients. This trend was also seen in the percent who withdrew due to adverse effects: 19% of clomipramine patients, 7.4% of paroxetine patients and 6.7% of placebo patients. Both clomipramine and paroxetine patients experienced dizziness and headache but clomipramine patients reported more sweating, dry mouth and weight gain. More paroxetine patients reported abnormal ejaculation. The author concludes that paroxetine is as effective but better tolerated than clomipramine and is necessary for the long-term treatment of panic disorder.

SSRI – saftey

Medicines and Healthcare products Regulatory Agency (MHRA) 2004

In the UK the licensing and post-licensing safety monitoring of medicines is undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA). During the development of this guideline the safety of some drugs used to treat PD (selective serotonin reuptake inhibitors (SSRIs), was formally reviewed by the MHRA on behalf of the Committee on Safety of Medicines (CSM). The CSM convened a working group to look at this issue (the SSRI Expert Working Group (EWG)). In particular, data on discontination/withdrawal symptoms, cardiotoxicity, dose, and suicidality and self-harm, were used, together with information on

changes to produce licences as a result of the EWG's report to the CSM (MHRA, 2004). The Marketing Authorisation Holder (the pharmaceutical company responsible for the drug in question) analysed data from clinical trials for each relevant drug, in accordance with a protocol specified by the EWG. These reviews formed the basis of the EWG's deliberations, and it should be noted that not all trial data were made available to the EWG (MHRA, 2004). The EWG used other data, including a number of analyses of the General Practice Research Database, along with spontaneous reporting of adverse drug reactions (via the MHRA's Yellow Card scheme).

Withdrawal symptoms included dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. While generally mild to moderate, in some patients they may be severe in intensity.

7.5.1.2.2. Benzodiazepines

RCTs

Benzodiazepine (clonazepam) versus placebo

Valenca et al 2000

Twenty four patients from a laboratory of panic and respiratory disorders in Rio de Janeiro were randomly assigned to receive either clonazepam at 2mg/day or placebo for 6 weeks. Change in panic attacks from baseline revealed that 11.1% of patients in the placebo group were panic free compared to 61.5 % of clonazepam patients. Reduction in HAM-A scores were recorded in 50% of placebo patients and in 76.9% of clonazepam patients (Fisher's exact test, p=0.079). This difference is not statistically significant. The authors conclude that this trial provides evidence for the efficacy of clonazepam in panic disorder.

Impact of benzodiazepines on psychological therapy

Van Balkom et al 1996

This RCT sought to assess whether long-term benzodiazepine (BDZ) users responded poorly to treatment. Ninety six patients were randomly assigned to exposure in vivo alone, psychological panic management (including breathing retraining with exposure in vivo; exposure in vivo and placebo and exposure in vivo with fluvoxamine. Analysis of results is given on the 76 completers. The main outcome variable assessed was agoraphobic avoidance using a subscale of the Fear questionnaire (FQ), the Symptom Checklist and the Mobility Inventory avoidance scale. The number of panic attacks per day was also measured using a diary that recorded the weekly number of attacks. Patients were defined as either non-users, long-term users or incidental users. Long-term BDZ use was associated with less treatment gain compared with incidental or non-use in all four treatment conditions.

Westra et al 2002

This study sought to measure the as needed ('prn') use of benzodiazepines in 43 patients who had a confirmed diagnosis of panic disorder with or without agoraphobia according to DSM-IV, in a naturalistic setting. Using a battery of pre-agreed suitable measures including the Beck Anxiety Inventory (to measure somatic arousal), the Panic Attack Questionnaire Revised (to measure panic frequency in the past month), the Beck Depression Inventory (to measure depression), the Anxiety Sensitivity Index (to measure fear of bodily arousal sensations) and the Fear Questionnaire Agoraphobia subscale (to measure agoraphobic avoidance) treatment

outcome of 10 sessions of CBT were assessed. This research sought to investigate the way in which benzodiazepines may inhibit the outcome of CBT. To that end, the type, dose, chronicity and frequency of BDZ use as well as manner and frequency of pill taking were recorded on a Likert scale (1: never 7: always). Also measured were how often BDZ were used to control panic, to facilitate exposure to fear-provoking situations, and to control generally heightened feelings of anxiety. Not all patients were pure panic disorder sufferers. Results were presented for the 10 unmedicated patients and the 33 BDZ users. This latter group were divided between prn users and regular users. Taken together, all patients, as measured by the battery of measures improved significantly with CBT. Of all three groups, regular BDZ users (if they scored below the median of 3.5 on frequency of BDZ use for coping and above the median of 3.5 on the frequency of regular BDZ use), prn BDZ users (if they scored above the median of 3.5 on the composite score of frequency of BDZ use for coping and blow the median of 3.5 on the frequency of regular use of BDZ) and non-medicated patients, the non-medicated patients demonstrated the most positive outcome to treatment with CBT and prn BDZ users the worst. The authors conclude the findings of 'variable outcome as a function of manner of BDZ use, suggest that this variable should be systematically controlled in any investigation of treatment outcome with CBT'.

7.5.1.2.3. Tricyclics

Tricyclic (imipramine)

Systematic review

Cox et al 1992

In this review 34 papers were included. Papers were quality assessed for inclusion into the review, details were given of search terms and databases used. Details of patient characteristics of studies included are not given. It is not possible to determine if the included studies used an intention to treat analysis. This review used strict diagnostic inclusion criteria of panic disorder or panic disorder with agoraphobia. However, the authors state that the most common diagnosis in the majority of included studies was agoraphobia with panic attacks (DSM-III). It is not stated from this paper whether included studies that measured the use of imipramine (as well as in vivo exposure and alprazolam) were placebo or active comparator controlled studies. Several variables, deemed dependent variables, were assessed to measure the efficacy of the treatments under review. As the focus was on comparing the three treatments, conclusions assess which of the three examined therapies yielded the greatest effect in controlling panic. However, there is clear presentation of effect sizes. In relation to imipramine in the treatment of panic disorder symptoms (dependent variables within the review), the author's concluded that imipramine was found to be generally ineffective but that claims of superiority (statistically) for one treatment over another are still premature at this time (1992).

Mattick et al 1990

This systematic review including meta-analysis of 54 studies examining the treatment of panic and agoraphobia included 4 studies on imipramine reviewed from 1978 to 1986. Databases were given but not search terms. The review used pre-post analyses. Scant details about quality assessment and methods of combining studies of included studies are given. One study published in 1978, falls before the included diagnostic criteria of DSM-III (1979) and another of the 4 studies is an unpublished Ph.D. dissertation. Effect sizes on all symptoms measured is greater than 0.8. However, there is no data on side-effects. This review is of limited use and methodological quality.

RCTs

Tricyclic (imipramine) – side effects

Mavissakalian et al 2000b

This paper describes the side effects reported by 110 patients who partook in an RCT published elsewhere (trial reported in Mavissakalian et al 2000a). The study protocol was a 24 week double-blind placebo-controlled trial of imipramine against placebo. Side-effects were recorded using a 15 items inventory. Analysis of side-effects was carried out using hierarchical linear modelling that allowed for analysis of change over time against 4 predictor variables (demographic details, dosage, heart rate response and linear quadratic changes). Data from this analysis of side effects of only severe examples or only of completers to, as the author's state, better gauge the clinical significance of the findings. On all but three of the side effects, there was a curvilinear pattern of response with an increase within the first four weeks, to a peak and then a linear drop-off to 8 weeks, when side effects decreased. The three side effects that continued to be troublesome after this time were dry mouth, sweating (which did not show significant burden within the short-term) and constipation. Raised heart rate, sustained over treatment was found but it was worse in younger rather than older patients. The authors discuss the findings calling for a need to compare imipramine with SSRIs.

7.5.1.3 Cost effectiveness of pharmacological agents

The available evidence relating to the cost effectiveness of pharmacological treatments is fragmented and often studies have been conducted using single drugs versus placebo or alternative dosages of single drugs which means that it is very difficult to make any judgements about comparative cost effectiveness across alternative drug regimens. A study was conducted in the US by Nurnberg that compared three SSRIs (paroxetine, fluoxetine or sertraline) in terms of their comparative cost effectiveness and concluded that all three drugs conferred significant benefits for a modest extra cost to the health care budget. However there are difficulties in transferring these results to a UK setting because of differences in health care systems and the observation that the majority of patients included in this study had a primary diagnosis of depression rather than anxiety. In order to make an informed assessment of the cost effectiveness of alternative pharmacological agents it is important that studies of a randomised or controlled before and after design are conducted within a UK setting.

Jacobs et al 1997

This study examined the effectiveness of clinically titrated doses of clonazepam versus placebo on quality of life and work productivity in patients with panic disorder within the context of a randomised double blind placebo controlled trial. No assessment of costs was undertaken. The SF-36 and Work Productivity and Impairment (WPAI) questionnaire were used to assess health related quality of life and work productivity respectively administered at baseline (prior to randomisation) and after 6 weeks. All patients included met the criteria for panic disorder with or without agoraphobia according to DSM-III-R. Baseline assessments were made before randomising patients to receive clinically titrated doses of clonazepam or placebo. Follow up assessments were obtained after 6 weeks of therapy with the test drug or premature termination from the study. A total of 144 patients were evaluated for HRQL and 98 patients were employed and evaluated using WPAI. Improvement on the SF-36 mental health component was more than twice as great with clonazepam than with placebo ($p=0.03$). Clonazepam patients improved ($P<0.05$) on all five measures of mental health related quality of life, three of five measures of physical health related quality of life and both measures of work productivity. Placebo patients

improved on three of five measures of mental health related quality of life but on no other measures. The greatest gains on the SF-36 mental health summary scale were exhibited by patients with marked improvements on clinical measures of panic disorder severity, especially avoidance and fear of the main phobia.

Study limitations

- no assessment of costs
- HRQL/WP data were not universally collected on all RCT patients hence it is impossible to rule out patient selection or physician selection bias. Survey participation was voluntary and some centres did not always distribute surveys as required. However little evidence was found that such biases were responsible for differences between the clonazepam and placebo groups
- study results limited to 6 weeks – unclear as to whether improvement would be sustained over longer therapy duration common to clinical practice
- study population demonstrated less psychiatric morbidity than would be seen in psychiatry or primary care settings

Conclusions from study

A 6 week regimen of clinically titrated doses of clonazepam significantly improved mental HRQL and WP in panic disorder patients. Lesser improvements were seen with placebo.

Mavissakalian et al 2000a

This study examined the medical costs and effectiveness of acute treatment with imipramine versus acute treatment plus two different maintenance therapies for panic disorder. The authors note in their introduction that there is little information on the economic impact of panic disorder. A clinical decision model was developed to assess the impact of pharmacological treatment for panic disorder on economic and clinical outcomes. Costs and outcomes were estimated over an 18 month period based upon the medical literature and clinician judgement. The model simulates three clinical scenarios typical of panic disorder treatment in the US. The patient enters the model at the point of diagnosis, receives acute treatment and is followed for a period of 18 months. A diagnosis of panic disorder was in accordance with the SSM-III-R criteria. Individuals were considered to be responders during acute treatment (or in stable remission during the maintenance phase) if an end state functioning score of > 6 was achieved.

A Markov state transition model was developed to estimate QALYs, panic remission rates and medical costs over the 18 month period. The length of each cycle that these parameters were estimated for was 8 weeks. Treatment arms of the model included acute treatment with imipramine with no maintenance treatment and acute treatment with imipramine plus half dose maintenance treatment or full dose maintenance treatment.

Costs were calculated based upon standard treatment regimens. Data were provided on treatment patterns and typical resource use based upon the experiences of a university based anxiety disorders clinic. Patients receiving acute treatment were scheduled for 6 clinic visits during the first 8 weeks of treatment. Patients continuing on acute treatment averaged 1 visit per month during weeks 8-16, bi-monthly visits during weeks 16-24 and quarterly visits during maintenance treatment. Patients entering the half dose maintenance phase received 1 session of cognitive behavioural therapy (CBT). Efficacy values were derived from published clinical literature.

Utilities were estimated based upon utilities for depression/anxiety related health states. The utility for remission is 0.86 and for symptomatic panic disorder is 0.4. QALYs were calculated by weighting time duration in each state by the relevant utility score and then providing an aggregate of scores over all states in the model. Incremental cost effectiveness ratios (ICERs) were calculated based upon the estimated QALYs and medical costs for each treatment scenario. A number of sensitivity analyses were conducted to assess the robustness of the model to a) alternative assumptions relating to the status of patients who withdrew from treatment (these patients may continue to be asymptomatic or they may relapse) and b) alternative estimates of health state utilities.

The base case analysis assumes that half of the patients who withdrew during maintenance treatment continued to be responders and half relapsed. Costs in this analysis are in US dollars at 1997 prices. For the base case analysis, the 18 month medical costs of acute imipramine therapy (2.25mg/kg day) without maintenance therapy was $US 3691 and the associated QALYs were 0.979. The total costs and QALYs associated with half dose maintenance therapy [imipramine 1.1 mg/kg day $US3377 (1997 prices) QALYs=0.991] and full dose maintenance therapy [imipramine 2.25 mg/kg day $US3361 QALYs=0.992] were almost identical; both were cost saving compared with acute imipramine therapy.

Study limitations

- utilities were estimates and not derived directly from patients with panic disorder
- primary sources of efficacy data were the result of RCTs conducted by a single investigator and hence results of this study may not be generalisable to the treatment of patients with panic disorder in primary care settings

Conclusions from study

Imipramine maintenance treatment is cost effective compared with acute imipramine treatment for patients with panic disorder. The basic findings are not affected after modifying model assumptions for clinical response in patients withdrawing from treatment. The economic analysis provides evidence for the cost effectiveness of imipramine based upon well designed and systematic set of clinical trials. The results need to be extended to determine the cost effectiveness of imipramine versus SSRI treatment for panic disorder.

Grudzinski 2001

(Note: abstract only - article unavailable at British Library)

Excessive costs associated with anxiety disorders, especially panic disorder, result from a combination of factors including unnecessary or inappropriate diagnostic tests and high levels of medical help-seeking behaviour by patients. Little information has been available on the economic effects of pharmacotherapy for anxiety disorders but recent studies have shown that SSRIs are associated with a shift in medical resource utilisation (lower rates of emergency department and laboratory visits) which can potentially result in decreased health care expenditures. Facilitating an increased awareness amongst primary health care providers of anxiety disorders and appropriate diagnostic and treatment strategies can benefit patients and lead to more effective and efficient healthcare expenditures.

7.6 Psychological interventions for panic disorder

Recommendations

1. Cognitive behavioural therapy (CBT) should be used (A)
2. CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols (A)
3. CBT in the optimal range of duration (7–14 hours in total) should be offered. (A)
4. For most people, CBT should take the form of weekly sessions of 1-2 hours and should be completed within a maximum of 4 months of commencement. (B)
5. Briefer CBT should be supplemented with appropriate focussed information and tasks. (A)
6. Where briefer CBT is used, it should be around 7 hours and designed to integrate with structured self-help materials. (D)
7. For a few people, more intensive CBT over a very short period of time might be appropriate. (C)

Evidence statements

1. *Cognitive behaviour therapy with or without exposure is effective. (Ia)*
2. *Characteristics of cognitive behavioural therapy that are more likely to make it effective:*
   - *reducing therapist contact reduces effectiveness (Ib)*
   - *brief CBT, supplemented with appropriate focussed information and tasks, is as effective as longer CBT (Ib)*
   - *CBT is more likely to be effective if there are high expectations on behalf of the user, there is work between sessions, and there is high credibility of the intervention (Ib)*
   - *CBT is more likely to be effective if therapists are appropriately trained (Ib)*
   - *CBT is more likely to be effective if adhere treatment protocols are adhered to (Ib)*
3. *Applied relaxation is more effective than waiting list placebo. (Ib)*
4. *There is limited evidence that preference for psychological treatment type does not moderate treatment response . (Ib)*
5. *Eye movement desensitisation and reprocessing (EMDR) is ineffective in panic disorder. (Ib)*
6. *There is a lack of evidence to support the use of the following interventions in panic disorder:*
   - *hypnosis*
   - *interpersonal therapy*

- *neurolinguistic programming*
- *problem solving*
- *progressive muscular relaxation*
- *psychoanalysis*
- *solution focussed therapy*
- *stress control*
- *stress management*
- *psychodynamic therapy*
- *bilateral stimulation*

7. *There is some evidence that prior long term use of benzodiazepines is associated with a poorer response to subsequent psychological therapies. (Ia)*

7.6.1 Research literature evidence

7.6.1.1 Psychological interventions compared with psychological interventions

7.6.1.1.1 Cognitive therapies

RCTs

Cognitive therapy versus exposure versus combined cognitive + exposure

Williams & Falbo 1996

Forty eight participants with panic disorder took part in this study. They were randomly assigned to one of four groups: cognitive treatment, performance-based exposure treatment, combined cognitive/performance treatment or a no-treatment control group for an 8 week study period.

Participants in all three active treatment groups showed significant improvement compared to the no treatment group at the end of the study period. Improvement was maintained at follow-up 6 weeks later for 69% (n=9) in the cognitive group, 67% (n=8) in the performance group and 62% (n=8) in the combined group. At long-term follow-up, 50% (n=6) in the cognitive group remained free of panic, 80% (n=8) in the performance group and 58% (n=7) in the combined group. Those participants in the control group showed no improvement. Performance treatment was significantly more effective compared to cognitive therapy for Fear Questionnaire (FQ) total phobia score, panic coping self-efficacy and Agoraphobic Cognitions Questionnaire (ACQ). Those participants with low levels of agoraphobia showed much greater panic reduction than those with high levels of agoraphobia both at post treatment and at follow-up.

Cognitive therapy versus exposure

Arntz 2002

The purpose of this study was to compare cognitive therapy (CT) with interoceptive exposure (IE) for the treatment of panic disorder without agoraphobia. The Dutch study included 69 patients randomly allocated to treatment. Of these, four dropped out of the CT group and 7 out of the IE group. Both treatments consisted of 12 weekly sessions (most individual sessions but 15 patients were treated in groups) and follow-up at 1 and 6 months. Outcome measures included panic frequency, daily anxiety levels, Fear of Fear Questionnaire, Fear Questionnaire, State-Trait Anxiety Inventory and SCL-90. There were no significant differences between treatments on outcome measures post treatment ad at both follow-up assessments. Post treatment beliefs correlated strongly with symptoms post treatment and at follow-up in the CT group but not in the IE group with regard to reduction in idiosyncratic beliefs about the catastrophic nature of bodily sensations. Both completer and intention-to-treat analyses are presented.

Hecker et al 1998

The purpose of this 12 week cross-over study of two psychological treatments for panic disorder was to assess whether cognitive restructuring and interoceptive exposure treatment were effective interventions for panic disorder and whether both treatment order and treatment preference affected overall treatment outcome.

Of the 22 patients randomised, 18 were included in the results analysis. There was no intention to treat analysis employed in the examination of study outcomes. A battery of measures were used to assess treatment efficacy including self-report measures and structured interview. Patients also rated the expected benefit of treatment on a 0 to 8 pint Likert-type scale. Treatment was the between-subjects factor (i.e. exposure therapy versus cognitive therapy) and trials was the within-subject factor (i.e. assessment 1,2,3). Five assessments made: 1. before treatment, 2. after first 4 treatments in block, 3. after one month of no contact, 4. after the second block of 4 sessions in the untried treatment, 5. after final one month of no contact. Patients were either in condition 1: exposure therapy followed by cognitive therapy or condition 2: cognitive therapy followed by exposure therapy.

The most significant changes occurred between assessments 1 & 2 for all measures except that for agoraphobic avoidance which showed continued improvement throughout, and the FQGL (phobic distress) which showed non-significant improvement between assessments 1 & 2 and assessments 2 & 3. Structured interview data revealed significant trial effects (GL-rate: $F(1,12)=13.36$, $p<.005$; PS-Rate: $F(1,13)=12.23$, $p<.005$; A/D-Rate: $F(1, 12)=7.57$, $p<.05$). However, on these measures there was no significant treatment by trial interactions.

In the order of treatments comparison, repeated measures analysis of variance were again carried out for questionnaire measures. Treatment order, i.e. whether exposure therapy or whether cognitive therapy was administered first, was the between-subjects factor and, as before trials at assessment 1, 4 and 5 was the within-subjects factor. Again, significant improvements were measured on all but the FQAD (anxiety/depression symptoms) and Trait. There was no significant treatment by trial interaction but participants showed significant positive change between assessments 1 & 4. Nonsignificant differences were found for all questionnaire measures between assessments 4 & 5 with the exception of FQAG ($F (1, 11)=6.39$, $p<.05$) and the FQSW ($F(1,11)=8.80$, $p<.05$). It was noted that the mean score at assessment 5 on the FQAG was still significantly lower than at assessment 1. However on the FQSO, the difference between participants' scores at assessments 1 and 5 was not statistically significant ($F(1,11)=0.90$, $p>.30$). Structured interview data analysed at assessments 1 and 5 revealed no significant treatment by trial interactions (GL-Rate: $F(1,9)=61.36$, $p<.001$; PS-Rate: $F(1,13)=19.89$, $p<.001$; A/D-Rate: $F(1,10)=5.14$, $p<.05$).

There were no significant differences between treatment groups on the proportion of patients to meet clinically significant improvement criteria.

Methodological limitations included small sample size. Treatment procedures as administered in this study were very similar i.e. both treatments provided information about the disorder and models of understand the problem. The two procedures were not identical to those used in the two most well-known CBT packages for panic disorder, referred to as Barlow's Panic Control Therapy which limits the generalisablity of findings. There was no direct measure of panic used in the analysis of findings despite one administered. Patients tended not to complete it if they did not have a panic attack and some only completed it if they had a panic attack. The investigators therefore abandoned it.

The authors conclude that both forms of therapy lead to improvement in measures of psychopathology associated with panic disorder. Specifically, participants showed significant

improvement in catastrophic thinking (i.e. a decrease of), fear of physical sensations associated with panic, phobic avoidance and depression. Only one variable showed a difference between groups, that being participants' ratings of global disturbance within the cognitive therapy group. Findings are extremely limited due to methodological limitations.

Cognitive therapy versus exposure versus relaxation training

Murphy et al 1998

This 13 week randomised controlled trial measured the effects of self-directed in vivo exposure in the treatment of panic disorder with agoraphobia. Seventy four patients were randomly assigned to receive cognitive therapy plus graded exposure, relaxation training plus graded exposure or therapist-assisted graded exposure alone. Each of the randomised groups received training in self-directed exposure to practice in conjunction with their therapy. Diary data on behavioural responses included degree and severity of panic attacks as well as ability to endure a Standardized Behavioral Avoidance Course (5-BAC) comprising a 1-mile long course in a busy urban area. For this, several Subjective Unit of Disturbance Scale (SUDS) assessments were taken at 20-minute intervals. Also measured, were severity of symptoms with the Global Assessment of Severity Scale (GAS). Several hypotheses were put forward including frequency and duration of self-direct exposure practice would be negatively correlated with frequency of in vivo panic attacks; high marital satisfaction and low depression would predict low levels of anxiety as measured by the Subjective Units of Distress Scale. It was also hypothesised that relaxation therapy and cognitive therapy groups would demonstrate greater efficacy of self-directed exposure than the graded exposure alone group because the former two therapies included additional anxiety management strategies that graded exposure alone does not. This study did not incorporate an intent-to-treat analysis. Included patients were adult panic disorder sufferers according to DSM-III criteria between 18 and 65 years. Treatment consisted of 16 weekly 2.5 hour sessions, with two sessions per week for the first 3 weeks and one session per week for the remaining 10 weeks. Together with the SUDS, a packet of validated measures were given to test these hypotheses. Statistically significant findings were obtained across almost all diary measure domains at $p<.05$. CT outperformed RT on in vivo anxiety at post-treatment but this difference was not maintained at 3 month follow-up. GE fell in the midrange on this variable and the authors note that the difference is therefore due to chance. All diary measures revealed statistically significant improvement at $p<.05$ in weekly outings and events, time spent out (alone and accompanied), and distance travelled from pre to post-treatment. It was found that the greater the frequency and duration of self-directed exposure practice the less the number of in vivo panics, i.e. when there was no practice (at pre-treatment) t-tests revealed significant findings for both total time alone and frequency of alone events. T-tests on between group differences on depression scores revealed significant differences indicating the greater the degree of depression, the greater the level of anxiety at all assessment periods ($p<.05$). Also, the greater the level of marital satisfaction, the lower the differences in in-vivo anxiety. There was no connection between this observation and level of self-directed exposure. The results highlight that once a critical threshold of self-directed exposure practice is achieved, anxiety management emerges as an important dimension of treatment outcome. They conclude that from the powerful repeated measures effects seen in all diary variable domains across treatments that all three treatment modalities were highly effective in fostering SDE practices and in facilitating decreases in in vivo anxiety. The results point to the importance of self-directed exposure in the treatment of panic.

Interoceptive exposure versus breathing retraining

Craske et al 1997

In this RCT, 38 self-selected patients suffering from panic disorder with or without agoraphobia were randomly assigned to CIE or CBE for 12 weeks. Participants were follow-up at 6 months. Interoceptive exposure was more efficacious than breathing retraining, on certain measures, when each was combined with cognitive restructuring and in vivo exposure. These effects were manifested in decrease in panic frequency, overall severity and functioning at post-treatment and follow-up. The follow-up data is limited due to rates of attrition.

EMDR versus EFER

Feske & Goldstein 1997

In this study of 43 outpatients with panic disorder, participants were randomised to one of three groups. The first group received six sessions of eye movement desensitisation and reprocessing treatment (EMDR), the second group received the same treatment but without the eye movement component (EFER) and the third group was a waiting list control. Several outcome measures were used including the Agoraphobic Cognitions Questionnaire (ACQ), the Body Sensations Questionnaire (BSQ), Mobility Inventory for Agoraphobia (MI), Beck Anxiety Inventory (BAI), and Panic Appraisal Inventory (PAI). These scales were used to construct three composite scales (Social Concerns-General Anxiety, Agoraphobia-Anticipated Panic-Coping and Physical Concerns) and a single composite scale for self-monitoring date (Generalised Anxiety-Fear of Panic). Also reported was panic frequency. Secondary symptoms were measured with the Beck Depression Inventory (BDI), Brief Symptom Inventory (BSI) and Social Adjustment Scale Self-report (SAS-SR).

After the average three week treatment period, EMDR (n=15) was found to be significantly more effective than the waiting list control (n=12) for all four composite measures as well as panic frequency. When the EMDR (n=18) group was compared with the EFER (n=18) group, EMDR was more effective on two composite measures only (Agoraphobia-Anticipated Panic-Coping and General Anxiety-Fear of Panic). At three month follow-up there were no significant differences between the EMDR (n=14) group and the EFER (n=14) groups for any of the composite scales or for panic frequency.

This study had a small sample size and the results for the primary outcome measures were not reported. No blinding was reported and no follow-up data for the waiting list control group (they went on to have active treatment).

Cognitive therapy

Brown et al 2001

The participants for this study were taken from those participating in a comparative outcome study on cognitive therapy (CT) for panic disorder. It is not clear how they were chosen and what percentage of the original study sample was included. Of the 21 participants, 14 had a secondary diagnosis (including major depression, generalised anxiety disorder and alcohol or other substance abuse) and all of the 21 participants were receiving medication. Outcome measures included frequency of panic attacks, Hamilton Anxiety Rating Scale, Beck Anxiety Inventory and Beck Depression Inventory. Of the 21 taking medication while receiving CT, 9 were able to withdraw from their medication and remain medication free at 1 year follow-up. Improvements for patients with panic disorder receiving CT were maintained at 1 year follow-up. Treatment effectiveness was not affected by reduction or withdrawal of medication.

7.6.1.2 Psychological interventions

7.6.1.2.1 Cognitive therapies

Meta-analysis and systematic reviews

Oei et al 1999

This paper reviewed literature dating back to 1966 and up to 1996. Details were given of databases searched and search terms used. Details of any quality assessment undertaken to determine inclusion of studies is not given. Various study designs and outcome measures were used in studies included. In line with the guideline scope, studies of efficacy of treatment should not pre-date DSM-III diagnostic criteria (1979). Analysis of included studies revealed that all but one study were published post 1979. There were two aims of this analysis: one was to examine the effectiveness of CBT as a treatment for panic disorder with agoraphobia and the other to evaluate whether the efficacy of CBT treatments is related to the change to cognitive processes that are postulated to be important to the cognitive models of PDA. Results of findings in response to this latter aim are not considered here as they are outside the requirements of the scope. Thirty five studies were included and 17 of those were randomised controlled trials. Sixty per cent of included studies employed measures of panic and all of those reported improvement by either post-treatment and/or follow-up. With regard to panic and the other outcomes, findings suggest that CBT leads to positive changes on the measures used in the included studies. These changes are positive for (as stated) panic, fear and avoidance, approach behaviours, severity and intensity of condition, endstate functioning and improvement, clinical anxiety, depression, assertiveness and locus of control. A meta-analysis of those studies that used the Fear Questionnaire (FQ) (11 studies measure the Agoraphobia subscale of this measure and 7 studies measure the total score) compared data obtained from those studies with community and collegiate normative data. The authors use the Jacobson criteria of movement of at least 2 standard deviations of the "normative" groups is considered clinically significant. It is concluded from this meta-analysis that CBT, causing an average shirt from 2.11 to 0.38 standard deviations of the collegiate mean at post-treatment and to 0.29 SDs at follow-up resulted in clinically significant improvement and that these improvements are maintained at follow-up. This finding is echoed in the comparison with the general population norms whereby the panic disorder patients moved 097 to –0.48 SDs at post-treatment and –0.47 SDs at follow-up. The authors are less definitive in their conclusions of long-term follow-up and point to a need to conduct further studies in this area. One study is highlighted that found 67.4% of those treated to have remained in remission over 7 years. In summary, CBT reduces the symptoms of PD as measured in the included studies of this review but firm conclusions about the long-term benefit are not made but rather, a call for future research is made.

RCTs

Petterson & Cesare 1996

This very small study explored the relationship between panic disorder and CBT. A six week programme of cognitive behaviour therapy was used to treat 27 patients with panic disorder. Patients were randomly assigned to this treatment or to a control group. T control group received a phone call every week as a reminder to complete the panic attack records. Three self report measures were used, Anxiety Sensitivity Index, State-Trait Anxiety Inventory Scale-Trait Scale and number of panic attacks. Also reported were physiological measures such as blood

pressure, pulse and finger temperature as secondary outcomes. After six weeks, all three self-report indices showed significant improvement in the CBT group compared to the control group. No follow-up period was mentioned in the study.

7.6.1.2.1 Other studies

Predicting patients who drop out

Keijsers et al 2001

Keijsers et al (2001) studied the characteristics of 32 dropouts from a study where 161 patients with a diagnosis of panic disorder, with or without agoraphobia, were receiving cognitive behaviour therapy for their condition. Dropout was defined as termination by the patient before the end of the 14 sessions, either with or without discussing it with the therapist or without their approval. In a logistic regression analysis, education and motivation were both significant predictors of dropout, whilst three selected symptom severity measures, catastrophic cognitions, agoraphobic avoidance and panic frequency were not.

Different levels of contact time

Sharp et al 2000 (note: same study as Power et al 2000, below)

This 12 week randomised controlled trial conducted in a primary care setting sought to measure the efficacy of a standard cognitive behavioural therapy intervention with bibliotherapy compared to a reduced contacted cognitive behavioural therapy with bibliotherapy and bibliotherapy alone in patients with panic disorder with or without agoraphobia according to DSM-III-R. The study does not employ a strict intention to treat analysis, and analyses instead, data from all defined completers (i.e. those that had at least 42 days of treatment and provided full endpoint data). Of 132 patients referred, 104 were randomised to receive one of the three interventions. A total of 91 patients were considered 'defined completers' and their results analysed. Outcome of therapy was assessed using the global symptoms severity scale (for severity of illness), the clinical global improvement scale (for change in symptoms) and the Sheehan Disability Scale (for social functioning). Standard therapist contact consisted of 8 sessions of 45 minutes. Minimum contact consisted of six sessions with a maximum of 2 hours therapist contact. The bibliotherapy group received the book only that was also given to the other two groups. Significant effects were revealed with analysis of variance for group ($F=3.23$ for [2, 85] d.f.; $p<0.05$), time ($F=89.28$ for [1, 85] d.f.; $p<0.001$) and group by time interactions ($F=13.12$ for [2 85] d.f.; $p<0.001$). Both the minimum therapies contact group and the bibliotherapy group showed significantly lower ratings of global symptom severity although all 3 groups showed significant reduction in global symptoms severity pre to post-treatment. The psychologist therapist ratings for change in symptoms showed that standard therapist contact and minimum therapist groups had significantly lower ratings indicating a change in symptoms compared to the bibliotherapy only group. It was noted that there was a significant correlation between the ratings of the psychologist therapist and the patients ratings ($r=0.96$; $p<0.001$). Similar results were noted with the Sheehan Disability scale. Analysis of variance revealed significant time effects ($F=32.87$ for [1, 87] d.f.: $p<0.001$) and interaction effects ($F=5.86$ for [2, 87] d.f.: $p<0.01$). Similarly with the social life scale for time ($F=41.67$ for [1, 87] d.f.: $p<0.001$) and interaction effects ($F=4.14$ for [2, 87] d.f.: $p<0.01$) but only for time with the home life scale ($F=24.23$ for [1, 87] d.f.: $p<0.001$). The standard therapist contact group showed significantly lower ratings on disruption to work but both CBT groups had significantly lower scores on disruption to social and home life post-treatment.

Of all three groups, the standard therapy group showed the greatest improvement. Of particularly note is the short duration of the standard CBT, the authors conclude that it 'represents a useful and efficient treatment for panic disorder and agoraphobia in primary care."

Power et al 2000

The objective of this study was to compare CBT for panic disorder and agoraphobia in the primary care setting through three modes of delivery: standard therapist contact, minimum therapist contact and bibliotherapy. A total of 104 patients were randomly allocated to one of the three groups. Of these, 13 dropped out during treatment. Patients were included in the analysis if they completed treatment to mid point (day 42). All patients received an identical treatment manual. Treatment endpoint assessments were undertaken by an independent assessor blinded to treatment allocation. In the standard contact group, patients received eight 45 minute sessions over 12 weeks (6 hours). In the minimum contact group, patients received six sessions of 30 minutes and three sessions of 10 minutes (2 hours contact). In the bibliotherapy group, patients received only the manual and 1 and a half hours of therapist contact for assessment only. Measurements were taken at pre-treatment, mid treatment (day 42), treatment endpoint (day 84) and 6 months follow-up. Outcome measures included Hamilton Anxiety Scale (HAM-A) and the patient rated Symptom Rating Test (SRT). Agoraphobia was measured using the agoraphobia sub-scale of the Fear Questionnaire, panic attacks were recorded using a panic diary. At treatment endpoint, both standard and minimum therapist contact groups showed significant reductions on all measures. For the bibliotherapy group, significant reductions were significant for therapist and patient rated measures of anxiety. The standard therapist contact group was significantly improved in comparison to the bibliotherapy group, significant differences between the standard and minimum groups were found on therapist-rated anxiety only.

Clark et al 1999

In Clark et al's study, which compared full cognitive therapy against a briefer cognitive therapy programme and a control group, in patients with current panic disorder of six months or longer duration and with, or without agoraphobic avoidance, the authors randomised 43 patients, with an average age of 34 (SD 11.1) years to one of these three groups. Full cognitive therapy involved receiving up to 12 weekly one hour sessions (patients actually received a mean of 10.4 (SD 2.1), range 5-12), whilst brief therapy involved five contact sessions in total, scaled down from a first session of one and a half hours to a final session of half an hour, over a three month period along with some self-study modules. Both groups were followed up at three and 12 months, with both receiving an average of one and a half one hour booster sessions during the first three-month follow-up period. Thus the total cognitive therapy treatment amounted to 11.9 hours and 6.5 hours for the full and brief programmes respectively. Outcome measures included the use of a panic-anxiety composite measure, patient and assessor scored panic frequencies, panic-related distress or disability, and general tension and anxiety, the Beck Anxiety Inventory, Beck Depression Inventory, the Brief Body Sensations Interpretation Questionnaire Panic Scale, the Agoraphobia Cognition Questionnaire Frequency and Belief, and agoraphobic avoidance. No differences were seen between the three groups, pre treatment, but both the full and brief cognitive therapy groups had statistically significantly improved scores (all $p<0.005$) compared with the control group, post treatment. There were no significant difference between the brief and full treatment groups at either three or 12 months follow-up and patients in both groups had maintained their initial gains. As a measure of the gain achieved, effect sizes for the panic-anxiety composite score were between 2.8 and 3.2 in both treatment groups (confidence intervals were not given). The study results imply that brief cognitive therapy may be as successful as full therapy, but with only 14 subjects per group (1 dropout) the study is likely to be underpowered to detect any significant difference between these two interventions.

Treatment compliance

Schmidt & Woolaway-Bickel, 2000

The main objective of the study was to ascertain whether or not quantity or quality of CBT homework completed by participants was a better predictor of outcome. In total, 48 patients took part in the study all of who had panic disorder with or without agoraphobia. All patients had group-administered CBT for 12 sessions over a 12 week period. Ten patients dropped out, therefore only 38 were included in the analysis. Assessment was conducted by the therapist as well as by and independent assessor blinded to patient outcome. Major outcome measures were clinician ratings (panic frequency, panic intensity, anticipatory anxiety, overall severity) and self-report (Sheehan Patient-Rated Anxiety Scale, Motility Inventory for Agoraphobia alone and accompanied and Beck Depression Inventory). There was significant improvement on all measures post treatment. Patient ratings showed no significant relationship to outcome although the overall number of days spent conducting homework was significantly related to increased levels of self-rated disability. Therapist ratings of compliance significantly predicted positive changes on most outcome measures. Quality ratings were better predictors of outcome relative to quantity ratings both for therapist ratings and the independent evaluator.

Therapist variables

Huppert et al 2001

The main objective of the study was to investigate the relationship between the 14 therapists involved and treatment outcomes. This study included five groups: panic control treatment (CBT), panic control treatment plus placebo, panic control treatment plus imipramine, imipramine alone and placebo alone. In order to investigate the relationship between therapist and treatment outcome all CBT groups were combined. A total of 312 people with panic disorder took part in the study, of which 205 were randomised to CBT. Data from 183 patients receiving CBT were examined. Independent assessment of outcomes was undertaken by clinicians unaware of patient assignment. Measurements were collected at pre-treatment and after 12 weeks of treatment. The following measurements were recorded: ADIS=R, Panic Disorder Severity Scale (PDSS), Clinical Global Impressions Scale anchored for panic disorder, Hamilton Anxiety Scale (HAS), Hamilton Depression Scale. Self-report measures included the Anxiety Sensitivity Index (ASI) and the Subjective Symptom Scale. The following therapist characteristics were examined: experience, age, sex and orientation. Experience was associated with improved outcome though only on some measures. Orientation, gender and age were not significantly related to outcome. Therapist effect sizes varied depending on the outcome measure. The ASI showed the greatest therapist effect: 18%, $F(13,120)= 3.03$, $p = 0.001$. The PDSS, ADIS-R and HAS also all showed significant therapist effect sizes.

Allocation by preference

Bakker et al 2000

In the second study to determine if people with agoraphobia who choose a therapy do any better than those allocated to the same therapy, 35 patients who were randomised to receive cognitive therapy (the other two arms in this trial provided medication therapy) were compared with 31 trial refusers, unwilling to receive medication and with an expressed a preference for cognitive therapy, which they then received (Bakker et al 2000). Cognitive therapy comprised 45 minute weekly sessions for 12 weeks with psychologists and psychiatrists, based upon the approach of Clark (1986). The average age of the patients was 33.9 (SD 8.3) years and 74 percent were

female. No differences were found between the two groups in the number of panic attacks and the number of dropouts was similar. Dropouts differed from those who remained in the trial, in that their scores on the Agoraphobic Cognitions Questionnaire and the Montgomery-Asberg Depression rating Scale were significantly higher. Preferred choice of treatment does not seem to offer any better prognosis than random allocation in patients with agoraphobia receiving cognitive therapy. However, as with Clark et al (1999) subject numbers were small, no power calculation was reported, and the study is likely to have been underpowered.

Van Dyck & Spinhoven 1997

Sixty four patients were randomised to receive either exposure therapy alone or in combination with self-hypnosis for 4 weeks and then crossed-over to receive the other therapy depending on their first course of treatment. Patients were from an outpatient clinic in the Netherlands and were suffering from panic disorder with or without agoraphobia. No other treatment was permitted in recruited patients other than continuing, unchanged with long-standing medication (recorded as always benzodiazepines). Patient preference was recorded using a visual analogue scale. Half of the patients were allocated to their preferred treatment prior to the cross-over and half were randomised. Outcome measures were completed at pre-test, at intermediate between the first and second treatments at crossover and at the end of the second treatment. There was a significant change in patient preference from 37 (versus 27) recorded as preferring combined treatment at the intermediate stage and 49 (versus 15) at posttest (chi square (2df) = 10.9, $p<.006$). However, there was no effect for preference in terms of response to treatment. There were significant main effects for both treatments regardless of preference and place of therapy (i.e first or second treatment received).

Location of treatment

Stuart et al 2000

This paper presents the results of a one-year follow-up study of 81 patients diagnosed as suffering from panic disorder with or without agoraphobia treated in a community mental health centre in the United States. The analysis of efficacy at one year follow-up is done by comparing data from patients measured on the Fear Questionnaire, the Beck Depression Inventory, the positive and negative affect schedule to results obtained on the same measures in other, benchmarking studies (Barlow et al 1989, Craske et al 1991 and Telch et al 1993). The authors describe this comparative analysis as, 'benchmarking strategy'. It involves a comparison of treatment outcome data obtained in service settings with data obtained in efficacy studies. Of particular significance in this study is the research setting, i.e. within a Community Mental Health Centre which allows an analysis of effectiveness as well as efficacy. The study design is described as quasi-experimental. The original study referred to, was an analysis of the effectiveness of 15 sessions of CBT on a cohort of 81 participants. Of the 81 participants in the original study, the investigators were able to contact 57 of the former participants. It was thought that others had moved out of the area. Results indicate that treatment gains obtained at post-treatment were maintained at one year follow-up and equate to findings of the 'benchmarking' efficacy studies (noted above). The relevance of this is further highlighted by the fact that participants in this study were more agoraphobic, had more generalised anxiety, depression and medication use, than the populations in the benchmarking studies and yet, the magnitude of change was also affected in this study. Although the authors conclude that 89% of those at follow-up were panic free, it is apparent that this 89% is from the proportion of 'contactable' clients at follow-up, i.e. 89% of 57.

7.6.1.1.2 Exposure therapy

Matched pair study

Fava et al 2001b

This case control study was designed to assess psychological well-being and residual symptoms in a sample of 30 patients who had recovered from panic disorder following an affective disorders treatment programme. Thirty consecutive patients who met DSM-IV criteria for panic disorder with agoraphobia who had no axis I or II according to DSM-IV comorbidity or other medical illness and had successful response to behavioural exposure homework and feedback from a therapist (without therapy aided exposure) were enrolled if they could be rated as either 'better' or 'much better' according to Kellner's global scale of improvement. Patients and controls were administered Paykel's Clinical Interview for Depression (Paykel 1985), the Scale for Personality Disturbances (Van Praag, 1989), the Scales of Psychological Well-being (Ryff, 1989) and the Symptoms Questionnaire (Fava et al 1983 & Kelner, 1987). The latter scale measured 4 scales of distress and 4 of well-being. Using a non-parametric permutation test (adapted by Pesarin 1990) to compare the two groups, remitted patients displayed significantly more psychological distress than controls according to the CID and the SQ ($p>0.001$). The most common residual symptoms were generalised anxiety, somatic anxiety, low self-esteem, agoraphobia and hypochondriasis. Further difference of significance were that remitted patients showed less psychological well-being than controls $p<0.001$. Significant negative correlations were found between environmental mastery, purpose in life and self-acceptance for the patient group whereas the only significant correlation was with environmental mastery for controls. Significant negative correlations were also measured in the patient group between personality disturbance and environmental mastery, positive relationships, purpose in life and self-acceptance. In controls this variable was related to three of these four (not to purpose in life) and autonomy.

The authors observe that as panic disorder remits, there is, what they term, a roll-back phenomenon of the illness 'recapitulating' many of the symptoms that were seen during the time the panic disorder developed. It is concluded that the findings suggest the need of multidimensional assessment to determine recovery from panic disorder and also to decide on more sustainable treatment strategies.

Long term follow study

Fava et al 2001a

One hundred and thirty two patients suffering from panic disorder with agoraphobia, who had been successfully treated with exposure therapy at the University of Bologna over a period of 12 years were followed-up. Patients had undergone behavioural exposure homework therapy with feedback from a therapist during the once fortnightly sessions. Each patient had 12 sessions. Treatment therefore extended over 6 months. None of the patients received any treatment during follow-up unless they relapsed. Relapse was defined as the occurrence of DSM-IV panic disorder. Patients were assessed before treatment, at the end of treatment, at 6 month and 1 year follow-up and subsequently on a yearly basis. At each follow-up visit, the occurrence of relapse was recorded as was the clinical state of the patient during the previous year, or 6 months, if it was the first follow-up. Time to relapse into panic was measured via survival analysis. The range of follow-up years was from 2 to 14 years with a median time of 8 years. 23% had a relapse of panic disorder during follow-up. Cumulative probabilities of remaining in remission were calculated for the first 2 years (as all patients had a minimum of 2 year data) and estimated

93.1% remaining in remission. This rate dropped for 5 years follow-up with the percentage dropping to 82.4% and 78,8% after 7 years and 62.1% after 10 years. Sixteen risk factors were examined and 6 were measured as clinically significant. These included the presence of a personality disorder (χ^2=13.00, p<0,001) being the highest risk factor, followed by pre-treatment level of depressed mood (χ^2= 4.55 p<0.05). Also found to be significant risk factors were, level of residual agoraphobia, specifically, presence of residual agoraphobic avoidance after behavioural treatment (χ^2= 4.55 p<0.05). Two other risk factors identified were whether patients were still taking Benzodiazepines (χ^2= 4.80 p<0.05) or antidepressants (χ^2= 6.43 p<0.05). The younger the age of the patient, the better the outcome (χ^2= 5.29 p<0.05). The 31 relapsed patients were offered a new course of treatment and became panic free with 6 having a second and two a third relapse. Three had to undertake another course of treatment (not specified). Eight patients developed major depressive episode that was treated with Imipramine (150-200mg/day). This treatment was tapered after 6 months due to a satisfactory response.

The authors make mention of the fact that variables are not controlled and hence there is a methodological weakness. They conclude that the results show that behavioural treatment based on exposure in vivo 'can provide lasting relief to the majority of patients' with panic disorder. The disappearance of residual agoraphobic avoidance and not just panic attacks should be the final aim of exposure therapy.

7.6.1.1.3 Internal/external cues

Ito et al (2001)

Ninety outpatients suffering from panic disorder with or without agoraphobia according to DSM-IV were randomised to receive one of four therapies: exposure therapy (E); self-exposure to interoceptive cues (I); self-exposure to both external and interoceptive cues (E+I), or control (no treatment at all during the 10 week period of treatment). Participants were assessed at weeks 0, 6 and 10 on a battery of measures and again at 3 follow-up points: month 3, 6 and 12. The three treatment groups improved significantly on target avoidance, the HAS, CGI scale and Agoraphobic Cognitions Scale (p<0.001). There was no significant difference between groups on the same scores. Each of the three treatment groups improved significantly in comparison to placebo (p<0.001) with large effect sizes in comparison to control (E 2.5; I 3; E+I 1.6). At follow-up, treatment gains were maintained and effect sizes improved as follows: E 4.7, I 3.5; E+I 3.8, effect size as measured by the CGI: E 4.1; I 3.3; E+I 4.3 and as measured by the HAS E 2.8; I 3.5; E+I 3.4. The authors conclude that self-exposure to external or to interoceptive cues each improved panic disorder plus agoraphobia significantly and similarly up to 1 year after treatment ended, and each was better than a 10-week waiting-list control condition. Combining the two forms as represented in the E+I condition did not yield a synergistic result.

7.6.1.1.4 Eye movement desensitisation and reprocessing (EMDR)

Goldstein & de Beurs 2000

In this study eye movement desensitisation and reprocessing (EMDR) was compared with a waiting list control group and a credible attention-placebo group for the treatment of panic disorder with agoraphobia. A total of 46 outpatients took part in this American study. Both treatments consisted of six 90 minute sessions held over an average of 4 weeks. The credible attention-placebo group consisted of progressive muscle relaxation therapy and association therapy. Self-report instruments were completed prior to the onset of treatment (or waiting list), 1 week following the final treatment session and 506 weeks following final treatment session. Self-report instruments included the Agoraphobic Cognitions Questionnaire, Body Sensations

Questionnaire, Brief Body Sensations Interpretation Questionnaire, Panic Appraisal Inventory, Mobility Inventory, Beck Depression Inventory, Beck Anxiety Inventory, Brief Symptom Inventory, Social Adjustment Scale-Self-Report, the Distress Questionnaire. In addition to these, the Panic Disorder Symptom Severity Interview was conducted at each assessment point. Raters were not blinded to group assignment. Not all participants initially randomised were included in analysis (not ITT). With regard to EMDR versus. waiting list control comparison, EMDR was significantly better for some outcome measures (diary and panic and agoraphobic severity) but not for panic attack frequency and anxious cognitions. With regard to the EMDR and attention-placebo group comparison, there were no statistically significant differences between the two groups for any measure.

7.6.1.1.5 Psychoanalytic therapy

Milrod et al 2001

This study was a pilot study designed to estimate the degree of symptoms change in sufferers of panic disorder with or without agoraphobia. Twenty-one patients suffering from panic disorder with or without agoraphobia underwent 24, twice weekly sessions of psychodynamic psychotherapy over 12 weeks. Patients were eligible if aged between 18 and 50 years and met DSM-IV criteria for panic disorder. Eligible patients had to have at least 1 panic attack per week for the month prior to the study and if on medication, had to maintain medication throughout the duration of the study. The exact type of therapy offered was Panic Focused Psychodynamic Psychotherapy (PFPP). Each session lasted 45 minutes and was in three phases: treatment of acute panic; treatment of panic vulnerability and termination. The core principles of the therapy were importance of unconscious mental dynamisms, fantasies etc. used to inform interpretive efforts. Data from subjects was gathered pre and post-treatment on the Anxiety Sensitivity Inventory (ASI), the Marks and Matthews Fear Questionnaire (FQ), the Panic Disorder Severity Scale (PDSS) and the Social Adjustment Scale. The authors state that these measures provide secondary predictive measures. Also used were the HAM-A the HAM-D and the Sheehan Disability Scale (SDS). An intention to treat analysis of data was performed. Just over three quarters of patients had primary DSM-IV panic disorder with agoraphobia and just under one quarter had panic disorder without agoraphobia. 80% of participants had at least one other Axis I diagnosis. There was significant within patient reduction on panic and agoraphobia in 16 of the 21 study participants. Improvements were reported as significant in primary psychiatric symptoms, in phobic sensitivity and in overall quality of life. These improvements were maintained at 6-month follow-up. The authors are quite explicit about the need for a more rigorous randomised controlled trial methodology to measure the efficacy of psychodynamic psychotherapy in comparison to a control or other treatment.

7.6.1.1.6 Cost effectiveness of psychological therapies

Shapiro et al 1982

This study randomly assigned 44 US based out-patients being treated for anxiety and depression to one of three treatment modalities: a CBT group (n=10), a traditional process orientated interpersonal group (n=13) and CBT in an individual format (n=12). All three treatments consisted of 10 weekly sessions (1.5 hours for group and 1 hour for individual). Beck's depression inventory, Speilberger's state trait anxiety inventory and Gay and Galassi's adult self expression scale were administered pre and post treatment. All three experimental groups significantly improved on all dependant measures from pre to post treatment and no differential treatment effects were found.

Study limitations

- relatively small numbers of patients in each group and US setting
- limited assessment of resource use and costs

Conclusions from the study

The equivalence of psychotherapeutic outcomes as measured by three indices of psychological functioning after treatment suggests that cost considerations can become more important when decisions are made on particular treatments. Group therapy is a less costly clinical intervention and is as effective as individual treatment.

7.7 Other interventions for panic disorder

Recommendations

1. Bibliotherapy based on CBT principles should be offered (A)
2. Information about support groups, where they are available, should be offered. (Support groups may provide face-to-face meetings, telephone conference support groups [which can be based on CBT principles], or additional information on all aspects of anxiety disorders plus other sources of help.) (D)
3. The benefits of exercise as part of good general health should be discussed with all patients as appropriate. (B)
4. Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. [NICE 2002]

Evidence statements

1. *Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE 2002:TechApp 51)*

2. *One study found that exercise, albeit a rather harsh routine, was associated with significant treatment gain in patients with panic disorder. (Ib)*

7.7.1 Research literature evidence

7.7.1.1 Self help

CCBT

NICE published a technology appraisal about the use of computerised cognitive behavioural therapy (CCBT) for anxiety and depression in October 2002. CCBT is a terms that describes a number of methods of delivering CBT via an interactive computer interface. CCBT systems if available would increase access to CBT. NICE noted that the acquisition costs of the individual packages varied from £350 to £10,000 and depended on whether the purchase price included dedicated computer systems, technical support, training and clinical support.

Evidence from 11 RCTs and 4 uncontrolled studies were considered. The studies had been conducted in a number of countries. Nine studies had been conducted in the UK. RCT evidence was available for 3 packages that were available in the UK. Follow up periods in the studies ranged from 3 weeks to 12 months and study quality was reported as varied. Four RCTs used blinded assessors, the studies could not be realistically conducted under double blind conditions. Two of the RCTs were adequately powered to demonstrate equivalence. Five RCTs enrolled more than 80 individuals.

Five out of six RCTs found no evidence of any difference between CCBT and therapist delivered CBT in the treatment of phobias, panic disorder, major and minor depression or major depression. However, all but the panic and phobia study were inadequately powered to demonstrate differences.

The technology appraisal committee having considered evidence for clinical and cost effectiveness, from published and unpublished sources as well as responses from professional experts and patient and carer groups concluded:

> "the evidence presented in both written and verbal form supported the opinion that computer-aided delivery of CBT many have potential as an option in certain groups of patients, and it may be most suitably delivered as past of a 'stepped-care' protocol. However the Committee considered that whilst there was higher quality RCT evidence for Beating the Blues and FearFighter, the evidence base for CCBT as a technology was underdeveloped and therefore further research was required." (NICE 2002, 4.3.6)

Their guidance was that:

Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE 2002:TechApp 51)

Carlbring et al 2001

Forty one people from public advertising in a Swedish population qualified to partake in this on-line investigation of whether a six moduled self-help treatment could be used to reduce the symptoms of panic disorder. Participants had to have a computer at home with access to the internet. An online screening questionnaire was divided in three parts, the first to ascertain demographic details, the second, panic disorder details and the third was a self-assessment of MADR-SR. The treatment itself was derived from a book entitled 'An end to panic: breakthrough techniques for overcoming panic disorder' with 20% of input from Barlow & Craske, 1994's 'Mastery of Your Anxiety and Panic II' and Franklin's 'Overcoming panic: a complete nine-week home-based treatment program for panic disorder' (1996). 6 modules were constructed such that participants could only access the next module by having completed the previous module and completing and returning questions on that module just completed. The modules were comprised in turn of psychoeducation, breathing retraining, cognitive restructuring, interoceptive exposure, in vivo exposure and relapse prevention. The self-help programme was evaluation by means of a specially formulated questionnaire that included 13 open-ended questions assessed on a Likert-type scale. When each of the treatment participants was ready to complete the post-test measure, a wait-list person was also contacted to do the same. Wait-list patients were offered the treatment at the end of the study. The mean time spent on each participant was approximately 90 minutes and the time from beginning of treatment to post-test was between 7 and 12 weeks. Responses to each stage of the treatment completion were received and queries answered via e-mail. The daily diary showed significant time by treatment interactions for full-blown panic attacks for all dimensions including frequency, duration and intensity but not on limited symptoms attacks. All but the Mobility Inventory recorded significant time by treatment interactions with clinically significant improvement of panic attack frequency (being no occurrence of full-blown panic attacks, and no limited symptom attacks during the 2 weeks post-treatment). These results indicate that Internet-administered self-help plus minimal therapist contact via e-mail is a 'promising new treatment approach for people suffering from PD'.

Bibliotherapy

Gould, Clum & Shapiro 1993

This randomised controlled study of a US university population suffering from panic disorder according to DSM-III, was a preliminary examination of bibliotherapy, a self-help technique in managing panic disorder symptoms compared with a Cognitive Therapy (CT), called, Individual Therapy using Guided Imaginal Coping (ITGIC) and a Wait List (WL) condition. It was conducted over 7 weeks, 2 weeks baseline, 4 weeks treatment and 1 week follow-up (post-treatment). Wait-list subjects were told that they were on a waiting-list to receive treatment after 7 weeks. Two separate sets of measures were used; one from pre- to post-treatment, and other measures that were completed at weekly intervals. Thirty three subjects were randomised with two dropouts. Thirty one patients were included in the analysis. Results were therefore not an intention to treat analysis. Subjects did significantly better on bibliotherapy than in WL ($p<.05$) with 73% remaining panic free at the end of the study compared to 56% receiving ITGIC and 37% of WL patients. Results point to the significance of bibliotherapy as an approach to treating the symptoms of panic disorder.

Hazen et al 1996

The primary objective of this study was to assess whether or not anxiety sensitivity was responsive to cognitive behavioural treatment and to assess whether or not anxiety sensitivity was a stable, personality variable. The subjects were randomly divided into four groups: individual administration of self-help manual, use of manual in a self-help treatment group, use of manual in a professionally led treatment group and a wait list control group. Four outcome measures ASI, FQ-AG, SPRAS and CGI were used in this 14 week study of 106 patients with anxiety (with or without agoraphobia). Subjects in all active treatment groups had significantly lower anxiety sensitivity scores than wait-list controls at post treatment. Those in the professionally led group had significantly lower anxiety sensitivity compared to the group that independently used the self-help manual. Clinical Global Improvement ratings for the four groups although obtained were not reported. Also not reported were the statistical differences between the four groups with regard to the FQ-Ag and SPRAS instruments. Those subjects who showed improvement based on CGI ratings also showed reduction in anxiety sensitivity. Effect sizes for ASI were greater than those of FQ-Ag and SPRAS.

Exercise

Broocks et al 1998

Forty six patients from a German outpatient clinic were randomised to receive either exercise therapy (n=16), placebo (n=15) or clomipramine (licenses for obsessional and phobic disorders) (n=15) for 10 weeks following a 3 week washout period. Patients in the exercise therapy group were instructed to identify a 4-mile trail for walking/running near their home. During the first week of exercise, participants in the exercise group were instructed to walk the 4 miles 3 to 4 times per week building up to including running bursts of 2-4 minutes with gradual prolongation of running for the remaining weeks. Placebo and clomipramine patients were instructed to take a pill once a day for the first week, 2 per day in the second week and 3 per day in the third week and subsequent weeks of the study. All patients kept activity diaries. These were taken to weekly meetings with therapist in which clinical history, recent important events, panic attacks during the preceding week, side effects of medication and exercise-related problems were discussed. Principal outcome measures were the Hamilton anxiety scale, the observer-rated and patient-rated version of the Panic and Agoraphobia Scale and the 'rater' version of the CGI. Measures were completed at screening interview, at baseline, and after 2,4,6,8 and 10 weeks. In an intention to treat analysis, exercise was shown to be significantly more effective then placebo

(HAM-A p=0.0007, CGI p=0.003, Observer-rating panic and agoraphobia scale score p=0.002, patient-rating, panic and agoraphobia scale score p=0.03). So too was clomipramine with comparisons all highly significant. It appears that the 'time course of the treatment effects' pertained to completer analysis only and not an intention to treat group and revealed that both treatments were significantly better than placebo at the end of treatment. More side effects were recorded in both the placebo and clomipramine groups including dry mouth, sweating, mild tremor, dizziness, tachycardia, nausea, constipation, diarrhoea and rarely, impaired erection or ejaculation. It was noted that these effects were highest during the first 4 weeks of treatment after which there was a gradual decline. Exercise condition patients reported mild and transitory muscle aches and pains. The results indicate that exercise alone is associated with significant treatment gain in patients with panic disorder and may be a particularly useful treatment in those patients who either do not wish or cannot take medication.

8. Care of individuals with generalised anxiety disorder

Recommendations: care of people with generalised anxiety disorder

Step 2: Offer treatment in primary care

The recommended treatment options have an evidence base: psychological therapy, medication and self-help have all been shown to be effective. The choice of treatment will be a consequence of the assessment process and shared decision-making.

There may be instances when the most effective intervention is not available (for example, cognitive behavioural therapy [CBT]) or is not the treatment option chosen by the patient. In these cases, the healthcare professional will need to consider, after discussion with the patient, whether it is acceptable to offer one of the other recommended treatments. If the preferred treatment option is currently unavailable, the healthcare professional will also have to consider whether it is likely to become available within a useful timeframe.

1. If immediate management of generalised anxiety disorder is necessary, any or all of the following should be considered:
   - support and information (D)
   - problem solving (C)
   - benzodiazepines (A)
   - sedating antihistamines (A)
   - self help (D)
2. Benzodiazepines should not usually be used beyond 2-4 weeks. (B)
3. In the longer-term care of individuals with generalised anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalised anxiety disorder should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order are:
   - psychological therapy (A)
   - pharmacological therapy (antidepressant medication) (A)
   - self-help (A)
4. The treatment option of choice should be available promptly. (D)
5. There are positive advantages of services based in primary care (for example, lower rates of people who do not attend) and these services are often preferred by patients. (D)

Psychological interventions

6. CBT should be used. (A)
7. CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols. (A)
8. CBT in the optimal range of duration (16-20 hours in total) should be offered. (A)
9. For most people, CBT should take the form of weekly sessions of 1-2 hours and should be completed within a maximum of 4 months of commencement (B)
10. Briefer CBT should be supplemented with appropriate focussed information and tasks. (A)
11. Where briefer CBT is used, it should be around 8-10 hours and be designed to integrate with structured self-help materials. (D)

Pharmacological interventions

12. The following must be taken into account when deciding which medication to offer:
    - the age of the patient (D)
    - previous treatment response (D)
    - risks
        - the likelihood of accidental overdose by the person being treated and by other family members if appropriate. (D)
        - the likelihood of deliberate self harm, by overdose or otherwise (D)
    - tolerability (D)
    - the preference of the person being treated (D)
    - cost, where equal effectiveness is demonstrated. (D)
13. All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. (C)
14. Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (D)
15. Unless otherwise indicated, an SSRI should be offered. (B)
16. If one SSRI is not suitable or there is no improvement after a 12-week course, and if a further medication is appropriate, another SSRI should be offered. (D)
17. When prescribing an antidepressant, the healthcare professional should consider the following
    - Side effects on the initiation of antidepressants may be minimised by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. (D)
    - In some instances, doses at the upper end of the indicated dosage range may be necessary and should be offered if needed. (B)
    - Long-term treatment may be necessary for some people and should be offered if needed. (B)
    - If the patient is showing improvement on treatment with an antidepressant, the drug should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. (D)
18. If there is no improvement after a 12-week course, another SSRI (if another medication is appropriate) or another form of therapy should be offered. (D)
19. Patients should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. (C)
20. Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should extended period of time. (C)
21. All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly . (C)

22. Healthcare professionals should inform patients that the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. (D)
23. Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (D)
24. If discontinuation/withdrawal symptoms are mild, the practitioner should reassure the patient and monitor symptoms. If severe symptoms are experienced after discontinuing an antidepressant, the practitioner should consider reintroducing it (or prescribing another from the same class that has a longer half-life) and gradually reducing the dose while monitoring symptoms. (D)

Self-help interventions

25. Bibliotherapy based on CBT principles should be offered. (A)
26. Information about support groups, where they are available, should be offered. (Support groups may provide face-to-face meetings, telephone conference support groups [which can be based on CBT principles], or additional information on all aspects of anxiety disorders plus other sources of help). (D)
27. Large group CBT should be considered. (C)
28. The benefits of exercise as part of good general health should be discussed with all patients as appropriate. (B)
29. Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. [NICE 2002]

Step 3: Review and offer alternative treatment if appropriate

30. If, following a course of treatment, the clinician and patient agree that there has been no improvement with one type of intervention, the patient should be reassessed and consideration given to trying one of the other types of intervention.. (D)

Step 4: Review and offer referral from primary care if appropriate

31. In most instances, if there have been two interventions provided (any combination of medication, psychological intervention or bibliotherapy) and the person still has significant symptoms, then referral to specialist mental health services should be offered. (D)

If venlafaxine is being considered

32. Venlafaxine treatment should only be initiated by specialist mental health medical practitioners including General Practitioners with a Special Interest in Mental Health. (D)
33. Venlafaxine treatment should only be managed under the supervision of specialist mental health medical practitioners including General Practitioners with a Special Interest in Mental Health. (D)
34. The dose of venlafaxine should be no higher than 75 mg per day. (A)

35. Before prescribing venlafaxine an initial ECG and blood pressure measurement should be undertaken. There should be regular monitoring of blood pressure, and monitoring of cardiac status as clinically appropriate. (D)

Step 5: Care in specialist mental health services

36. Specialist mental health services should conduct a thorough, holistic, re-assessment of the individual, their environment and social circumstances. This reassessment should include evaluation of:
    - previous treatments, including effectiveness and concordance
    - any substance use, including nicotine, alcohol, caffeine and recreational drugs
    - comorbidities
    - day to day functioning
    - social networks
    - continuing chronic stressors
    - the role of agoraphobic and other avoidant symptoms

    a comprehensive risk assessment should be undertaken and an appropriate risk management plan developed (D)
37. To undertake these evaluations and to develop and share a full formulation, more than one session may be required and should be available. (D)
38. Care and management will be based on the individual's circumstances and shared decisions arrived at. Options include:
    - treatment of co-morbid conditions
    - CBT with an experienced therapist if not offered already, including home based CBT if attendance at clinic is problematic
    - structured problem solving
    - full exploration of pharmaco-therapy.
    - day support to relieve carers and family members
    - referral for advice, assessment or management to tertiary centres (all D)
39. There should be accurate and effective communication between all healthcare professionals involved in the care of any person with generalised anxiety disorder and particularly between primary care clinicians (GP and teams) and secondary care clinicians (community mental health teams) if there are existing physical health conditions that also require active management. (D)

Monitoring and follow up

Psychological interventions

4. There should be a process within each practice to assess the progress of a person undergoing CBT. The nature of that process should be determined on a case-by-case basis. (D)

Pharmacological interventions

5. When a new medication is started, the efficacy and side-effects should be reviewed within 2 weeks of starting treatment and again at 4, 6 and 12 weeks. Follow the Summary of Product Characteristics (SPC) with respect to all other monitoring required. (D)

6. At the end of 12 weeks, an assessment of the effectiveness of the treatment should be made, and a decision made as to whether to continue or consider an alternative intervention. (D)
7. If medication is to be continued beyond 12 weeks, the individual should be reviewed at 8- to 12- week intervals, depending on clinical progress and individual circumstances. (D)

Self-help interventions

8. Individuals receiving self-help interventions should be offered contact with primary healthcare professionals, so that progress can be monitored and alternative interventions considered if appropriate. The frequency of such contact should be determined on a case-by-case basis, but is likely to be between every 4 and 8 weeks. (D)

Outcome measures

9. Short, self-complete questionnaires (such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder) should be used to monitor outcomes wherever possible. (D)

9. Interventions for generalised anxiety disorder

9.1 Pharmacological compared with psychological compared with combined interventions for GAD

Recommendations

1. If immediate management of generalised anxiety disorder is necessary, any or all of the following should be considered:
   - support and information (D)
   - problem solving (C)
   - benzodiazepines (A)
   - sedative antihistamines (A)
   - self help (D)
2. Benzodiazepines should not usually be used beyond 2-4 weeks. (B)
3. In the longer-term care of individuals with generalised anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalised anxiety disorder should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order are:
   - psychological therapy (A)
   - pharmacological therapy (antidepressant medication) (A)
   - self-help (A)
4. The treatment option of choice should be available promptly. (D)
5. There are positive advantages of services based in primary care (for example, lower rates of people who do not attend) and these services are often preferred by patients. (D)

Evidence statements

1. *There is no evidence that will allow the clinician to predict which of the three broad intervention groups (pharmacological, psychological or self help) will be effective for an individual patient, based on duration of illness, severity of illness, age, sex, gender, or ethnicity. (IV)*

9.1.1 Research literature evidence

9.1.1.1 RCTs

Benzodiazepine(diazepam) versus cbt versus benzodiazepine (diazepam) + CBT

Power et al 1990

The purpose of this study was to compare cognitive behaviour therapy alone and in combination with either Diazepam or placebo against either diazepam or placebo alone on patients who presented to their general practitioner with GAD according to DSM-III. At the time of publication, this was one of the first studies to make this comparison of combined drug and psychological therapy against drug treatment (or placebo) or psychological therapy alone. Following a 1 week placebo washout period, 113 patients were randomised to one of the five

treatment arms: CBT alone; CBT with Diazepam 15mg/day; CBT with placebo; Diazepam alone 15mg/day or placebo alone. Data was analysed for all patients who provided baseline data. 101 patient provided at least baseline data on the HAM-A (on days 0, 7, 14, 28, 42, 56, 63 & 70), The Kellner and Sheffield Symptom Rating Test (SRT) (on day –7 and all other assessment days as per the HAM-A) and the General Health Questionnaire (GHQ) on days 0 and 70. Adverse reactions were recorded at each visit using an open-ended interview. Patients were also reassessed on the same measures at 6 month follow-up. Drug and placebo active treatments lasted 6 weeks followed by 3 weeks graded withdrawal. The CBT groups received up to 7 sessions over the period the DZ and PL groups received double-blind treatment and withdrawal. Significant difference between the PL and CBT + DZ group were noted from day 28 of the trial on the HAM-A. By day 42, in addition to the above difference, there was a significant difference between DZ and DZ + CBT. This trend continued and by day 62, no difference had emerged between any of the groups that involved CBT on the HAM-A. During the graded withdrawal, there was no increase in the HAM-A scores in any of the DZ or CBT groups. This is commented upon in the results as being of major clinical significance. By day 42 only, significant differences emerged between the PL and DZ+CBT groups on the SRT ratings. This trend continued until the end of the study. By day 56 further significant differences emerged between the DZ and DZ+CBT and between PL and CBT groups. On the GHQ, there were significantly lower scores for all the treatment groups apart from the placebo group alone.

Using the Jacobson et al criteria for clinically significant change, the DZ +CBT group consistently had the largest proportion of patients that met this criterion on all measures. This was also observed in the CBT group but with less pronounced magnitude. The PL + CBT group also achieved results to fulfil this criterion excluding results on the SRT. The DZ patients also achieved this criterion excluding results on the HAM-A. At 6 month follow-up, there was a significant difference in the number of patients who received subsequent treatment between groups (χ^2=17.96, df=4, p<0.005). Most of the PL and DZ patients received subsequent treatment and most of the CBT, DZ+CBT and PL+CBT patients did not. Results are presented for follow-up only for those patients who did not have subsequent treatment. This meant that the pure DZ and PL attenders who had, in the main received treatment post study, could not provide results for the study. The DZ+CBT and CBT groups maintained initial treatment gains. The authors conclude that, despite the fact that benefits of CBT are not evident until day 28 of treatment, they are well maintained at 6 month follow-up with, in comparison to other treatments, little recourse to other treatments once initial treatment is complete.

Long term follow up

Durham et al 1993

Durham et al (2003) have examined the much longer term outcomes of cognitive therapy for generalised anxiety disorder by following up patients who had previously participated in two earlier randomised controlled trials, one of which compared cognitive therapy against drug therapy, placebo, and combinations of cognitive therapy with either a drug or placebo, whilst in the second, cognitive therapy was compared against analytical psychotherapy and anxiety management training. The original studies took place in 1985-1988 and 1989 to 1991. From the first trial 33 of the 93 patients who could be contacted from an original 111, agreed to participate in the follow-up, and the numbers were 61, 93 and 110 respectively in the second. Since all of the same questionnaires were not used in both of the earlier studies, each patient completed the same questionnaires as those originally and this also meant that not all data from the two studies could be combined. A reduction in symptom severity was found in all treatment groups in both studies. There were significant changes from patients' pre-treatment to long-term follow-up scores (Hamilton Rating Scale for Anxiety, Kellner and Sheffield Symptom Rating Scale) in the cognitive therapy patients from the first study but not in the non-cognitive therapy patients,

whilst both groups from the second study should significant improvements across time (State Trait Anxiety Inventory and the Brief Symptom Inventory global severity index). However the differences achieved were not significantly different between the cognitive and non-cognitive therapy groups in either group. Furthermore, there were no differences in achieved, maintained, or overall rates of recovery between the cognitive and non-cognitive therapy groups in either study. The small proportion followed up from the original studies and the lack of commonality in outcome measures used make it difficult to interpret from the results of this study if there is any benefit, and at what level, from cognitive behaviour therapy in the long term compared with other therapy options.

9.2 Pharmacological compared with psychological interventions for GAD

Evidence statements

1. *Cognitive and behavioural techniques combined had greater effect sizes than the individual interventions. (Ia)*

2. *In the short term, cognitive and behavioural techniques were as effective as pharmacological therapies, but evidence is lacking for long term effectiveness. (Ia)*

3. *The Gould meta-analysis found no difference in treatment outcomes for men and women. (Ia)*

9.2.1 Research literature evidence

9.2.1.1 Meta-analyses & systematic reviews

Pharmacotherapy versus cognitive therapies

Gould et al 1997

This paper is a meta-analysis of studies examining cognitive behaviour therapy and pharmacotherapy for generalised anxiety disorder. Thirty five studies were distilled from a search of PsychLit for the years 1974 to 1996 and MedLine for the years 1966 to 1996, search terms were given. Included studies used self-report and clinician-rated measures of change. Statistical techniques, including dealing with heterogeneity, appear appropriate. More details about any other quality assessment of included studies is not given. Only studies that used a control group were included. A wide range of diagnostic criteria including DSM-III, DSM-III-R or DSM-IV. Also included were studies found in the reference section of relevant articles and unpublished studies to counterbalance publication bias of positive results. Two different effect sizes were calculated for each study; one for anxiety or worry and one for depression and were computed at post-treatment and at follow-up, if available. Where a study employed a cross-over design, ES were calculated at the point of first cross-over. Studies were considered short-term if their duration was less than 16 weeks. They were divided between cognitive behavioural and pharmacological interventions. It was recognised that cognitive behavioural incorporated studies that examined cognitive or behavioural or both techniques. It is stated that relatively few studies had pure GAD disorder patients with no concurrent Axis I problems. The cognitive therapies included cognitive restructuring, relaxation training, anxiety management training, situational and imaginal exposure, and systematic desensitisation. Behavioural therapy alone included graded exposure, functional analysis of behaviour chains, and relaxation training. The mean effect size (ES) across the 13 studies utilising 22 interventions under the umbrella of CBT was 0.70 (95% CI=0.57 to 0.83. The mean depression ES was 0.77 (95% CI=0.64 to 0.90). These results were statistically significant when compared to a null hypotheses $t(21)=10.01$; $p<.0001$; $t(14)=10.99$; $p<.0001$ respectively. The mean dropout rate for CBT studies was 10.6%. Those studies that employed both a cognitive and a behavioural intervention had a mean ES of 0.91. ES were compared for the different CBT interventions and the only significant difference was found between cognitive-behavioural treatments versus relaxation training with biofeedback.

CB training was found to be significantly superior, $t(10)=2.88$; $p<.05$. Treatment duration and format, i.e. whether group or individual, did not have a significant impact on outcome.

The mean ES across all 24 pharmacotherapy studies employing 39 separate treatment interventions was 0.60 (95% CI=0.50 to 0.70) and the mean depression ES was 0.46 (95% CI=0.41 to 0.51) and both were significantly greater than zero $p<.0001$. The mean dropout rate was 0.70. The mean ES for the most commonly examined drug type, benzodiazepines, was 13.1%. Diazepam had the largest effect size (0.76, dropout = 16.9%). Buspirone's average ES was 0.39 and a dropout rate of 16.8%. There were no statistically significant differences between all these classes of drugs. When pharmacotherapy studies were compared with CBT studies, no statistically significant differences were found for either mean effect sizes or attrition rates. Neither duration nor severity of symptoms affected treatments significantly. Comparisons were also looked at in terms of control group used. In general, the pharmacotherapy trials used a pill placebo as control and non-directive treatment conditions were fairly common in CBT studies. The mean ES for each respectively were 0.65 and 0.52 and for wait-list conditions, was 0.73. The difference between them was statistically significant $F(2, 59)=.26$; $p=.77$. The authors state that this difference could be more to do with the treatments themselves rather than the control conditions. Other methodological considerations examined were whether use of concomitant medication affected outcome and whether there was a difference in ES for studies that performed completer analysis and studies that performed endpoint analysis. Neither was found to impact significantly on outcome.

Of those studies that employed a 6 month follow-up (n=16), results suggest that gains were maintained over time. Some slippage was noted in diazepam-treated patients.

The authors conclude that there is no statistically significant difference in ES between treatment modalities. CBT did elicit greater gains on depression with effects maintained over time, whereas, there was some diminution in benefit with drug therapies. Several recommendations are made for future studies including adhering to a uniform DSM criteria, better assessment and control of concurrent medication, and better assessment of long-term relapse rates.

9.3 Pharmacological interventions for GAD

Recommendations

1. The following must be taken into account when deciding which medication to offer:
    - the age of the patient (D)
    - previous treatment response (D)
    - risks
        - the likelihood of accidental overdose by the person being treated and by other family members if appropriate. (D)
        - the likelihood of deliberate self harm, by overdose or otherwise (D)
    - tolerability (D)
    - the preference of the person being treated (D)
    - cost, where equal effectiveness is demonstrated (D)
2. All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. (C)
3. Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and the possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (D)
4. Unless otherwise indicated, an SSRI should be offered. (B)
5. If one SSRI is not suitable or there is no improvement after a 12-week course, and if a further medication is appropriate, another SSRI should be offered. (D)
6. When prescribing an antidepressant, the healthcare professional should consider the following
    - Side effects on the initiation of antidepressants may be minimised by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. (D)
    - In some instances, doses at the upper end of the indicated dosage range may be necessary and should be offered if needed. (B)
    - Long-term treatment may be necessary for some people and should be offered if needed. (B)
    - If the patient is showing improvement on treatment with an antidepressant, the drug should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. (D)
7. If there is no improvement after a 12-week course, another SSRI (if another medication is appropriate) or another form of therapy should be offered. (D)
8. Patients should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. (C)
9. Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should extended period of time. (C)

10. All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly. (C)
11. Healthcare professionals should inform patients that the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. (D)
12. Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (D)
13. If discontinuation/withdrawal symptoms are mild, the practitioner should reassure the patient and monitor symptoms. If severe symptoms are experienced after discontinuing an antidepressant, the practitioner should consider reintroducing it (or prescribing another from the same class that has a longer half-life) and gradually reducing the dose while monitoring symptoms. (D)

If venlafaxine is being considered

14. Venlafaxine treatment should only be initiated by specialist mental health medical practitioners including General Practitioners with a Special Interest in Mental Health. (D)
15. Venlafaxine treatment should only be managed under the supervision of specialist mental health medical practitioners including General Practitioners with a Special Interest in Mental Health. (D)
16. The dose of venlafaxine should be no higher than 75 mg per day. (A)
17. Before prescribing venlafaxine an initial ECG and blood pressure measurement should be undertaken. There should be regular monitoring of blood pressure, and monitoring of cardiac status as clinically appropriate. (D)

Evidence statements

1. *A number of different classes of medication have been shown to be effective in GAD:*
   - *SSRIs (paroxetine) (Ia)*
   - *benzodiazepines (Ia)*
   - *SNRIs (venlafaxine) (Ia)*
   - *antihistamines (hydroxyzine) (Ib)*
2. *The evidence is equivocal for buspirone (Ia)*
3. *The evidence is that the following are not effective for people with GAD:*
   - *MAOIs (Ib)*
   - *beta blockers (Ib)*
   - *antipsychotic medications (Ib)*
4. *There is no evidence that suggests, in the short term (1-3 weeks) management of GAD, that any one medication group is more effective than another. (Ib)*

5. *There is no evidence for the very long term effectiveness of pharmacotherapy. (Ia)*

6. *There is a high placebo response in all studies. (Ia)*

7. *There is no clear evidence about the withdrawal or discontinuation effects of many medications used for anxiety disorders. (Ib)*

8. *Discontinuation syndromes have been found with all the major classes of antidepressants (Ib)*

9. *Evidence for use of antihistamines has only been for the short term – the evidence suggests that it is the sedating properties of this group of drugs that makes it effective. (Ib)*

10. *There is no evidence as to what constitutes an appropriate time to prescribe TCAs, SSRIs, or venlafaxine. (Ia)*

11. *There is no evidence that in the longer term, that either TCAs, SSRIs or venlafaxine is more effective than each other. (Ia)*

12. *75mg/day is the optimal dose for extended release venlafaxine preparations and there is no evidence that higher doses improve effectiveness. (Ib)*

13. *There is no evidence of a gender difference in response to any medication for GAD. (Ia)*

14. *Evidence of efficacy beyond the age of 65 years is difficult as most clinical trials have an age cut-off for entry between 65 and 70 years of age. (Ib)*

15. *Evidence for effectiveness in different ethnic groups is lacking. (Ia)*

16. *The available evidence is that there are no differential effects across the different levels of severity in GAD. (Ia)*

9.3.1 Research literature evidence

9.3.1.1 Pharmacological interventions compared with pharmacological interventions

9.3.1.1.1 Meta-analyses & systematic reviews

Imipramine versus paroxetine

Kapczinski et al 2003

In this Cochrane review, the use of antidepressants as a class of drugs is reviewed. The main results for antidepressants included analysis of imipramine, venlafaxine and paroxetine. All three were found to be superior to placebo in treating generalised anxiety disorder. The calculated number needed to treat (NNT) for antidepressants in generalised anxiety disorder is 5.15. Dropout rates did not differ between antidepressants. Those data that pertain to imipramine are highlighted in the data extraction. Two included studies looked at imipramine; one compared to placebo (and also trazodone but results were not presented) and the other to paroxetine. Imipramine fared as well as other antidepressants on efficacy and acceptability.

The term tolerability refers to, it would appear, acceptability as measured by side-effects and numbers of dropouts from the trial including post-randomisation exclusions. In that regard, imipramine and paroxetine are said to demonstrate equivalent efficacy and tolerability. Placebo controlled trials demonstrated that both drugs were well-tolerated. Very little discussion is given on venlafaxine. It is mentioned in a group sense with the other antidepressants under review.

The Cochrane Reviewers' conclusions were that the available evidence suggests that antidepressants are superior to placebo in treating generalised anxiety disorder. There is evidence from one trial suggesting that paroxetine and imipramine have a similar efficacy and tolerability. There is also evidence from placebo-controlled trials suggesting that these drugs are well tolerated by generalised anxiety disorder patients. Further trials of antidepressants for generalised anxiety disorder will help to demonstrate which antidepressants should be used for which patients.

SSRIs versus other pharmacotherapy

Roerig 1999

This is a formal review of all aspects of generalised anxiety disorder. It describes the data sources, data extraction, and data synthesis. Based on the analysis the author makes conclusions. Years searched are 1975 – 1999. For the purposes of this review, only information relating to treatment is summarised. Thirty five per cent of patients show marked benefit from generalised anxiety disorder when taking benzodiazepines, and 40% moderate benefit from benzodiazepines. However the paper quoting this result is a supplement of J Clin Pharm. Dubovsky 1990. It is not clear if the supplement is a pharmaceutical company sponsored publication. Other research findings on benzodiazepines are that they are conjugated slower in women; oral contraception may slow metabolism; women using lorazepam and the oral contraceptive pill had greater mental impairment than women just using lorazepam. Benzodiazepines can cause ante-grade amnesia. Withdrawal symptoms reported in up to 44% of patients who have been prescribed medication for no longer than 6 weeks. Severity and timing of symptoms associated with dose, half-life and duration of symptoms. The author does not specify which references relate to specific factors, hence it is difficult to know for which of these a specific evidence base exists. During withdrawal, there is some evidence that short half-life compounds more likely to be associated with seizures. A study comparing withdrawal seizures in short and long half-life compounds found little difference; however the authors note that the lorazepam was used for a shorter duration and at a lower daily equivalent dose, than diazepam. In the case of benzodiazepine overdose where alcohol is taken, this can cause respiratory depression and lead to death. Teratogenesis is reviewed by Alteshuler et al. pooled risks for oral cleft 2.4 greater than for women not taking benzodiazepines. The authors suggest that increased risk of cleft palate is primarily associated with alprazolam (0.7% compared to baseline of 0.06%). Withdrawal effects in the new born baby can be anticipated.

The review of buspirone found that side effects experienced were dizziness, headaches, nausea, nervousness and paraesthesia. Its effectiveness was examined in a meta-analysis undertaken by: Uhde and Tancer. DSM III criteria was used (therefore symptoms need not have been present for more than six months). Fourteen studies are reviewed: 10 placebo controlled, 13 compared buspirone to a benzodiazepine. Five placebo controlled studies showed buspirone no more effective than placebo. However, there are no details of the size of the studies, nor of the duration of treatment. In the non-placebo comparison studies buspirone was shown to be as effective as benzodiazepines.

A number of side effects are described of anti-depressants, however it is not clear whether this differing according to whether they are treating generalised anxiety disorder or depression. It is

stated that teratogenesis is a poorly studied area. The review quotes Alteshuler et al as saying that tri-cyclics and fluoxetine have low teratogenic risks, but no evidence is quoted to support this view, or comparing it to the use of benzodiazepines.

The review quotes Liebowitz's review of tri-cyclics in anxiety states. Eighteen papers compared doxepin to benzodiazepines. Nine showed no difference between active treatments. Four found doxepin superior to benzodiazepines and 2 found the reverse. This review does point out that the studies were of a poor quality on a number of issues.

Several studies examine the efficacy and safety of the antidepressant imipramine. Three studies compared imipramine in the management of anxiety but all were pre DSM IV criteria. Kahn and colleagues, in an 8-week multi centre study compared imipramine (135mg/day) with. chlordiazepoxide (55mg/day) and included 242 patients with DSM III anxiety. They found imipramine more effective than placebo or chlordiazepoxide in the first 2 weeks of treatment. Hoehn-Salic and colleagues, again using DSM III diagnostic criteria compared alprazolam (2.2mg/day) and imipramine (91mg/day) and found each equally effective. Rickels and colleagues, in an 8 week randomised, double blind, placebo controlled, trial found that when imipramine (142mg/day) was compared to trazodone (225mg/day) and diazepam (26mg/day) found that diazepam was most effective at 2 weeks, and at 3 weeks, all treatments were superior to placebo and at 4 and 6 weeks, imipramine was superior to all other treatments. When compared to paroxetine (20mg/day), imipramine at 75mg/day was found not to differ in effect. (Rocca 1997). In this paper, DSM-IV criteria was used.

One study is quoted on nefazodone. DSM-IV criteria is used in this 8 week study; in which 57% of patients improved according to the CGI.

Three randomised controlled trials of venlafaxine are examined. Diagnostic criteria was DSM-IV and it was found that venlafaxine was effective at treating generalised anxiety disorder, that it was superior to buspirone and its effects were felt at week one and were also recorded at 6 month follow-up.

Fifty per cent of patients treated with chlorazepate or buspirone relapse on discontinuation at six months (1 ref). Patients treated with benzodiazepines are twice as likely to suffer recurrence of symptoms after six months, as non benzodiazepine anxiolytics (2 refs)

SSRIs (paroxetine) versus TCAs (imipramine) versus chlordesmethyldiazepam

Wagstaff et al 2002

This ADIS drug evaluation reviews the major pharmacological features of paroxetine and its use to treat depression, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder and post traumatic stress disorder. For the purposes of this review, it is possible to view data pertaining to both panic disorder and generalised anxiety disorder in isolation from the other disorders. Included studies, were large, well-controlled trials but available evidence was heavily weighted towards short-term placebo-controlled double-blind trials. Unless otherwise stated, included studies employed and intention to treat analysis and diagnostic criteria used was DSM-III-R.

In the treatment of generalised anxiety disorder, the primary outcome measures were change from baseline in HARS and proportion of patients experiencing relapse (defined as an increase in CGI severity of illness of at least 2 points to GE 4 at week 12). When compared with placebo, paroxetine administered between 20 and 50 mg/day significantly improved symptoms of anxiety in two 8 week randomised double blind trials involved 324 ITT and 426 evaluable outpatients. In a third 8 week trial, the reduction in HARS total score from baseline was numerically greater

with paroxetine (20-50 mg/day) than placebo. In a 32 week relapse prevention study, significantly fewer patients receiving paroxetine relapsed (defined as an increase in CGI severity of GE 2 points to a score of at least 4 or withdrawn due to lack of efficacy) than those receiving placebo (10.9 versus 39.9%). In a 32 week relapse prevention trial, significantly fewer in the paroxetine group (10.9%) relapsed than in the placebo group (39.9%). The trial by Rocca et al (reviewed below) where paroxetine administered at 20 mg/day is compared to imipramine (50-100 mg/day) and 2'-chlordesmethyldiazepam (3-6 mg/day) was also reviewed (see relevant narrative).

The most common adverse events recorded in all psychiatric disorders where paroxetine was administered were nausea, sweating, headaches, dizziness, somnolence, constipation, asthenia and sexual dysfunction. The incidence of abnormal ejaculation among patients with generalised anxiety disorder and panic disorder ranged from 21-28% with a dosage range from 10-60 mg/day. This is commonly associated with all SSRIs. All SSRIs have been implicated in the development of serotonin syndrome, a potentially life threatening complication. There have been reports of serotonin syndrome developing when paroxetine was coadministered with MAOIs or other SSRIs or after a switch from another SSRI without a washout period. A meta-analysis of 39 studies of treatment of depression showed a statistically significant lower proportion of patients receiving Paroxetine (64%) experienced adverse events with an incidence of >1% than those receiving clomipramine (77%, p=0.02) or another TCA (77%, p<0.001). There was a trend toward a lower incidence of withdrawal due to adverse events with paroxetine compared to TCAs which reached significance with clomipramine. When compared to other SSRIs in studies of depression, it has been shown to have a similar tolerability profile. SSRIs also seem to be generally better tolerated than TCAs in the elderly with equal tolerance among the SSRIs based on depression studies.

The authors conclude that paroxetine is better tolerated than TCAs and, in relation to GAD and PD, it is an appropriate first-line therapy. They stated that given its success in the treatment of depression and anxiety, and the fact that there is a high degree of psychiatric comorbidity of depression and anxiety it is an important first-line option.

SSRIs versus benzodiazepines

Davidson et al 2001

This paper reviews benzodiazepines, 5-HT_{1A} partial agonists and all classes of antidepressants. Only SSRIs are considered in this narrative. The study by Rocca et al (1997) comparing paroxetine to imipramine and 2-chlordesmethyldiazepram in 8 week double blind study is presented. While no statistically significant differences found at 8 weeks in HAM-A between 3 drugs (differences measured as improvement from baseline), Paroxetine demonstrated the most improvement. At 4 weeks the difference between paroxetine and 2-chlordesmethyldiazepram were statistically significant. The paper also reports on three studies of paroxetine, one fixed dose and 2 flexible dose studies. All show the same trends in results. The fixed dose study (Bellow (2000) presented as a poster APA but has subsequently been published in Am J Psychiatry April 2003) is a large American multi-centred trial, fixed dose study, that compared paroxetine 20 and 40 mg/day to a placebo in 566 patients with GAD. Analysis was by intention to treat. At week 8, both doses of paroxetine showed statistically significant improvement in HAM-A from baseline that was supported by other tests (CGI and patient self-rated Sheehan Disability Scale). No differences between the different doses of paroxetine were reported. The authors conclude that paroxetine is an effective treatment for generalised anxiety disorder. The other two studies reviewed were flexible dose studies presented at the European College of Neuropsychopharmacology Congress 2000. In all 3 studies the trend was to an improvement in

a greater number of subjects taking paroxetine than those taking placebo although only one result was statistically significant.

There were not statistically significant differences in side effect profile or tolerability between the paroxetine groups and the placebo group in any of the studies.

The implied premise of this review is that although benzodiazepines are effective in treating anxiety, due to the risk of dependency, they are not the preferred option. In addition, depression is a frequent comorbidity and hence the appeal of treating generalised anxiety disorder with antidepressants. The authors conclude by stating that due to the frequency of comorbid depression, anti-depressants are preferable to benzodiazepines with SSRIs or SNRIs preferable to TCAs due to the anticholinergic side effects elicited by TCAs, particularly in the elderly.

9.3.1.1.2 RCTs

Paroxetine versus imipramine versus 2'chlordesmethyldiazepam

Rocca et al 1997

This 8 week randomised controlled trial sought to measure the efficacy of paroxetine 20mg daily or imipramine, 50-100mg daily or 2'-chlordesmethyldiazepam (2'-CD), 3-5mg daily.

Eighty one patients suffering from generalised anxiety disorder according to DSM-III, who at the time were in treatment in a psychiatric clinic in Turin in Italy, were randomised to receive one of the three treatment drugs. The primary outcome measure was the Hamilton Rating Scale for Anxiety, the Hamilton Rating Scale for Depression, the COVI Anxiety rating scale (CARS), the Clinical Global Impression, Severity (CGI-1) scale and the Clinical Global Impression, Improvement (CGI-2) scales. A significant improvement was noted for all three groups. The 2'-CD group showed the greatest change within the first 2 weeks. By week 4, paroxetine was showing greater improvement than both imipramine and 2'-CD and by week 8, both imipramine and paroxetine showed greater improvement than 2'-CD. 2'CD showed greater efficacy in reducing somatic symptoms within the first 2 weeks and almost as effective as paroxetine and imipramine on this dimension at 8 weeks. In contrast, both imipramine and paroxetine showed greater efficacy than 2'-CD in dealing with psychic symptoms from week 4 onwards. Paroxetine versus imipramine on the somatic cluster, F=19.32, $P<0.001$, psychic cluster at week 4 $F=12.42$, $p<0.001$ and at week 8 $F=5.38$, $p<0.01$. Both the CARS and the CGI-I showed a similar trend with the CARS reporting a statistically significant improvement. There was no statistically significant difference between groups on the HRSD. In each of the groups, side effects were experienced: the 2'CD patients experienced drowsiness more than the other treatment groups; nausea was reported more frequently in paroxetine-treated patients and imipramine patients experienced the anticholinergic effects including dry mouth and constipation most. Other side effects reported in all three patient groups were dizziness, nervousness and tiredness. Others experienced were not specified. The authors conclude that this study shows the anxiolytic effects of paroxetine that is comparable to imipramine and 2'-CD. However, further studies are recommended.

Buspirone versus diazepam

Shah et al 1991

In this study, comparing DZ with buspirone, 80 Indian patients were randomised in a double-blind, 4-week trial. Patients underwent a 1 week wash-out followed by 4 weeks of treatment. Weekly visits were punctuated by measurement of symptoms using the HRS, HRS-D, Profile of

Mood States and the Symptom Checklist. Intention to treat analysis could not be confirmed. Both drugs significantly improved symptoms at $p<0.05$.

Buspirone versus lorazepam

Laakmann et al 1998

This randomised double-blind placebo control trial sought to measure the anxiolytic properties of buspirone compared with a benzodiazepine, lorazepam and placebo. Overall, buspirone did not elicit as great a response as lorazepam as measured by the HAM-A, the Covi Anxiety Scale, the STAI-X2 and the CGI. Response was defined as ≥ 50% reduction of the HAM-A score. Twenty six patients dropped out of the study but there was no statistical difference in the rate of dropouts between groups. More side effects were experienced in the lorazepam than in the buspirone and placebo groups although the difference was not significant. Both active treatments, in the analysis of efficacy, were demonstrated to be superior to placebo with lorazepam patients demonstrating superior reduction in anxiety during the treatment and taper periods compared to buspirone. However, during the placebo control period (weeks 7-10), the anxiolytic response developed during the treatment and taper periods on buspirone were sustained but not so with the lorazepam treated patients who worsened. Placebo treated patients continued to improve during the 4 week placebo period. ANOVAs revealed that there were significant patterns of response on the STAI-X2 and the CGI (item 1) over time. Of particular note is the observation that early onset of improvement within the first 2 weeks of medication is a good estimation of longer-term therapeutic response for GAD. Approximately 78% of buspirone-treated patients who did not fulfil at least ¼ of the criterion of improvement after the first 2 weeks, continued to be non-responders.

Buspirone versus venlafaxine

Davidson et al 1999

In a double-blind comparison of venlafaxine XR 75 or 150mg/day with buspirone 30mg/day, 365 patients of 405 eligible patients were included in an efficacy analysis of venlafaxine XR, buspirone and placebo in outpatients with generalised anxiety disorder without concomitant major depression. Efficacy was assessed by the HAM-A, the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI Improvement scale (CGI-I), the HAD using the anxiety subscale only, the Covi Anxiety Scale and the Raskin Depression Scale. Response to treatment was defined as a decrease of at least 50% from baseline in HAM-A or CGI – I score of 1 or 2. Evaluation of responders shows that at the end of the 8-week period, 62% of venlafaxine 75mg group, 49% of the venlafaxine 150mg/day group and 55% of the buspirone group were considered to have responded. There is no statistical difference between the effectiveness of venlafaxine 75 and 150 mg/day at any stage of the study. However 150 mg/day did produce more side effects, nausea, dizziness, asthenia, and dry mouth than 75mg/day. Buspirone proved to be more effective than placebo at six weeks using the CGI –I measure (CGI-I was greater every week than placebo, but only became statistically significant after 6 weeks). The authors conclude that venlafaxine XR is a safe and effective once-daily treatment of GAD where there is no comorbid depression and that it is also significantly superior to buspirone as measured by the HAD anxiety subscale. However, buspirone showed statistical significance versus placebo on a measure of anxiolytic response. It is noted that there is a dosing difference between venlafaxine and buspirone. Venlafaxine is a once daily dose, and buspirone is a thrice daily dose.

Diazepam versus buspirone

Ramchandran et al 1990

Generalised anxiety disorder sufferers in an Indian surgery were randomised for treatment on either diazepam(DZ) or buspirone over 4 weeks following a 1 week washout period. Results were not an intention to treat analysis. Groups were similar at baseline on all outcome measures scores (HRSA, HRS-D, Symptom Checklist, Profile of Mood States and Raskin & Covi scales) except for inferiority with the buspirone group scoring 8.67 +/- 0.59 and the DZ group 10.32 +/- 0.49 ($p<0.05$). When all indices were considered together, a significantly larger proportion favoured buspirone over DZ (69% versus 31%, $p<0.05$). The preference for buspirone over DZ was also reflected in both patients' and physicians' ratings as "very much better". Differences on this index however, were not statistically significant. More patients in the buspirone group desired to continue than did in the DZ group (75% versus 68%). Numbers of side effects in each group were similar but 6 in the buspirone group withdrew due to side effects and 4 from the DZ group. However, more dropped out of the buspirone group dropped out compared to 9 in the DZ group although reasons for this are not stated. The authors conclude that buspirone offers a clear improvement over diazepam in terms of anxiolytic effect.

Hydroxyzine versus buspirone

Lader & Scotto 1998

In this multi-centred, primary care study, 244 patients suffering from generalised anxiety disorder according to DSM-IV with an admixture of depression, were randomised to receive either hydroxyzine, 50mg/day, buspirone, 20mg/day or placebo. The study design included a 1 week placebo washout period, followed by four weeks of treatment and a 1 week placebo treatment. Doses were fixed and administered three times daily. The study operated an intent-to-treat analysis and measured changes on the HAM-A as the primary outcome measure. Significant differences were found only between hydroxyzine and placebo on this primary outcome measure ($p<0.02$). Hydroxyzine revealed significant differences compared to placebo on all secondary measures as well including the HAD depression scale and the Clinical Global Impression Scale as did the buspirone group. The investigators state that record of side effects revealed that both treatments were very well tolerated with 39.5% of hydroxyzine patients, 38% of buspirone treated patients and 28% of placebo treated patients experiencing one or more side effect. Of side effects affecting more than 5% of the hydroxyzine group somnolence occurred in 9.9% hydroxyzine group compared to 4.9% in the buspirone group. This somnolence was recorded as transitory in all but one patient and had disappeared by day 10 in the rest of the patients reporting this symptom. It is noted that this adverse event may be more quickly remediable in the clinical context as opposed to this trial setting where dose is fixed. It is noted that only ¼ patients were judged to have pure generalised anxiety disorder with the rest having an admixture of symptomatic depression. The authors note that hydroxyzine was equally effective in both groups of patients (i.e. pure generalised anxiety disorder or those suffering an admixture of depression).

Hydroxyzine versus bromazepam versus placebo

Llorca 2002

The aim of this study was to assess whether short-term effects such as that noted in the foregoing study, were maintained in a longer, three month, double-blind study. This study was carried out by 89 French general practitioners. Patients with a diagnosis of generalised anxiety disorder

according to DSM-IV were randomised, after a 14 day single-blind placebo washout period to receive either hydroxyzine 50m/mg day, bromazepam 6mg/day or placebo for. The treatment phase was 12 weeks during which, patients were measured on the HAM-A, the CGI severity scale, the HAD and the Peturrson and Lader scale (used during the run-out phase, a 4 week single-blind run-out phase, to measure drug withdrawal). Responders, defined as those who had $\geq$ 50% reduction in HAM-A from baseline were significantly greater in both the hydroxyzine and the bromazepam group compared to placebo at $p \leq 0.05$ on day 42 and $p \leq 0.01$ on day 84 (end of treatment). Bromazepam patients faired better consistently from day 42 with significant differences at $p \leq 0.03$ on day 63 compared to placebo. The authors stipulate that this study was not adequately powered to detect a difference between these two treatments in a head-to-head comparison. Significantly more patients remitted (i.e. had a score of $\leq$ 7 on the HAM-A) in the hydroxyzine group than the placebo group on day 84 $p \leq 0.03$. In the bromazepam treated group, significantly more patients responded at days 63 and 84 than placebo $p \leq 0.01$. Rebound effect was also measured by recording on-demand treatment and was found to occur more often in the placebo and bromazepam patients (51 and 51.1% respectively) than in the hydroxyzine group (40.2%) although no statistical difference was required. There were no statistically significant differences in the occurrence of treatment emergent adverse events. The most common adverse event in the hydroxyzine group was drowsiness (3.9% of patients) but drowsiness occurred twice as much in the bromazepam group (7.9%) and was lower in the placebo group (1.8%). The authors conclude that hydroxyzine showed both efficacy and safety in the treatment of GAD and appears to be an effective alternative treatment to benzodiazepine prescription.

Benzodiazepine (chlordiazepoxide) versus beta-blocker (propanol)

Meibach et al 1987

This 4 week, double-blind randomised controlled trial tested the safety and efficacy of propranolol administered in doses of 80mg/day, 160mg/day and 160mg/day increasing to 320mg/day for 3 weeks compared to doses of 30mg/day and 45mg/day of chlordiazepoxide and placebo on patients with generalised anxiety disorder. Treatment began following a one-week placebo washout period. Patients received a weekly physical examination where vital signs and concomitant medication was checked. Physicians completed the Clinical Global Impressions (CGI) scale, the Hamilton Rating Scale for Anxiety (HAM-A) and the Covi Anxiety Scale (CAS) at baseline, weeks 1, 2 and 3 for each patient. Patients completed the Symptom Checklist 90 (SCL-90) at weeks 1 and 3 and the Profile of Mood States (POMS) at baseline and weeks 1, 2, and 3. 175 of 196 enrolled patients were analysed for drug efficacy. All treatment groups (including placebo) showed improvement in HAM-A and CGI over 4 weeks of study (significance rates not calculated). HAM-A fell from 24.9 to 14.3 for all groups, and CGI 4.65 to 3.2 (each group had 55 – 62 participants). Specific treatment effects were seen by the end of week 1 with the high-dose chlordiazepoxide groups significantly better than the placebo group on both somatic and psychic subscales and the low-dose propranolol groups were significantly better than the placebo group on the psychic subscale. There was a positive dose response curve with chlordiazepoxide and a negative dose response curve with propranolol. However by week 2, none of the chlordiazepoxide dose groups were significantly superior to the placebo group. At week 3, neither active drug was superior to placebo due to continued improvement within the placebo group. It is reported that all those patients who dropped out due to adverse events experienced CNS complains including sedation, drowsiness and fatigue (3 Propranolol, 6 chlordiazepoxide and 1 placebo patient). Drowsiness, change in libido, fatigue and indigestion were side-effects experienced more frequently in the treatment groups. There were no clinically significant abnormal laboratory findings. There were no significant withdrawal effects. The authors conclude that propranolol appears to be safe and effect in the treatment of generalised anxiety of moderate severity in patients with both psychic and somatic symptoms. In addition,

propranolol does not cause unwanted side effects such as dependence, psychomotor function impairment as can occur with benzodiazepines.

9.3.1.2 Pharmacological interventions

9.3.1.2.1 Antihistamines

RCTs

Hydroxyzine versus placebo

Darcis et al 1995

This study sought to measure the short-term the efficacy and tolerability of hydroxyzine on patients suffering from generalised anxiety disorder. It was conducted in general practice patients in the south of France, who were suffering from generalised anxiety disorder. The study did not employ an intent-to-treat analysis of efficacy as 18% of randomised patients were deemed ineligible subsequent to randomisation and were not included in the analysis of efficacy. Patients were randomised to receive either 50mg hydroxyzine or placebo for 4 weeks. Efficacy was analysed by measuring response on the HAM-A, HAM-D, the Brief Scale for Anxiety (BSA) the 12-item Ferreri anxiety Rating Diagram (FARD) and Global Clinical Impressions Scale and a 58 item questionnaire of anxiety-related symptoms. Patients were assessed at week 0, at the end of weeks 1 and 4 and then again one week after treatment finished. There was a significant reduction in generalised anxiety in the hydroxyzine group compared to placebo (weeks 1 and 4 $p<0.001$ and $p=0.001$ at week 5). Fifty two per cent of hydroxyzine patients and 35% of placebo treated patients reported treatment-related adverse events. The most commonly reported adverse event, i.e. sleepiness did not reach statistical difference compared with placebo ($p=0.114$), nor did the other reported adverse events (dry mouth, weight gain, insomnia, nervousness). The authors conclude the hydroxyzine is an effective and well-tolerated treatment for generalised anxiety.

9.3.1.2.2 Benzodiazepines

RCTs

Diazepam versus placebo

Pourmotabbed et al 1996

In this 6 week placebo-controlled study designed to assess symptom attenuation according to HAM-A, STAI STATE Form, the Somatic Symptom Checklist (SSS) and the Hopkins Symptom Checklist, women with a diagnosis of generalised anxiety disorder according to DSM-III-R, were assigned to receive diazepam (DZ) or placebo. Abrupt discontinuation of DZ after 6 weeks of treatment affected psychic versus somatic symptoms. During the study, subjects were tested 3 times; at initial session (week 0), after 6 weeks (week 6) and 2 weeks after discontinuation. An intention to treat analysis was performed on data up to the end of the 6 weeks of treatment. For both treatment-week effects and discontinuation effects, ANOVAs were performed with repeated measures. Both placebo and DZ patients improved significantly with maximum improvement occurring for DZ patients within the first 3 weeks of treatment. Thereafter, placebo patients continued to improve. The authors conclude that DZ can significantly reduce symptoms of generalised anxiety disorder with maximum improvement up to week 3 of treatment, after which,

differences disappeared because the placebo group continued to improve. This effect applied to psychic symptoms for week 1 only. Rebound anxiety, i.e. that experienced before medication, was experienced after withdrawal of medication.

Diazepam withdrawal

Power et al . 1985

Twenty three patients with a diagnosis of generalised anxiety disorder were randomised to receive either diazepam (DZ) at 15 mg/day or pill placebo for 6 weeks, preceded by 1 week washout period. Twenty patients were included in an intention to treat analysis and assessed using the Kellner and Sheffield rating scale for distress. Randomised patients were assessed using the and HAM-A on day 0, 7, 14, 28 and 42 (during 6 week double blind) and then at 2 week follow up i.e. day 56. Both groups using t tests and ANOVA with repeated measures over time, showed a significant reduction in anxiety. In addition, DZ patients exhibited a significantly greater number of withdrawal symptoms with qualitatively different symptoms from treatment period and new symptoms were reported. The authors point out that this has important implications for treatment management of anxiety with benzodiazepines. They state that results of this study suggest that withdrawal symptoms occur within a relatively short period of time (suggestive of dependence).

The results of this 6-week study in which diazepam was compared to placebo indicate that, even within a short treatment period, rebound symptoms can occur upon cessation. Diazepam in this study was administered at 15 mg/day in doses of 5mg, 3 times daily.

9.3.1.2.3 Antidepressants - SSRIs

RCTs

Paroxetine (dosage)

Rickels et al 2003

This 8-week, multi-centre randomised controlled trial was designed to measure the safety and efficacy of two fixed doses of paroxetine (20mg and 40mg per day) against placebo. Five hundred and fifty six patients were randomised from 661 eligible patients. The primary outcome measure was the change from baseline in the total score on the HAM-A. Remission was defined as a score of 7 or less on the HAM-A scale. Response to paroxetine was defined as a rating of "very much improved" or "much improved" on the Clinical Global Impression Scale. At 8 weeks, 68% and 80% of the paroxetine 20 and 40mg per day groups achieved responses respectively compared with 52% of the placebo recipients (χ^2=24.3, df=2, p<0.001). Significantly greater remission rates were achieved within the paroxetine patients than the placebo patients at 8 weeks: Paroxetine 40mg per day=36%, paroxetine 20mg day=30% and placebo=20% (χ^2=11.20, df=2, p=0.004). The authors also quote the proportion of patients who completed and achieved remission (42%, 36% and 24% respectively). Results were also significantly in favour or paroxetine as reported in the Sheehan disability scale for work, social and family life. The proportion of patients reporting at least one adverse event were in the paroxetine 40mg/day group 86%, in the 20mg/day group 88% and 74% in the placebo group. The most common adverse events were asthenia, constipation, dry mouth, abnormal ejaculation, decreased libido, nausea, somnolence, decreased appetite, sweating, yawning, and female genital disorders. Most adverse events were reported as mild to moderate and more likely to occur at the beginning of treatment and to diminish over time. The most common adverse event was

somnolence and lead to discontinuation in 1.5% of the paroxetine 40mg/day group, in 3.7% of the 20mg/day group and 0.6% of the placebo group (χ^2=5.10, df=2, p<0.08). Clinically meaningful changes in laboratory measures of blood pressure were more likely to occur in the placebo than in the paroxetine groups. The authors conclude that this study demonstrates that paroxetine is an efficacious and well-tolerated treatment for generalised anxiety disorder. The authors state that this study was not a dose response study but that the numerically greater number of patients who achieved remission in the 40mg group compared to the 20mg group may indicate that some individuals would benefit from a higher dose. Further long-term studies are recommended by the authors.

Paroxetine

Pollack 2001

This article discusses optimisation of pharmacotherapy in patients with generalised anxiety disorder with the aim of attaining remission of symptoms. Generalised anxiety disorder is a chronic condition and can lead to more severe symptoms. It is therefore advisable to treat symptoms as early as possible and to try and attain a balance between drug therapeutic effects and drug side-effects. The authors state that although there are long-term performance studies on drug therapies, the majority of these have been done using the DSM-III diagnostic system in which generalised anxiety disorder is a residual diagnosis. Evidence for long-term performance of drug therapy for generalised anxiety disorder is described therefore as inconclusive. The aim of any therapeutic agent should be complete remission from symptoms and a table is presented from Ballenger et al (1999) outlining measure of remission of generalised anxiety disorder. Specifics are given for HAM-A score improvement of 70%, HAM-D score of 70% improvement and a Sheehan score of $\leq$ 1. The right drug should be chosen to suit the patient and take account of their psychiatric history. It is stated that 3 groups of drugs have been shown to be effective in generalised anxiety disorder: benzodiazepines, azapirones and antidepressants. Benzodiazepines are useful in the short-term treatment of generalised anxiety disorder due to their fast action. Distinction is made between the quickly metabolised and slower metabolised benzodiazepines and their use. Quickly metabolised benzodiazepines are more useful for acute anxiety and the slowly metabolised ones such as diazepam are more useful for less acute anxiety. The known dependency issues and issues of interaction with other central nervous system depressants is highlighted. However, it is recognised that they are the mainstay in the treatment of generalised anxiety disorder and that some studies have showed they are associated with low remission rates.

Buspirone is introduced within the azapiron group of drugs and is described as preferential for patients for whom benzodiazepines are contraindicated. Its anxiolytic effects are slower (between 2-3 weeks) than benzodiazepines and it does not have the same muscle-relaxant or hypnotic properties of the benzodiazepines. The side-effects of dizziness and light-headedness are pointed out and their importance when prescribing to the elderly.

It is stated, that due to the side-effect profile of TCAs such as imipramine, it can no longer be considered a first-line treatment for generalised anxiety disorder.

Newer antidepressants such as the SNRI, venlafaxine and the SSRI paroxetine have been shown to reduce the symptoms of GAD as well as those of depression. They have been shown to be safe and effective in the short and long-term treatment of GAD.

The authors state that due to the chronicity of generalised anxiety disorder, along with effectiveness, both tolerability and safety of therapy prescribed must be considered. The TCAs have a narrow therapeutic effect which predisposes them to toxicity. It is likely that there is a time lag for any antidepressant agent to take effect. Little is known about how to manage when

therapeutic agents do not attain the desired remission but there is some evidence to suggest that combinations of antidepressants with benzodiazepines can affect a better response. One study quoted underscores the need for long-term treatment where 25% of participants achieved remission after 2 years and 38% did so after 5 years of treatment. The authors conclude that the greater spectrum of the newer antidepressants and more favourable tolerability and safety profile ensures that patients with generalised anxiety disorder will be more likely to achieve remission. This would lead to improved quality of life.

SSRI – saftey

Medicines and Healthcare products Regulatory Agency (MHRA) 2004

In the UK the licensing and post-licensing safety monitoring of medicines is undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA). During the development of this guideline the safety of some drugs used to treat GAD (selective serotonin reuptake inhibitors (SSRIs), was formally reviewed by the MHRA on behalf of the Committee on Safety of Medicines (CSM). The CSM convened a working group to look at this issue (the SSRI Expert Working Group (EWG)). In particular, data on discontination/withdrawal symptoms, cardiotoxicity, dose, and suicidality and self-harm, were used, together with information on changes to produce licences as a result of the EWG's report to the CSM (MHRA, 2004). The Marketing Authorisation Holder (the pharmaceutical company responsible for the drug in question) analysed data from clinical trials for each relevant drug, in accordance with a protocol specified by the EWG. These reviews formed the basis of the EWG's deliberations, and it should be noted that not all trial data were made available to the EWG (MHRA, 2004). The EWG used other data, including a number of analyses of the General Practice Research Database, along with spontaneous reporting of adverse drug reactions (via the MHRA's Yellow Card scheme).

Withdrawal symptoms included dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances. While generally mild to moderate, in some patients they may be severe in intensity.

9.3.1.2.4 Antidepressants – SNRIs (venlafaxine)

Meta-analysis and systematic reviews

Meoni et al 2001

Five randomised-controlled trial study results were pooled in a meta-analysis conducted to evaluate the efficacy of venlafaxine extended release (XR) on individual items on the HAM-A and the Brief Scale for Anxiety (BSA) on adults aged 18 years and over. Details of databases searched and search terms used are not given. Details of how studies were pooled was provided. All studies included an intention to treat analysis and 2021 patients were randomised to received venlafaxine in doses between 37.5mg/day and 225mg/day for 8 weeks. Of the 2021 included in the analysis of results at 8 weeks, data were also analysed on the 767 who were treated for a total of 6 months. Mean effect sizes were calculated for the individual items of the two included scales. Similar patterns of results were seen for items on each of the scales, (i.e. greatest effect size at week 8 on the HAM-A, anxious mood, tension, intellectual and behaviour at interview) this increased at 6 months with these patterns extending to the BSA, inner tension, worrying over trifles and muscular tension. The authors conclude that on the HAM-A and the BSA, items that most closely corresponded to DSM-IV diagnostic criteria for generalised anxiety disorder showed the largest improvement during treatment with venlafaxine XR. It should be noted that two of the included studies were abstracts in journals rather than full journal articles. Also, the

probity of pooling these studies where disparate doses of venlafaxine are administered detracts from the validity of findings (reviewers note).

Katz et al 2002

Data from 5 prospective, multi-centre randomised-controlled trials examining the efficacy and safety of venlafaxine ER were pooled. Details of databases searched and terms used were not given, which makes it difficult to be confident that all relevant studies were identified. Some criteria for study selection are given but insufficient details to assess if quality assessment of included studies was undertaken. The included studies were reasonably combined. Two studies were conducted in Europe and 3 in the US. Four of the five studies used fixed doses (between 37.5mg/day, 75mg/day, 150mg/day and 225mg/day) and one, flexible doses (75-225mg/day). 1839 patients were included in an intention to treat analysis. The primary efficacy variables included the HAM-A, the HAD and the CGI-I. Patient data was divided between those who were under 60 years and those who were over 60 years. Both patients over and under 60 years had a significantly better response on venlafaxine ER than patients receiving placebo; $p<.01$ for older patients and $p<.001$ for younger patients. Discontinuations due to adverse events did not reveal significant differences between age-groups. 15% of venlafaxine ER versus 14 of placebo discontinued due to adverse events in the older adults group and 15 of venlafaxine ER versus 8 of placebo patients discontinued in the younger adults group. The authors conclude that venlafaxine ER is equally safe and well tolerated by older and younger patients suffering from generalised anxiety disorder. Analysis of efficacy revealed no significant differences in older and younger adults in comparison to placebo.

Montgomery et al 2002

Two randomised controlled trials, one US based and one European-based were pooled and Kaplan-Meier survival curves were calculated to evaluate the efficacy of venlafaxine XR in patients with GAD according to DSM-IV. Details of databases and search terms were not given although details about how studies were assessed for inclusion and how study results were pooled are given. The included studies appear to have been combined appropriately. One trial administered a flexible dose from 75 to 225 mg/day (including 238 patients) compared to placebo and the other examined three fixed doses of 37.5mg, 75mg or 150mg per day (529 patients). Efficacy and safety analysis were carried out at weeks, 4, every two weeks up to week 12 and every fourth week thereafter up to 6 months using, what the authors describe as 'conventional' assessment methods. In both studies, venlafaxine XR saw better survival than did placebo recipients ($p<0.001$, log-rank test). In the flexible dose study, week 8 and month 6 were the two end-points analysed for discontinuation rates. Venlafaxine showed significantly greater decreases in HAM-A scores at 6 months ($p<0.01$) against placebo. However, differences were noted between 1 to 2 weeks of treatment. In the fixed dose study, HAM-A scores revealed a significant reduction compared to placebo in the two higher doses, i.e. 75 and 150mg/day dose ($p<0,01$). Overall, there was a significantly better response (i.e. $\geq$ 50% reduction in baseline HAM-A) in venlafaxine XR patients (66%) compared to placebo treated patients (39%). Subgroup analysis revealed that there was no significant difference between the moderate and severe anxiety groups in rates of response to venlafaxine XR or placebo. Likewise with the numbers of remitters; significantly more patients were free from symptoms (i.e. a score of ≤ 7 on the HAM-A) in the venlafaxine group, 34% than the placebo group, 12% $p<0.001$. Of those who had responded but not remitted at 8 weeks in the venlafaxine XR group, 61% were in remission at 6 months compared to 39% of placebo patients. Treatment emergent adverse events were recorded for those who discontinued but not for those who continued and therefore, this aspect of venlafaxine response is not possible to comment on from this study. Eighteen per cent of venlafaxine patients and 14% of placebo patients discontinued due to adverse events. The authors conclude that this analysis provides further insight into the outcome of long-term

treatment of generalised anxiety disorder with venlafaxine SR and shows for the first time that long-term treatment might be necessary to achieve and maintain remission of symptoms.

RCTs

Venlafaxine dosage

Allgulander et al 2001

Fifty five sites across five European countries partook in this multicentre, double-blind, randomised controlled trial of venlafaxine ER, in three doses, compared to placebo on patients diagnosed according to DSM-IV as suffering from generalised anxiety disorder. Following a 4-10 day washout period, randomised patients received one of three non-titrated fixed doses; 37.5mg per day, 75mg per day, 150mg per day or a pill placebo for 24 weeks and were assessed at weeks, 1, 2, 3, 4, 6, 8, 10, 12, 16,20, 24 and 25 on several measures of psychological functioning. The primary outcome variables were measured using the HRSA, total, psychic anxiety factor, the HAD anxiety sub-scale and the CGI-I rating. Data were pooled from all 55 sites using the last observation carried forward. 529 patients were included in the ITT analysis with results of short term equivalent to eight weeks medication and long-term results equivalent to 24 weeks participation. Patients receiving doses of both 75mg/day and 150mg/day showed significantly greater improvement than patients in the placebo group on all outcome variables ($p<0.01$). Those that received 37.5mg/day showed significantly greater improvement than placebo in terms of the HAD anxiety scale ($p<0.01$) at week 8 and at week 24. Significant improvement was found on this lower dose at week 24 on the HRSA total and the HRSA Psychic subscale $p<0.01$. The 150mg/day group showed significantly greater improvement than that 37.5mg/day group on all outcome measures at $p<0.01$ at week 8 and significantly greater improvement than the 37.5mg group for HRSA psychic anxiety factor and the HAD anxiety scale at $p<0.01$ at week 24.. The 75mg/day group showed significantly better improvement on the HAD anxiety scale than the 37.5mg/day group at week 8 ($p<0.01$). Patients in the placebo group were significantly more likely to withdraw from the trial due to lack of efficacy than the patients in the venlafaxine groups ($p<0.01$).

Rickels et al 2000

This 8 week multi-centre double-blind randomised controlled trial, sought to measure whether fixed doses of venlafaxine XR was efficacious and safe in the short-term treatment of generalised anxiety disorder. Initially, 370 patients were randomised but 21 did not give a primary efficacy evaluation and were therefore included in the safety but not the efficacy analysis in which 349 patients were included. The primary efficacy variables were change from baseline for the total and psychic anxiety factor scores on the Hamilton anxiety scale and on the CGI severity and improvement items. A patient was considered a responder to treatment if he or she had a score of 1, (very much improved) or 2, (much improved) on the CGI global improvement item. Adverse events were measured by patients' evaluations, routine physical examinations, laboratory determinations, and ECGs. Following a 4 to 10 day placebo washout period, venlafaxine XR was administered in a dose of 75mg per day for one week. Those assigned to one of two higher doses, either 150mg or 225 mg per day, received 150mg/day up to day 15 and those on the highest dose, i.e. 225mg/day had their dose increased from day 15 onwards. Results demonstrated greater efficacy of Venlafaxine XR at all doses from week one onwards. Efficacy over placebo continued for the 8 weeks of the study and by week 8 venlafaxine XR at all doses was significantly better than placebo ($p<0.05$). The most positive results were in the group on 225mg/day. The most common treatment emergent adverse event in the venlafaxine XR groups was nausea, followed by insomnia, dry mouth, somnolence,

dizziness, and asthenia. These were mild to moderate. Nausea, insomnia and dizziness were the most frequent adverse events that lead to discontinuation from the study. The authors state that overall venlafaxine was well-tolerated. All physical examinations that revealed any abnormality were mild and transient. The authors conclude that venlafaxine XR has significant anxiolytic properties and that it may be a useful alternative to currently available treatments for anxiety.

Venlafaxine – saftey

Medicines and Healthcare products Regulatory Agency (MHRA) 2004

In the UK the licensing and post-licensing safety monitoring of medicines is undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA). During the development of this guideline the safety of some drugs used to treat GAD (venlafaxine) was formally reviewed by the MHRA on behalf of the Committee on Safety of Medicines (CSM). The CSM convened a working group to look at this issue (the SSRI Expert Working Group (EWG)). The EWG's findings were made available to the GDG, and used in addition to the efficacy and safety data reviewed during the guideline development process in drawing up recommendations. In particular, data on discontination/withdrawal symptoms, cardiotoxicity, dose, and suicidality and self-harm, were used, together with information on changes to produce licences as a result of the EWG's report to the CSM (MHRA, 2004). The Marketing Authorisation Holder (the pharmaceutical company responsible for the drug in question) analysed data from clinical trials for each relevant drug, in accordance with a protocol specified by the EWG. . These reviews formed the basis of the EWG's deliberations, and it should be noted that not all trial data were made available to the EWG (MHRA, 2004). The EWG used other data, including a number of analyses of the General Practice Research Database, along with spontaneous reporting of adverse drug reactions (via the MHRA's Yellow Card scheme).

The EWG recommended that treatment with venlafaxine should only be initiated by specialist mental health practitioners, including GPs with a special interest, and there should be arrangements in place for continuing supervision of the patient. Venlafaxine should not be used in patients with heart disease, (e.g. cardiac failure, coronary artery disease, ECG abnormalities including pre-existing QT prolongation), patients with electrolyte imbalance or in patients who are hypertensive.

9.3.1.2.5 Antipsychotics - typical

Trifluoperazine versus placebo

Mendels et al 1986

Four hundred and fifteen of 491 patients with generalised anxiety disorder were randomised to receive an antipsychotic, trifluoperazine at a dose of between 2 and 6mg/day or placebo for four weeks. This was a multi-centre randomised controlled trial. All patients took two tablets per day of either placebo or a 2mg tables of trifluoperazine according to their study arm. The option was given to reduce dosage to one tablet per day. Assessments were taken on a weekly basis including a pill count and objective measurements of anxiety using the Hamilton Rating Scale for Anxiety, the New Physician's Rating List (NPRL), part 1 of the Clinical Global Impressions scale, the Physician's Severity of Illness Rating (PSIR) and the Hopkins Symptoms checklist. From week one, patients receiving trifluoperazine showed significant reduction in their anxiety symptoms compared to placebo. The number of patients who dropped out from either group was similar, i.e. 5.7% from the trifluoperazine group and 4.1% from the placebo group. Treatment

emergent adverse events, or those thought to be due to the treatment occurred in 62% of the trifluoperazine group and 46% of the placebo group. Extrapyramidal effects were reported by 41% of the trifluoperazine group and 8% of the placebo group. Abnormal involuntary movements were recorded by the AIMS and returned a score of 0 in 80% to 84% of study participants. AIMS scores of 3, 4, or 5 were recorded in 2% of the trifluoperazine group and 0.8% of the placebo group. The authors conclude that trifluoperazine is efficacious and safe for the short-term treatment of generalised non-psychotic anxiety. Any side-effects were concluded as 'as expected', with the most common one being drowsiness and that the symptoms reported are congruent with DSM-III symptoms of generalised anxiety disorder.

9.3.1.2.6 Buspirone

Meta-analysis and systematic reviews

Buspirone versus placebo

DeMartinis et al 2000

Eight of the studies that comprised the submission for FDA approval were analysed in this review to assess whether prior benzodiazepine use affected response to buspirone drug treatment in generalised anxiety disorder patients. The trials were 6 double-blind placebo trials carried out in the US, Canada and Germany (6 studies, 1 study and 1 study respectively). All studies included a 1 week placebo washout phase followed by 4 weeks treatment with up to 30mg of either buspirone or diazepam or a pill placebo. Results were analysed according to whether patients had prior benzodiazepine use; had no prior use within the preceding 5 years; remote use (≥1 month benzodiazepine-free) or recent use (<1 month benzodiazepine free). Results of efficacy, discontinuation rates and adverse events were recorded. Overall, patients who received either treatment drug responded better than did the placebo groups regardless of degree of prior benzodiazepine exposure. Patients who did not have any prior benzodiazepine usage had similar reduction in anxiety. Buspirone response was affected by the prior benzodiazepine treatment group and was lowest in the recent benzodiazepine treatment group. Patient discontinuation was related to prior benzodiazepine use in the buspirone treated patients but not in either the benzodiazepine or the placebo-treated patients. More patients dropped out of the recent benzodiazepine user group than from either the remote or no prior benzodiazepine use. More patients in the recent BZ group, receiving buspirone recorded adverse events than did remote or no benzodiazepine use. There were no differences in reporting of adverse events according to prior benzodiazepine use in either of the BZ treatment patients or placebo patients. The authors conclude that the data derived from these 8 studies suggest that initiation of buspirone therapy in generalised anxiety disorder patients who have recently taken benzodiazepines, should be undertaken with caution.

9.3.1.2.7 Cost effectiveness of pharmacological agents

Nurnberg et al 2001

This study presents the results of a naturalistic study of antidepressant utilisation and effectiveness in an outpatient psychiatric clinic and compares costs between SSRIs. Patients were evaluated and reviewed over a period of one year (n=2779), of whom 2140 received some form of antidepressant medication: 81% SSRI, 9% novel anti-depressant, 10% tricyclic antidepressant. The vast majority of patients were clinically diagnosed with mood disorder (69%) anxiety disorder was characterised by 19% of patients.

Efficacy and effectiveness of agent was defined principally in terms of switch rate and Clinical Global Impressions (CGI) score on admission and discharge. There were no significant differences on these measures amongst classes of anti-depressants and between SSRIs (if paroxetine, fluoxetine or sertraline are compared individually with each other).

For the cost analysis, the calculated actual average drug cost per day for each of the three SSRIs was determined by costing out the percentage of patients on each daily dose (sum of distribution multiplied by cost per day). The average cost per day was $1.79 for fluoxetine, $1.41 for paroxetine and $1.21 for sertraline.

Study limitations

- only 19% of patients included in the study were characterised by anxiety disorder (vast majority were characterised by depression) hence limited applicability
- naturalistic methodology rather than prospective RCT
- the patients included had varied and frequently multiple diagnoses and took other prescribed medications which may have affected outcomes e.g trazodone for sleep (17%) and benzodiazepines for anxiety (3%)

Conclusions from study

The three major SSRIs have earned that position on the basis of their cost effectiveness, derived from efficacy, safety, improved side effect profile and ease of use for psychiatric or primary care physicians. Although antidepressant pharmaceutical costs are a significant expense for health care organisations they still represent less than 5% of the total cost burden of the illness. Patients who switch their initial antidepressant and fail to respond, either because of lack of efficacy or dose-limiting side effects will be in treatment longer and cost approximately 50-100% more to treat.

This study found no clear differences in effectiveness amongst the three most frequently used SSRIs. The study authors recommend that until clear superiority in clinical effectiveness can be demonstrated for a particular SSRI, acquisition costs and stratification of doses used by patients can be applied to help guide the choice of agent for a population under managed care.

9.4 Psychological interventions for GAD

Recommendations

1. CBT should be used. (A)
2. CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols. (A)
3. CBT in the optimal range of duration (16–20 hours in total) should be offered. (A)
4. For most people, CBT should take the form of weekly sessions of 1-2 hours and should be completed within a maximum of 4 months of commencement. (B)
5. Briefer CBT should be supplemented with appropriate focussed information and tasks. (A)
6. Where briefer CBT is used, it should be around 8-10 hours and be designed to integrate with structured self-help materials. (D)

Evidence statements

1. *CBT is more effective than no intervention. (Ia)*
2. *CBT has been found to maintain its effectiveness when examined after long term follow up (8-14 years). (Ib)*
3. *Most patients at longer term follow up after treatment, have maintained treatment gains. (Ib)*
4. *In large group settings, cognitive therapy, behaviour therapy and cognitive behaviour therapy were more effective than attention placebo, both in the short and long term. (Ib)*
5. *CBT is effective for GAD in older people. (Ib)*
6. *CBT is more effective than psycho dynamic therapy and non-specific treatments (Ia)*
7. *For cognitive therapy, more contact with therapist (16-20 sessions) did not result in better outcomes than less contact (8-10 sessions). (Ib)*
8. *Anxiety management training, relaxation and breathing therapy are more effective than no intervention. (Ia)*

9.4.1 Research literature evidence

9.4.1.1. Psychological interventions compared with psychological interventions

9.4.1.1.1 Meta analysis

Fisher & Durham 1999

This systematic review pooled data from 6 RCTs analysing the efficacy of psychological therapies for treating GAD as measured by the STAI-T from baseline to end of treatment and at 6 months follow-up. This review gave details of databases searched and terms used. Inclusion criteria for included studies were given and included the use of diagnostic interviews and appropriate randomisation. Heterogeneity was appropriately addressed and studies were appropriately combined. Details are not given about whether included studies used an intention to treat analysis and additional details about quality assessment of studies for inclusion are not given. The criteria for clinically significant change was the Jacobson criterion c (where normative and dysfunctional population scores overlap (46)). An 8 point difference was required to ensure that reliable change had taken place. Data were analysed first to measures clinical significance of treatment effects in the various condition of the 6 studies and raw data for this analysis defined patients as worse, unchanged, improved and recovered from pre-treatment to 6-month follow-up. Wait list data provided a means of assessing spontaneous recovery or regression to the mean. Data were also analysed to assess overall recovery rates at post-treatment and 6-month follow-up. To this end, data were aggregated to reflect the various treatment approaches. Overall, a significant minority of patients remained unchanged (45% at post-treatment, 36% at follow-up). One quarter of patients improved but remained within a dysfunctional range at both post-treatment and follow-up. The best outcomes were seen in patients who received CBT and applied relaxation with CT as the most efficacious treatment condition at post-treatment and follow-up. In terms of recovery, individual behaviour therapy and analytical psychotherapy did very poorly with results comparable to the wait-list condition. Approximately 50% of patients who received either applied relaxation or individual cognitive behaviour therapy were recovered at the end of treatment and this was sustained in the majority at follow-up. Group cognitive behaviour and behaviour therapy and non-directive therapy elicited an intermediate pattern of results with 20-25% maintaining recovery follow treatment and 35-50% achieved recovery overall at follow-up.

9.4.1.1.2 Cognitive therapies

Large group cognitive therapy, including follow up study

White et al 1995

This non-randomised controlled trial of processed of change during treatment of 119 GAD sufferers detailed changes in three measures of generalised anxiety disorder symptoms. Diagnostic criteria is not specified, although year of publication indicates utilisation of DSM-V criteria. Patients were assigned to one of five group conditions including cognitive therapy (CT), behaviour therapy (BT), cognitive behaviour therapy (CBT), subconscious retraining therapy (SCR) and waiting list (WL). Results are discussed in terms of measurement instruments and compared to baseline within groups and between groups over time. Of all the treatments, BT

shows the steadiest improvement during treatment and this is maintained at follow-up. Cognitive therapy shows a marked disimprovement [?] on initiation of treatment but this trend reverses on all measures and improvement is maintained at follow-up. Cognitive behaviour therapy shows a dip in positive response to treatment at around week 3. This observation together with the CT process of change is attributed to an artefact of study design whereby automatic thoughts and information processing is dealt with at about this time in CBT as it is from the beginning of CT and hence why CT patients show an initial negative response to treatment. The SCR patients begin their treatment with relaxation tapes but their positive trend is not maintained over time although scores do not revert to baseline. The authors attempt to discuss common factors to explain the trends of response over time. However, no firm conclusions are reached.

White et al 1998

This paper details a two-year follow-up to patients who participated in the White 1995 study as summarised above (White et al, 1995). The authors state that due to the small number in the SCR group, there were no statistical analysis carried out and instead, group means scores were presented. Analysis however was carried out on CT, BT and CBT conditions. The data presented suggest that results at 6-month follow-up are maintained at two-year follow-up for CT, BT and CBT and even SCR although numbers are small. However, the authors caution that due to the fact that participating numbers are small and follow-up measures do not include one of worry, the main feature of GAD) and there is no face-to-face interview, results are tentative. The fact that results did not show differences across what they termed as 'didactic therapy' despite the fact that independent observation of taped transcripts, raises the need to investigate the active ingredient across therapies. It is concluded from this paper that despite the fact that GAD often begins early in life, it can be treated with psychological therapies.

CBT versus supportive counselling

Barrowclough et al 2001

This randomised controlled trial sought to measure the effectiveness of cognitive behavioural therapy in older adults with a range of anxiety disorders. Patients were aged over 55 years and had a diagnosis of an anxiety disorder according to DSM IV including GAD, panic disorder with or without agoraphobia, social phobia and anxiety disorder not otherwise specified. Patients on medication had to maintain constant dosage through the study. Randomised patients entered a 6 week baseline phase in which no treatment was administered before being randomised to between 8 and 12 1 hour sessions of either CBT or Supportive Counselling. Each patient completed a credibility questionnaire to assess treatment credibility at sessions 2, at the end of treatment and then at 3, 6, and 12 month follow-up. Of 225 referrals, 55 fulfilled the inclusion criteria. After baseline, 9 dropped out before therapy and a further 3 became seriously ill and 3 dropped out by the 4th therapy session. Thirty nine patients were available for 3 and 6 month follow up and 40 for 12 month follow-up. 51% of patients had Panic Disorder and 19% had GAD. The primary outcome measures concerned Global anxiety and included three self-report questionnaires (the Beck Anxiety Inventory, The Spielberg, State Trait Anxiety Inventory, Trait version and a 20 item measure of anxiety). The Hamilton Anxiety Rating Scale was also used. Depressive Symptomatology was measured but is not reported here. The study design did not employ an intention to treat analysis. Results were tested for skewness and parametric and nonparametric tests were applied as appropriate. ANCOVAs were performed using pre-treatment scores as the covariate.

There was no significant difference between groups on treatment credibility. CBT had a significantly better outcome than the SC group on the BAI ($F(1,42)=5.29$, $p<.05$ and the

Geriatric Depression Scale. There was a significant improvement within treatment on all measures apart from depression which did not improve. On all the measures, CBT, showed a significantly better outcome than the SC group with CBT also demonstrating a significant time by treatment interaction ($F(3, 105)=2.39$, $p<.08$).

To assess clinical significance, 2 measures of treatment response or magnitude of change were taken as being meaningful. This with endstate functioning being within the normal range. The 20% reduction was found to be a meaningful cut-off in earlier documented research (Stanley et al 1997).

Seventy one per cent of CBT and 39% of SC patients met the criteria for responders for anxiety at 12 month follow-up. More patients in the CBT group showed clinically significant response (χ^2 (1, N=40) = 3.88 $P<0.05$). There was no significant difference between groups in proportion of responders on depression symptoms. Neither was there any significant differences in endstate functioning between groups on either anxiety or depression. 41% of the CBT and 26% of the SC group had high endstate functioning at 12 month follow-up. The authors state that results from this study show that CBT treatment may be effective when delivered in a format of a mean of 10 sessions with a primary emphasis on cognitive techniques.

CBT versus supportive psychotherapy

Stanley et al 1996

This study originally included 48 participants 55 years or older although only 31 were included in the final analysis. The 17 dropouts were clearly described. The participants were randomised into two groups, CBT and supportive psychotherapy. Treatment was for 14 weeks and follow-up for 6 months. Both groups should significant improvement in outcomes and this was maintained over at the 6 month follow-up. Outcomes measured included global severity of GAD, Worry Scale, Penn State Worry Questionnaire, State Trait Anxiety Inventory-Trait Scale, Hamilton Rating Scale for Anxiety, Beck Depression Inventory, Hamilton Depression Scale and Fear Questionnaire. The study had a small sample size and did not have a 'no treatment' control group.

Cognitive therapy versus psychotherapy versus anxiety management training

Durham et al 1994

This randomised controlled trial sought to compare the efficacy of cognitive therapy with that of psychodynamic psychotherapy delivered at low contact (8-10 sessions) and high contact (16- 20 sessions) in patients with generalised anxiety disorder according to DSM-III-R. These two treatments were compared to low contact, Anxiety Management Training. One hundred and ten of 178 referred patients were randomised from general practises in the Dundee area of Scotland. 80% of the study participants had at least on other axis I diagnosis (e.g. agoraphobia, panic disorder, social phobia etc.). Psychotropic medications were noted and permitted including those who used alcohol as a form of self-medication. Length of treatment across conditions was broadly equivalent. At session 3, treatment expectations were measured for all groups and a one way ANOVA revealed significant differences across treatment groups. Patients in the AMT and CT groups had significantly higher perceptions of treatment suitability than the AP patients. Assessor ratings included the Hamilton Rating Scale for Anxiety and the Social Adjustment Scale. Patient ratings included the Brief Symptom Inventory (BSI), the State-Trait Anxiety Inventory (STAI-T) (both completed before and after treatment and at follow-up), the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), the Self-Esteem Scale (SES) and the Burns version of the Dysfunctional Attitude Scale (DAS). The data were analysed in one of

three ways; those data pertaining to the 80 completers, data pertaining to the 99 patients who started therapy on the BSI and STAI-T and Jacobson criteria of clinically meaningful change were applied to the BSI and STAI-T scores.

Results indicate that there was no significant main effect for frequency of contact or interaction between treatment and frequency of contact. Treatment effects on the outcome measures used indicated more improvement the CT. However, on all but the DAS, all three groups showed significant improvement. This was explained by there being a significant improvement in this measure in the CT group and a small, non-significant decrease in the AP group. This more favourable improvement in the CT as opposed to the AP group was also observed when t tests compared the treatment outcomes with data collapsed over frequency of contact. Comparison of symptoms change across treatments revealed that on 5 of the nine measures, AP patients did less well than the CT patients and less well than AMT on one measure, the SES. CT and AMT were superior to AP at follow-up on STAI-T and tension. As with comparisons between high and low contact, symptom change was significantly better on all measure apart from the DAS in the CT group and on seven of the remaining measures in the AMT group but on only four of the remaining measures in the AP group.

Overall categorical improvement was highest for the CT group ($\chi 2 = 7.4$, d.f.=2, $P<0.05$).

Two measures were used to assess proportion of patients meeting a clinically meaningful level of change, the BSI and the STAI-T both after treatment and at follow-up. As with all other measures of change, the best results were attained in the CT conditions. By follow-up, two thirds of patients were in the normative range on both these measures and the AMT group did better than the AP group and not as well as the CT group.

Conclusions drawn were that there was no added benefit of longer treatment as opposed to shorter treatment for any of the treatment conditions. CT has the greatest treatment gains that were sustained over time at follow-up and AMT can produce 'sufficient improvement' by trainee psychiatrists even through they received only brief instructions in administering this form of therapy.

Cognitive therapy versus applied relaxation

Ost and Breiholz 2000

In a second small study, Öst and Breitholz (2000) randomised 36 patients with a diagnosis of generalised anxiety disorder of at least one year's duration, to receive cognitive therapy or applied relaxation in hourly sessions, once a week for 12 sessions. Patients were tested pre-therapy, post-therapy and at one year follow-up. In both therapy groups, patients (n=33, 3 dropouts) improved with treatment and maintained this at follow-up, using a variety of independent assessor ratings and self-report scales, with no statistical differences between groups.

9.4.1.2 *Psychological interventions*

9.4.1.2.1 CBT

RCTs

Ladouceur et al 2000

Ladouceur et al (2000) found that cognitive behaviour therapy targeting intolerance of uncertainty, erroneous beliefs about worry, poor problem orientation and cognitive avoidance in patients with generalised anxiety disorder led to both statistically and clinically significant changes at post-test which were maintained at six and 12 months follow-up, compared with pre-test in patients. In addition 77 percent of their 26 patients also ceased to meet the criteria for that disorder diagnosis, post intervention. In their study they randomised 26 patients with a diagnosis of generalised anxiety disorder and a mean age of 39.7 (SD 10.8) years into a group (n=14) who received therapy immediately and a control group (n=12) who received therapy 16 weeks later. There were no dropouts from either group. Therapy consisted of 16 weekly one-hour sessions in which patients received information on the treatment rationale, awareness training, correction of erroneous beliefs about worry, problem-orientation training and cognitive exposure. Patients were followed up at six and 12 months

9.5 Other interventions for GAD

Recommendations

1. Bibliotherapy based on CBT principles should be offered. (A)
2. Information about support groups, where they are available, should be offered. (Support groups may provide face-to-face meetings, telephone conference support groups [which can be based on CBT principles], or additional information on all aspects of anxiety disorders plus other sources of help.) (D)
3. Large group CBT should be considered. (C)
4. The benefits of exercise as part of good general health should be discussed with all patients as appropriate. (B)
5. Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. [NICE 2002]

Evidence statements

1. *Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE 2002:TechApp 51)*

9.5.1 Research literature evidence

9.5.1.1 Self-help

Self-help approaches have an important role to play in the treatment of GAD. Often they are used as an adjunct to pharmacological or psychological interventions provided by health care professionals, and their use often enhances the overall package of care that is undertaken. In other instances self-help approaches are sufficient in its own right to be a successful intervention for many individuals. They also have a valuable role in providing a long-term approach to helping individuals with chronic conditions such as GAD.

Many individuals use self-help approaches because of a perceived lack of understanding by professionals and also because there are often lengthy waiting periods for many psychological services.

Self help can take many forms, including self-help manuals, often written by individuals who themselves have had the experience of having GAD. The role of self-help and support organisations can also be a very valuable one. They are important sources of information, support and help, not only for the affected individual but also for friends, family and carers who can play a significant role in the, often lengthy, recovery process.

CCBT

NICE published a technology appraisal about the use of computerised cognitive behavioural therapy (CCBT) for anxiety and depression in October 2002. CCBT is a terms that describes a number of methods of delivering CBT via an interactive computer interface. CCBT systems if available would increase access to CBT. NICE noted that the acquisition costs of the individual packages varied from £350 to £10,000 and depended on whether the purchase price included dedicated computer systems, technical support, training and clinical support.

Evidence from 11 RCTs and 4 uncontrolled studies were considered. The studies had been conducted in a number of countries. Nine studies had been conducted in the UK. RCT evidence was available for 3 packages that were available in the UK. Follow up periods in the studies ranged from 3 weeks to 12 months and study quality was reported as varied. Four RCTs used blinded assessors, the studies could not be realistically conducted under double blind conditions. Two of the RCTs were adequately powered to demonstrate equivalence. Five RCTs enrolled more than 80 individuals.

Five out of six RCTs found no evidence of any difference between CCBT and therapist delivered CBT in the treatment of phobias, panic disorder, major and minor depression or major depression. However, all but the panic and phobia study were inadequately powered to demonstrate differences.

The technology appraisal committee having considered evidence for clinical and cost effectiveness, from published and unpublished sources as well as responses from professional experts and patient and carer groups concluded:

> "the evidence presented in both written and verbal form supported the opinion that computer-aided delivery of CBT many have potential as an option in certain groups of patients, and it may be most suitably delivered as past of a 'stepped-care' protocol. However the Committee considered that whilst there was higher quality RCT evidence for Beating the Blues and FearFighter, the evidence base for CCBT as a technology was underdeveloped and therefore further research was required." (NICE 2002, 4.3.6)

Their guidance was that:

Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE 2002:TechApp 51)

RCT

Bibliotherapy

Sorby et al 1991

Two general practices in the UK participated in this 8 week randomised controlled trial to measure the effects of administering an education booklet on how anxiety operates in terms of a three factor theory (physical, mental and avoidance components). Both groups received their treatment as usual although what this entails is not specified in the study. 49 patients' data was included in the analysis (30 experimental and 19 control). Patients level of anxiety were measured on the HAD, the Hospital Anxiety and Depression Scale, miscellaneous nine point analogue rating scales measuring overall severity, frequency, predictability and understanding of anxiety modified for this study at baseline, weeks 2, 4 and 8. All scores improved significantly with time in both groups at $p<0.001$. All anxiety scores improved significantly more for the

booklet group compared to the control group. The same effect was not noted for the depression score indicating specificity for anxiety. The authors point out that several methodological weaknesses of the study detract from the results including the higher proportion of women than men participants. There is a difference in dropout rate between groups with the control group having a 14.3% dropout rate compared to zero in the control group of those eligible patients. The authors speculate that this may be due to the method of data collection. They also speculate that the booklet may have helped general practitioners use cognitive behavioural concepts but this is not possible to judge as there was no external measure of prior knowledge of anxiety.

Follow up study

Floyd et al 2002

This two year follow-up study sought to assess whether treatment gains from a Self-Examination Test to control the primary symptom of worry in generalised anxiety disorder were maintained at 2 –year follow-up. The original study was completed in 1997. The therapy investigated was known as SET (Self-Examination Therapy) -examination therapy. A community sample of 38 participants were recruited (recruitment methodology is not expanded upon in this paper) and randomised to receive either SET examination therapy or were put on a waiting list to receive SET therapy after the immediate treatment group were finished. Subjects were asked to follow a four-step process toward alleviating anxiety, depression and in the case of this study, the chronic worry of GAD. The first step involved determining what really matters; the second, thinking less negatively about things that do not matter; the third, investing energy in things that are important and finally, accepting and letting go of situations that cannot be changed. Sixteen of the participants in the original study partook in this follow-up and results showed that treatment gains, as measured on the HARS-R, and the STAI were maintained at follow-up. The authors conclude that given the chronic nature of generalised anxiety disorder, plus the fact that individuals who suffer with mild to moderate anxiety who seek to control their symptoms without therapist guided assistance, a self-help treatment such as SET afford promising findings for the treatment of generalised anxiety disorder.

9.5.1.2 Cost effectiveness

NICE Technology Appraisal (HTA 6(2))

Two different methods for costing CBT are reported. The first method uses the annual salary of a therapist (including on costs) and assumes that the therapist will deal with 50 new patients per year. The cost per completed treatment episode is estimated to be the salary divided by 50 (£700). However this estimate assumes that all of the therapist's time is taken up treating the 50 patients which is unlikely to be the case. The second method uses an annual rate for a therapist's time. This rate is multiplied by the mean number of sessions a therapist would need to yield a 50% improvement in a patient. This is estimated to be £606 per patient.

Additional NHS costs per patients from CCBT were estimated to be between £26 and £40 (depending upon volume of referrals and proportion of computer costs attributed).

Fear fighter (ST solutions)

A mean cost per patient of £549 for CBT is quoted. However this is based upon a mean time spent with a therapist of 9 hours per patient (taken from the British Association of Behavioural and Cognitive Therapy). The RCT evidence from the submission suggests that patients spent much less time than this on average with a therapist (4 hours 43 minutes) giving a mean cost per patient of £288.

10. Other relevant evidence

10.1 Relevant evidence not specifically about GAD or panic disorder

Evidence statements

1. *There is a lack of evidence about the effectiveness of counselling for individuals with generalised anxiety disorder or panic disorder. (IV)*

10.1.1 Counselling

Counselling is available in many primary care settings, provided by professional counsellors. Counselling is based upon the structured use of a professional relationship with a client/patient and is not a treatment for a specific condition as such e.g. depression, anxiety. Counsellors in primary care often work with people who are already on medication when they present. Those presenting may have many issues on which they wish to work with their counsellor.

Counselling uses a number of theoretical models (including those underpinning CBT) and may also integrate other approaches. This will depend on the needs of the client/patient and the counsellor's professional assessment.

Although trained counsellors may have another professional role, for example they may also be a nurse, the professional bodies for counsellors consider a counsellor to be someone who is clearly **not** in a dual role at the time that the counselling takes place. That is, a trained counsellor who is also a nurse only sees the individual patient as a counsellor and not also as a nurse.

Because counselling is often not addressing one specific condition, the conduct of trials to provide findings about its impact on any condition can be problematic. No trials, or other robust studies, were identified that gave condition specific findings about panic disorder or GAD. However there is a Cochrane review that looked at the evidence for the provision of counselling in primary care, which we have included as the basis for evidence statements and recommendations.

Bower et al 2003a

One Cochrane systematic review (Bower et al 2003a) examined the evidence for provision of counselling compared with normal GP care for patients with emotional problems, suffering from anxiety, depression, or distress. Seven randomised controlled trials were identified, all based in primary care in England or Wales. In six of the trials counselling was compared with usual GP care, in the seventh, antidepressant treatment was provided along with GP care. In one of the trials, counselling was compared with cognitive behavioural therapy in a third trial arm. The number of counselling sessions varied between trials from a mean of 4 to a mean of 8, with a range from 0 to 16, but all were provided by BACP accredited health care personnel. Length of follow-up also varied between trials. In one, follow-up was six weeks, but in the other six it ranged from 4 to 12 months. Clinical outcomes assessed included mental health, social function and patient satisfaction, using instruments such as the general health questionnaire, Beck's Depression Inventory, the Hospital Anxiety and Depression Scale, among others.

Participants were of a similar age across all the trials, with mean ages ranging from 36-42 years, and in the two trials in which ethnic details were given, most of the population were white. Patient numbers ranged from 52 to 140 in the intervention arm, and 51 to 89 in the control arm, with some trials using a recruitment rate of 2:1. Patients had a similar mental health profile in that they were included if they had psychological or emotional problems, anxiety or depressive disorders, mild to moderate depression but were excluded if they had psychoses, severe psychiatric problems, phobias, were suicidal, or had very severe anxiety or depression. In one trial, the patients' condition was chronic in that inclusion was dependent upon having had such symptoms for six months or more. In this same trial, and one other, patients were only included if they had a score of 14+ on the Beck's Depression Inventory. Overall the trials were scientifically robust although allocation procedures may have been inadequate in two of them.

The authors conducted a meta-analysis of the mental health and social function outcomes, using both fixed and random effect models. Overall, significant benefits were seen in mental health improvement from counselling compared with usual GP care, or GP care plus antidepressant treatment, in the short term (up to 4 months). For example, for counselling versus usual care across six trials of 772 participants, the standardised mean difference was –0.28 (95% CI -0.43, -0.13). However these benefits were not maintained in the longer term, over nine to 12 months. For example, for counselling versus usual care in four trials with 475 participants, the standardised mean difference was –0.09, (95% CI –0.27, 0.10). Benefits were also not seen in either the short or longer term in social functioning. There was also no significant benefit for counselling in some of the trials individually, such as the one with chronic patients, or those comparing counselling with either antidepressant treatment or cognitive behavioural therapy. Thus counselling is significantly more effective in reducing psychological symptoms in the short term but appears to provide no additional advantage in the long term.

10.1.2 Self help

Bower et al 2001

One systematic review was identified (Bower et al 2001) that examined the evidence for self-help using written materials (self-help leaflets and booklets), sometimes in conjunction with a telephone or face-to face contact, compared with normal GP care (or other written materials) for patients with anxiety, depression, stress or chronic fatigue, although in only one study was diagnosis confirmed using DSM. Eight randomised controlled trials were identified, however the quality overall was limited. Only two of the studies reported a power calculation and only one defined a main outcome a priori. Length of follow-up ranged from a maximum of 12 to 24 weeks, with interim follow-up at either/or two four, six and eight weeks. Clinical outcomes assessed included psychiatric symptoms, coping, locus of control, fatigue, and satisfaction.

Patients were predominantly female, ranging from 54% to 100% of the sample per trial, with a mean age of around 40 years in five of the trials, 53 years in a sixth. Information on age was not available for two studies or sex for one. Study populations could be grouped into small (n=22, 27), medium (n=62, 64) and relatively large (n=102, 103, 106,150) and follow-up rates ranged from 39% to 100%.

Effect sizes based on means and standard deviations could only be calculated for six of the eight studies and they were only available for short-term follow-up, (8 weeks -1 study, 12 weeks – 3 studies, 6 months – 1 study). For various outcome measures, the effect sizes ranged from –0.18 to 0.72, and the mean effect (using a random effects model) was 0.42 (95% CI 0.09, 0.72). The result suggests that using self-help written materials can have a small clinical effect on anxiety or depression although the impact on specific outcomes could not be determined from these data. Such interventions may have a greater or lesser impact on specific outcomes.

10.1.3 Exercise

There have a been a number of systematic reviews (Dunn et al 2001), some with meta analyses (Petruzzello et al 1991, Schlicht 1994, Long and Stavel 1995, and one study (Katula et al 1999) looking at the effect of exercise, including dose-response effects on anxiety and depression . Dunn et al, in their systematic review, excluded all pre-existing meta-analyses on depression and anxiety, including the one by Petruzzello et al (1991) because the majority of studies included in that analysis of effect sizes were from populations that were asymptomatic. However Dunn et al's decision to include observational studies as well as quasi-experimental in their review reduces the robustness of their evidence. Schlicht (1994) also excluded studies with clinical samples although in the studies he included, subjects had all been assessed using a mood or standardised anxiety questionnaire. Schlicht's search strategy identified publications from between 1980 to 1990, and some of the same publications were also included in Long and van Stavel (1995). However few of the studies included in Long and Stavel (1995) (search period 1975 – 1993) were picked up by Dunn et al (2001), (search period not stated but likely to be about 1970 – 2000) although the time frame covered was similar historically. This may be because Dunn et al's search strategy was limited to two databases compared with five for Long and Stavel. Both sets of authors used previous reviews and other publications as sources of reference material.

Long and van Stavel included 40 studies in their systematic review and meta-analysis, all of which had used clearly defined exercise training programmes of at least 20 minutes, two to three times per week for a minimum of six weeks, not just a single exercise session. However, ultimately they were unable to examine exercise duration as it was not always adequately documented and, in some studies, it changed over time. The studies included were either before and after, or those comparing between groups across time. Anxiety was an outcome measure, and both state and trait anxiety levels were assessed in all subjects using validated self-report measures. The 15 'before and after' studies involving 889 subjects were homogenous and the results were combined. The weighted average effect size was 0.45 and this was found to be statistically significantly different from zero. The 28 group comparison studies of 1322 exercise participants compared with 1106 controls, were not homogenous and they were therefore broken down into subgroups. A greater effect size (0.51) was seen for high stressed individuals compared with minimally stressed (0.28) and women only interventions were found to be less effective in reducing anxiety (weighted effect size 0.15) compared with male only (0.38) or mixed group interventions (0.39).

In terms of a dose response, Dunn et al, only found two studies that examined the effect of an exercise dose in terms of intensity, duration and frequency and in neither was there a reduction in symptoms by 50 percent or more, the criteria they set. In the study by Katula et al (1999), they had mixed results when they randomised 80 adults (average age 67) who were already participating in a randomised controlled trial of exercise, to either a light, medium or moderate exercise task. They found that whilst anxiety reduced in those doing the light intensity task, it increased in the high intensity task and there were no changes in the moderate intensity task. However, on Spielberger's State Anxiety Inventory used to measure anxiety levels before and after the task, the subjects' anxiety levels were all between 13 and 17, which suggests that while there was a change in anxiety, this paper does not provide supporting evidence that exercise is a useful intervention for reducing anxiety in those patients with clinical symptoms.

To summarise, there appears to be little robust published research evidence to support the use of exercise as a method of reducing anxiety levels in patients suffering from anxiety.

10.1.4 Cost effectiveness

Bower et al 2001

This study was a systematic review encompassing RCTs and controlled before and after studies of self help treatments for patients with anxiety and depression in primary care. A total of eight studies were identified examining written interventions based mostly upon behavioural principles. The majority of trials reported some significant advantage in clinical outcome associated with self help treatments in the short term. However there was no data concerning long term clinical benefits or cost effectiveness.

Study limitations

- methodological weaknesses in reported studies
- no data on cost effectiveness was available

Conclusions from the study

The available evidence is limited and more rigorous trials are required to provide more reliable estimates of the clinical and cost effectiveness of these treatments. However the review process provides some preliminary evidence that self-help packages may offer some clinical advantages over routine primary care. Further research is required to conduct economic analyses and to examine the key aspects of self help interventions that are important determinants of outcome, such as the extent of professional involvement and patient psychological characteristics.

Bower et al 2003b

This study formed a meta-analysis of individual patient data from trials of counselling in primary care which was compared with usual care by a GP. Four studies met the Cochrane eligibility criteria and included sufficient detail to be included in the analysis. The studies included were as follows:

Study	Type of counselling	Patient inclusion criteria	Follow up	Main clinical outcome	Data on service use	Sample size
King et al	Non-directive	Depression or mixed anxiety and depression	4 and 12 months	Beck depression inventory	Consultations psychotropic medications, referrals	134
Harvey et al	Method not standardised	Any emotional or relationship problem	4 months	Hospital anxiety and depression scale	Consultations, all prescriptions, referrals	162
Simpson et al	Psychodynamic or cognitive behavioural	Mild to moderate depression of 6 months or more	6 and 12 months	Beck depression inventory	Consultations, all prescriptions, referrals	181
Friedli et al	Non-directive	Emotional difficulty deemed to require brief psychotherapy	3 and 9 months	Beck depression inventory	Consultations, all prescriptions, referrals	136

Costs

The main analysis of costs in the long term indicated that counselling was associated with significantly greater total direct costs per patient (care by GP £272-£345 / counselling £411-£416) weighted difference in means £110 (95% confidence interval £38-£182).

Effectiveness

Counselling provided superior scores on the Beck Depression Inventory (BDI) in the short term but not in the long term.

Cost effectiveness analysis

This was based on patients with data available on both costs and effectiveness. The incremental cost effectiveness ratio for counselling compared with usual care by a GP over the long term was £196 per one point improvement on the Back depression inventory (counselling minus usual care incremental cost £110, incremental mean effect 0.56). The incremental cost effectiveness ratio for counselling compared with usual care in the short term was £50 per one point improvement in the BDI ((counselling minus usual care incremental cost £109, incremental mean effect 2.16).

Study limitations

- mainly a methodological paper to demonstrate that individual patient data can be used to overcome the sample size limitations often associated with economic analyses rather than an evidence paper
- typical ceiling ratios for a one point change in scores on the BDI are not known and hence make interpretation of incremental cost effectiveness ratios difficult.

Conclusions from the study

Provides evidence that counselling may be more effective in the short term for a modest extra cost but indicates that in the long run the benefits are similar to usual care by a general practitioner.

Bower et al 2000

This study compares the cost effectiveness of (6-12 sessions of) non-directive counselling or cognitive-behaviour therapy and routine general practitioner care in the management of depression and mixed anxiety and depression from a UK perspective. The study was designed as a cost effectiveness study with the Beck depression inventory as the main outcome and the EQ-5D as a secondary outcome measure. A societal perspective was taken for the measurement of costs. The main study sample consisted of 197 patients randomly allocated to one of the three treatments. Patients allocated to psychological therapy received 6-12 sessions with a qualified therapist. Patients in usual care were managed by their general practitioner.

Patients in all three arms of the trial improved on the primary outcome measure, but the patients in both psychological therapy groups made significantly greater clinical gains in the first four months after allocation. All groups had equivalent outcomes at 12 months. There were no significant differences in outcome between the three groups in terms of the EQ-5D.

Patients given usual GP care recorded more consultations, greater use of antidepressant drugs and more psychiatric referrals. However there were no significant differences in total direct NHS costs at 4 months or 12 months across the three treatment regimens (since the higher costs associated with GP care were balanced out by the extra therapy costs associated with CBT and

non-directive counselling). Total mean direct NHS costs at 4 months were £244 for usual GP care, £216 for CBT and £258 for non-directive counselling.

Study limitations

- low power of cost calculations, sample size was calculated on the basis of expected clinical outcomes only
- majority of patients had a primary diagnosis of depression and not anxiety

Conclusions from the study

The use of psychological therapies in general practice was associated with short term benefits in the mental health of depressed patients compared with usual GP care. At 12 months no significant differences were found between the three treatments in terms of outcomes or total costs and there was no evidence that psychological therapies were more cost effective than usual care in the long term. Given such equivalence the study authors suggest that service commissioners are in a position to decide on services based upon factors other than outcomes and cost, such as staff and patient preferences or staff availability.

11. Audit criteria & quality framework

11.1 Audit criteria

Criterion	Exception	Definition of terms
The patient shares decision-making with the healthcare professionals during the process of diagnosis and in all phases of care.	The patient with panic disorder or generalised anxiety disorder is unable to participate in an informed discussion with the clinician responsible for treatment at the time, and an advocate or carer is not available.	
The patient and his or her family and carer(s) are offered appropriate information on the nature, course and treatment of panic disorder or generalised anxiety disorder, including information on the use and likely side-effect profile of medication.	None	
The patient and his or her family and carer(s) are informed of self-help groups and support groups and are encouraged to participate in programmes.	The patient with panic disorder or generalised anxiety disorder is unable to participate in self-help groups or support groups.	
All patients prescribed antidepressants are informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly.	None	
Necessary relevant information is elicited from the diagnostic process.	The patient with panic disorder or generalised anxiety disorder is unable to participate in a discussion with the clinician responsible for treatment, and an advocate or carer is not available.	Necessary relevant information can be defined as personal history, any self-medication, and cultural or other individual characteristics that may be important considerations in subsequent care.
The treatment of choice is available promptly.	None	[MH291104: GDG 'definition' of promptly deleted in line with discussions with Mercia – see notes in KPs]
Individuals with panic disorder are not prescribed benzodiazepines.	None	

A patient with panic disorder is offered any of the following types of intervention, and the person's preference is taken into account: • psychological therapy • pharmacological therapy • self-help.	None, providing that there are no known drug sensitivities	Psychological therapy is CBT. Pharmacological therapy refers to an SSRI licensed for panic disorder; or if an SSRI is unsuitable or there is no improvement imipramine or clomipramine are considered. Self-help includes bibliotherapy based on CBT principles.
A patient with generalised anxiety disorder is not prescribed benzodiazepines for longer than 2–4 weeks.	None	
A patient with longer-term generalised anxiety disorder is offered any of the following types of intervention, and the person's preference is taken into account • psychological therapy • pharmacological therapy • self help.	as above	Psychological therapy is CBT. Pharmacological therapy is an SSRI. Self-help includes bibliotherapy based on CBT principles.
A patient is reassessed if one type of intervention does not work, and consideration is given to trying one of the other types of intervention.	None	
A patient who still has significant symptoms after two interventions is offered referral to specialist mental health services.	None	Two interventions can be defined as any combination of psychological intervention, medication or bibliotherapy.
A thorough, holistic re-assessment of the individual, his or her environment and social circumstances is conducted by specialist mental health services.	None, unless the patient refused referral	
Outcomes are monitored using short, self-complete questionnaires.	The individual with panic disorder or generalised anxiety disorder is unable to participate in a discussion with the clinician responsible for treatment	A short self-complete questionnaire such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder.

11.2 Quality and outcome framework

The changes to the contractual arrangements for primary care services, and particularly for general practitioners, have provided an opportunity to consider different ways of auditing the care that is provided through implementing these guidelines.

The new contractual arrangements provide a system for practices to be financially rewarded for delivering specific clinical outcomes in a number of different clinical domains. Although these clinical domains and the financial rewards are carefully described for GMS (general medical services) practices, there exists the flexibility to develop new and innovative clinical domains for PMS (personal medical services) practices.

The Guideline Development Group has therefore produced such a draft framework. The structure of this section mirrors the structure of a standard quality and outcome domain, but does not allocate any points, because this will be up to the discretion of the commissioning Primary Care Trust (PCT), and then by negotiation with the personal medical services (PMS) practices.

It should be stressed that PCTs, and PMS practices, may wish to amend and alter this draft framework to make it more appropriate for local needs.

Details of the rationale, indicators and proposed methods of data collection and monitoring

Anxiety – rationale for inclusion of indicator set

Anxiety is a common and debilitating condition that affects large numbers of people. Effective treatments are available. Anxiety frequently co-exists with other conditions, both physical and mental, and influences the resolution of these other conditions. Effective treatment for anxiety disorders will also have a beneficial impact on these other co-existing conditions.

Indicator	**Points***	**Max threshold**
Records		
A1a. The practice can produce a register of people with generalised anxiety disorder		
A1b. The practice can produce a register of people with panic disorder		
Treatment options		
A2a The percentage of people with generalised anxiety disorder on the register offered CBT		**No score**
A2b. The percentage of people with generalised anxiety disorder on the register offered medication *(a SSRI)*		**No score**
A2c. The percentage of people with generalised anxiety disorder		**No score**

on the register offered bibliotherapy		
A2 Total: the sum of the above		**25–90%**
A3a The percentage of people with panic disorder on the register offered CBT		**No score**
A3b. The percentage of people with panic disorder on the register offered medication *(a licensed SSRI, imipramine or clomipramine)*		**No score**
A3c. The percentage of people with panic disorder on the register offered bibliotherapy		**No score**
A3 Total: the sum of the above		**25–90%**
Referral to secondary care		
A4. The percentage of people on both registers who have been referred to secondary care services who have received two interventions in the last 12 months		**25–70%**

*** To be agreed locally**

Anxiety indicator 1
The practice can produce a register of either people with generalised anxiety disorder or panic disorder

Anxiety indicators 1a and 1b - rationale
To call and recall patients effectively in any disease category, and to be able to report on indicators, practices must be able to identify patients within the practice population who have either generalised anxiety disorder or panic disorder. Neither this quality and outcome framework nor the NICE guideline of which it is a part applies to people with mixed anxiety and depression, for which reference to the NICE depression guidelines should be made. This framework also does not apply to people who have a single panic attack, because they have not yet developed panic disorder.

Anxiety indicators 1a and 1b - preferred coding
Practices should record those with a current history of:
Generalised Anxiety Disorder Eu[X]41.1
Panic Disorder Eu[X]41.0.

Anxiety indicators 1a and 1b - reporting and validation
The practice reports the number of patients on both registers (for generalised anxiety disorder and panic disorder), and the number as a proportion of the total list size.
PCTs may compare the expected prevalence with the reported prevalence.

Anxiety indicators 2a, 2b, 2c and 2 Total
The number of patients with generalised anxiety disorder receiving either CBT, an approved medication, or self-help.

Anxiety indicators 2a, 2b, 2c and 2 Total – rationale

This guideline provides the evidence for supporting shared decision-making in selecting treatments that are effective. These three indicators allow patient choice within the parameters of

what is known to be effective. The sum of the total should account for all those on the generalised anxiety disorder register, to ensure that only effective interventions are offered.

Anxiety indicators 2a, 2b, 2c and 2 Total – preferred coding
Practices should record which medication, if any, is being prescribed.
Practices should record whether patients have been referred for CBT.
Practices should record whether patients have been referred for bibliotherapy.

Anxiety indicators 2a, 2b, 2c and 2 Total – reporting and validation
Practices should record the total percentage of patients on the generalised anxiety disorder register receiving an intervention.
PCTs should be able to scrutinise the computer print-out.

Anxiety indicators 3a, 3b, 3c and 3 Total
The number of patients with panic disorder receiving either CBT, an approved medication, or self-help

Anxiety indicators 3a, 3b, 3c and 3 Total - rationale
This guideline provides the evidence for supporting shared decision-making in selecting treatments that are effective. These three indicators allow patient choice within the parameters of what is known to be effective. The sum of the total should account for all those on the panic disorder register, to ensure that only effective interventions are offered.

Anxiety indicators 3a, 3b, 3c and 3 Total – preferred coding
Practices should record which medication, if any, is being prescribed.
Practices should record whether patients have been referred for CBT.
Practices should record whether patients have been referred for bibliotherapy.

Anxiety indicators 3a, 3b, 3c and 3 Total – reporting and validation
Practices should record the total percentage of patients on the panic disorder register receiving an intervention.
PCTs should be able to scrutinise the computer print-out.

Anxiety indicator 4
The number of patients referred to specialist mental health services who have had two effective interventions, but failed to improve

Anxiety indicator 4 – rationale
The majority of patients with generalised anxiety disorder or panic disorder can and should be cared for in primary care. It is appropriate to consider referral to specialist mental health services if two effective interventions have failed to produce an improvement for the patient. There will always be other reasons why referral may be necessary, which allows a slightly lower target than for the other indicators.

Anxiety indicator 4 – preferred coding
The practice should record which two interventions have been provided to patients who are referred.

Anxiety indicator 4 – reporting and verification
Practices should be able to produce a list of patients referred to specialist services for the management of generalised anxiety disorder or panic disorder, and for each patient, the number of effective interventions that patients had received.
PCTs should be able to scrutinise the list produced by the practice.

12. Research issues

There are considerable gaps in the evidence base. To improve the evidence base on which effective care for patients can be based, the guideline development group have identified areas that they think would benefit from further empirical research.

Which Interventions?

Research recommendations in this category of recommendations are perceived as having a high priority as they inform the current provision of services.

1. Cost effectiveness of interventions:
    a. Psychological interventions
    b. Self help interventions identified as being effective
    c. Medication identified as being effective
    d. Studies that compare the cost effectiveness of different types of interventions
2. The duration which interventions should be used to achieve a successful outcome:
    a. Psychological interventions
    b. Self help interventions
    c. Medication
3. Identification as to which interventions have long term benefits.

What other interventions may be effective?

This category of research recommendations allows the study of interventions which have not yet achieved a solid evidence base for their effectiveness, or which particular model of delivery is most effective or who might be best suited to provided a particular intervention

4. The role of counselling in primary care in providing treatment to people with panic disorder and generalised anxiety disorder, including:
    a. what interventions do counsellors offer?
    b. which are effective?
    c. what supervision and training is needed to offer these interventions?
5. The cost effectiveness of various models of CBT, including:

   a. the number of sessions
   b. intervals between sessions
   c. length of sessions
   d. substitution of sessions within increased homework.

6. What is the nature of the relationship between the clinical skills of the health care professional, the involvement of the patient, and the clinical outcome of the condition.
7. Who can deliver effective CBT or relaxation therapy for people with panic disorder of generalised anxiety (including new health care workers)?
8. What impact on outcomes does the use of patient self complete questionnaires prior to consultations with primary care professionals have?

What are the characteristics of the disorders?

This group of research recommendations informs the understanding of the disorders, the characteristics of those suffer from those disorders, and those that do not recover.

9. The effectiveness of all interventions in general clinical populations rather than highly selective populations.
10. Effective interventions for treatment resistance generalised anxiety disorder and panic disorder.
11. The relationship between individual characteristics (e.g. age, sex, gender or ethnicity) and likely success of treatment.
12. The relationship between duration and severity of illness and likely success of treatment.

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14. Appendices: